

Therapeutic Applications of Chondroitin Sulphate, Collagen and Rosehip Extract in the Musculoskeletal System

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Abstract:- The present review is based mainly on papers published between 2000 and 2020 and gives information about the properties of the Chondroitin sulphate, Collagen and rosehip Extract in chemical and biological systems and its possible role in preventing Musculoskeletal system diseases. The main aim of this report is to highlight their role and therapeutic applications in the Musculoskeletal system, also reported are their bioactive properties which may influence the development of treatments and protection against Musculoskeletal system cell damage. The paper will also examine recent observations in various fields.

I. CHONDROITIN SULPHATE IN THE MUSCULOSKELETAL SYSTEM

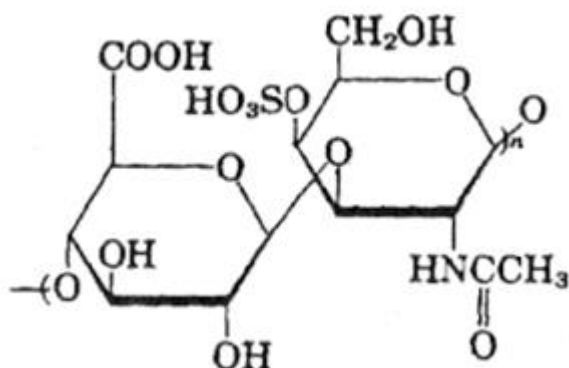


Fig 1:- Chemical structure of chondroitin sulphate.

Chondroitin sulphate is a sulfated glycosaminoglycan consisting of d-glucuronic acid and N-acetyl d-galactosamine alternating chains. CS can increase collagen type II and proteoglycan synthesis in human articular chondrocytes and are capable of reducing the development of specific pro-inflammatory mediators and proteases, reducing the cycle of cell death, and improving the anabolic/catabolic balance of the extracellular cartilage matrix. CS is available as products of pharmaceutical grade (pCS) and nutraceutical grade, while the nutraceutical grade shows notable differences in preparation, composition, and purity. The purity and/or production/purification of the CS compounds could direct the cycle of OA disease either towards an inhibition or stimulation of the catabolic pathways within the cartilage and could have a positive or adverse effect on the synthesis of collagen type II.

Chondroitin sulphate in the treatment of osteoarthritis: from in-vitro studies to clinical recommendations.

Chondroitin sulphate (CS) is being used as a therapeutic tool for the diagnosis of multimodal approaches in osteoarthritis (OA). This article intends to collect most of the knowledge available on CS and to clarify its usefulness in managing the OA. This paper was chosen because it demarcated Chondroitin sulphate with its Pharmacokinetic profile and Pharmacological uses and included some data on in-vitro and in-vivo effects on the treatment of Osteoarthritis OA associated with knee and hip.

Effects of Glucosamine and Chondroitin Sulphate on Cartilage Metabolism in OA: Outlook on Other Nutrient Partners Especially Omega-3 Fatty Acids

Osteoarthritis (OA) is a degenerative joint condition characterized by increased cartilage degradation, periarticular bone remodelling, and synovial membrane inflammation. Treatment with chondroprotective agents such as glucosamine sulphate, chondroitin sulphate, hyaluronic acid, collagen hydrolysate, or nutrients such as antioxidants and omega-3 fatty acids is a promising therapeutic option in addition to traditional OA treatment with non-steroidal anti-inflammatory drugs (NSAIDs). We may clarify their chondroprotective behaviour with a dual mechanism: (1) as an essential component of cartilage and synovial fluid, stimulate the cartilage anabolic process metabolism; (2) their anti-inflammatory action may delay many catabolic processes induced by inflammation in the cartilage. Those are two mechanisms that may slow the progression of cartilage destruction and can help to restore the joint structure, contributing to cartilage destruction, reduced pain, and increased joint mobility.

The reason to choose this paper includes detailed information on OA and its progression and also the explanation of the mechanism of the Chondroprotective effect.

Association of Pharmacological Treatments with Long-term Pain Control in Patients with Knee Osteoarthritis A Systematic Review and Meta-analysis

This meta-analysis is a systematic study and network meta-analysis of knee osteoarthritis research, and for at least 12 months. There was confusion regarding the predictions of the follow-up impact scale for pain shift with all placebo comparisons. Larger RCTs are needed to tackle the uncertainty effectiveness of knee osteoarthritis drugs.

This paper includes the randomized clinical trials conducted by various research teams with glucosamine sulphate (SMD, -0.42 [95% CrI, -0.65 to -0.19]), chondroitin sulphate (SMD, -0.20 [95% CrI, -0.31 to -0.07]), and strontium ranelate (SMD, -0.20 [95% CrI, -0.36 to -0.05]). It provides the meta-analysis of various pharmacological agents in comparison to a placebo.

The meta-analysis of chondroitin sulphate in the treatment of Osteoarthritis

CS may be useful in OA, but further trials are required for more extended periods of time in wider patient populations to prove its effectiveness as a symptom modifying drug in OA.

Effectiveness and safety of glucosamine and chondroitin for the treatment of osteoarthritis: a meta-analysis of randomized controlled trials

Despite the effectiveness of such symptomatic slow-acting medications, oral chondroitin is more successful in relieving pain and enhancing physical function than placebo. Glucosamine exerted an effect on the resulting stiffness. Further studies need to investigate the accuracy of effectiveness regarding the limited number of combination therapies. This knowledge, followed by the tolerability and economic costs of the treatments included would be beneficial to clinician decision making. This paper is the latest meta-analysis of the chondroitin sulphate for the treatment of OA from 2018.

Chondroitin for Osteoarthritis of the Knee or Hip

This systematic analysis collected details from 20 trials; the effects of chondroitin have been compared with either placebo or no therapy for osteoarthritis in hip or knee cases. Recent, high-quality tests showed minimal chondroitin or did not affect pain in the joint. Joint space impacts were inconclusive.

Chondroitin sulphate: A complex molecule with potential impacts on a wide range of biological systems

Chondroitin sulphate (CS) is commonly ingested by humans orally and by non-humans because it is believed to be helpful to those with joint-related pathologies. Studies are being continuously developed on the roles of chondroitin sulphate in this and other biological systems. Significant parameters were tested for CS, including bioavailability and uptake; it is clear that substantial difficulties remain in the identification of the functional impacts of structure, sequence, and scale, in the understanding of how the ingested material is altered during absorption and transported to the site of action, and how it affects biological processes. By recognizing these factors, it may be possible to predict impacts on biological processes and identify particular structures of chondroitin sulphate that may target specific pathologies.

Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: a network meta-analysis

Glucosamine Effect, chondroitin, or both associated with joint pain and on the radiological progression of

osteoarthritis disease hip and knee. Glucosamine, versus placebo, the combination of chondroitin does not reduce the joint pain or effects on joint space narrowing.

Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as six months after initiation of therapy: a randomized, double-blind, placebo-controlled pilot study using MRI

The Chondroitin Sulphate Effect (CS) treatment of volume loss in cartilage, subchondral bone marrow lesions (BML), synovitis, and symptoms of disease in Osteoarthritis (OA) in knee patients is explained.

CS therapy meant a significant reduction of loss of cartilage volume in OA knee starting at six months' care, and a 12-month BML. These findings suggest a joint protective effect of CS structure and have new in vivo details about the way it works in knee OA.

Collagen/Chondroitin Sulphate ratio of human articular cartilage related to the function

This article shows a correlation between the types of joints and the amounts of CS and Collagen present within these joints. Since then, weight-bearing and non-weight-bearing articular cartilage areas vary significantly in collagen and the quality of chondroitin sulphate if contrast is made between joints or between regions inside the same joint.

The mechanical role is essential in determining the structure of the articular cartilage is seen in results shown in an article in the form of tables: a higher polysaccharide content provides the requisite greater resilience in weight-bearing areas. It is well known that the earliest improvements in degenerating the knee occurs on the middle third of the joint surface of the femoral medial condyle and the femoral patellar surface layer. It is likely that the vulnerability of weight-bearing or stressed sites to degeneration is the vulnerability of weight-bearing or stressed sites to degeneration is likely is hoped to be tested in future research hypotheses.

❖ Clinical Trials on Chondroitin Sulphate

➤ Chondroitin Sulphate Trial on Osteoporosis

Study of the Effect of Chondroitin sulphate on Structural Changes in Knee Osteoarthritis Patients Assessed by MRI Trial ID: NCT01354145

The study involved a total of 194 patients from age ≥ 40 , of both sex with primary Osteoarthritis of the knee, according to the American College of Rheumatology ACR criteria with signs of synovitis, as criteria. The entire participants were under two arms (arm I - Chondroitin Sulfate 1200 mg/day *24 months and arm II - Celecoxib 1200 mg/day *24 months). This study was conducted to compare the cartilage volume loss at the baseline. **This study indicates a potentially more significant response to cartilage volume loss treatment with chondroitin sulphate in knee OA patients with low inflammation**

and higher cartilage catabolism levels. This research also demonstrated the effectiveness of CS over celecoxib in reducing CVL in knee OA patients, for the first time in a 2-year randomized controlled trial.

Efficacy and Safety of a New Formulation of Chondroitin Sulfate and Glucosamine Sulphate to Treat Knee Osteoarthritis

Trial ID: NCT01893905

The study involved a total of 154 patients from age ≥ 45 , of both sex with primary Osteoarthritis of the knee, according to the American College of Rheumatology ACR criteria with signs of synovitis, as criteria. This study aims to determine if, in treating patients with moderate to severe knee osteoarthritis, a new combination of chondroitin sulphate and glucosamine sulfate is given once daily is superior to placebo. The arm I was given Chondroitin Sulphate 200 mg+Glucosamine Sulfate 250 mg, and arm II was given a Placebo (Chondroitin Sulfate+Glucosamine Sulphate). **The findings of this trial indicate a lack of superiority of CS / GS combination therapy over placebo in reducing joint pain and functional dysfunction over six months in patients with symptomatic knee OA. The suitability of CS / GS combination therapy in OA patients could be thoroughly elucidated by further study.**

Study on Efficacy and Safety of Chondroitin Sulphate + Glucosamine Hydrochloride Versus Celecoxib in Knee Osteoarthritis (MOVES)

Trial ID: NCT01425853

The study involved a total of 606 patients from age ≥ 40 , of both sex with primary Osteoarthritis of the knee, according to the American College of Rheumatology ACR criteria. The arm I have given Chondroitin Sulphate 200 mg+Glucosamine hydrochloride 250 mg, and arm II was given a Celecoxib 200mg. **CS+GH has comparable effectiveness in minimizing discomfort, stiffness, functional weakness, and joint swelling/effusion after six months in patients with debilitating Osteoarthritis of the knee, with a strong safety profile.**

➤ Conclusion

- CS is capable of growing Type II collagen and proteoglycan synthesis in human articular chondrocytes.
- A variety of positive effects of chondroitin sulphate have been shown in clinical trials. Below you can find different aspects of the studies.
- CS over celecoxib helps reduce Cartilage Volume Loss in knee OA patients.
- CS / GS combination therapy was less superior over placebo for-joint pain and functional dysfunction for six months.
- Despite a good safety profile, CS+GH has comparable efficacy in reducing pain, stiffness, functional weakening, and joint swelling/effusion after six months in patients despite painful knee osteoarthritis.

II. COLLAGEN IN THE MUSCULOSKELETAL SYSTEM

Collagen is the main structural protein in the extracellular matrix in the various connective tissues in the body and, the most abundant protein in the human body, found in the bones, muscles, skin, and tendons. It is the substance that holds the body together. Collagen forms a scaffold to provide strength and structure. As the main component of connective tissue, it is the most abundant protein in mammals, making up from 25% to 35% of the whole-body protein content. There are at least 16 types of collagen, but 80 – 90 percent of the collagen in the body consists of types I, II, and III. These collagen molecules pack together to form long thin fibrils of similar structure.

Collagen Structure of Tendon Relates to Function

The paper talks about the role of collagen in the structure and functioning of a tendon. It also talks about the influence and the function of collagen in regulating mechanical stress and strain, as well as other mechanical properties. It also talks about how other cells and tissues are related to the increase or decrease in collagen.

Loss of Type I Collagen Telopeptide Lysyl Hydroxylation Causes Musculoskeletal Abnormalities in a Zebrafish Model of Bruck Syndrome

The paper talks about the *plod2* gene in zebrafish where a mutation in the gene caused severe skeletal abnormalities with evidence of bone fragility and fractures. *plod2* mutant zebrafish show molecular and tissue abnormalities in the musculoskeletal system. PLOD2 encodes the lysyl hydroxylase 2 (LH2) enzyme, which is responsible for the hydroxylation of lysine residues in fibrillar collagen telopeptides. This hydroxylation directs crosslinking of collagen fibrils in the extracellular matrix, which is necessary to provide stability and tensile integrity to the collagen fibrils.

Collagen Plays an Active Role in the Aggregation of Beta 2-Microglobulin under Physio-pathological Conditions of Dialysis-related Amyloidosis

This paper elucidates that collagen plays an important role in Beta 2-microglobulin amyloid deposition under physio pathological conditions. The authors have hypothesized that positively charged regions along the collagen fibre could play a direct role in Beta2-microglobulin fibrillogenesis.

Extracellular matrix changes in early osteochondritis defects in foals: a key role for collagen?

The paper discusses the role of collagen in Osteochondrosis in young horses (foals). They suggest that alterations of the collagen component, but not of the proteoglycan component, of the extracellular matrix might play a role in the early phases of Osteochondrosis, but have also mentioned that these changes might not be the primary cause of osteochondrosis.

Collagen XIII: A type II transmembrane protein with relevance to musculoskeletal tissues, micro vessels and inflammation

This paper discusses the involvement of Collagen XIII in the development, differentiation and maturation of musculoskeletal tissues and vessels and in maintaining tissue integrity. They elucidate its structure, genetic composition, ligands, expression, activation, biological functions and its possible medical applications.

Developmental and Osteoarthritic Changes in Col6a1-Knockout Mice: Biomechanics of Type VI Collagen in the Cartilage Pericellular Matrix

This study investigates if the lack of type VI collagen affects the development and biomechanical function of the pericellular matrix. It was found that mice lacking the Col6a1 gene (which codes for type VI collagen) showed accelerated development of Osteoarthritis joint degeneration, as well as other musculoskeletal abnormalities such as delayed secondary ossification and reduced Bone Mineral Density.

Efficacy of Vitamin C Supplementation on Collagen Synthesis and Oxidative Stress After Musculoskeletal Injuries

This study explores the possibility of Vitamin C being a viable supplement to enhance collagen synthesis. They found that vitamin C supplementation accelerates bone healing after fractures, increases type I collagen synthesis and reduces oxidative stress parameters but, only 10 studies were included due to the restrictions and criteria applied.

Growth hormone stimulates the collagen synthesis in human tendon and skeletal muscle without affecting myofibrillar protein synthesis)

The authors suggest that the availability of growth hormone stimulates the synthesis of growth hormone in skeletal tissues muscle and tendon. They found that the production of muscle and tendon collagen proteins increased significantly but myofibrillar protein wasn't affected.

Effect of administration of oral contraceptives in vivo on collagen synthesis in tendon and muscle connective tissue in young women

The authors tested the effect of oral contraceptives (OC) on collagen synthesis in tendon, bone, and muscle in 2 groups of women – habitual users and, non-OC users. These novel findings indicate that OC has a negative effect on the response to exercise in muscle collagen synthesis and tendon collagen protein synthesis rates both at rest and after exercise were lower in women exposed to a high concentration of synthetic female hormones compared with women exposed to a low concentration of endogenous female hormones.

Effects of Oestrogen Replacement and Lower Androgen Status on Skeletal Muscle Collagen and Myofibrillar Protein Synthesis in Postmenopausal Women

In this study, the authors tried to determine the synthesis rate of myofibrillar and collagen proteins in 20

postmenopausal women, who were either nonusers (Controls) or users of oestrogen replacement therapy (ERT) after hysterectomy. They found that muscle collagen FSR (Fractional Synthesis Rate) tended to be lower in ERT users compared with Controls.

❖ *Clinical Trials on Collagen*

➤ *Collagen Trials On Dental Patients*

Bone Remodelling After Immediate Implant Placement with and Without Bone Grafting

Trial ID: NCT02174198

The study involved 32 patients from age group 18 and above, who required one maxillary anterior implant and had the labial plate of bone present after extraction. 16 patients were given the Bios Collagen® graft while the other 16 were monitored as control and had no graft placed. Hopeless maxillary anterior teeth will be extracted and implants will be placed in a flapless procedure.

Significant to moderate changes were observed in the vertical dimension of Buccal Soft Tissue as well as in the Mean Bucco-Lingual Change, with no change being measured in the thickness of Keratinized Tissue.

An RCT Comparing Xenograft and Allograft for Ridge Preservation

Trial ID: NCT02330523

40 patients were selected for this study ranging from the ages of 18 – 70 with the subjects indicated for posterior tooth extraction and implant replacement falling in the criteria of inclusion. Subjects were divided into 2 groups – one of 21 patients and the other of 19 patients. The subjects in the first group were implanted with a demineralized freeze-dried allograft + x-link collagen membrane and the latter with a xenograft + non-x-link collagen. These were going to be used for guided bone regeneration of dehiscence buccal defects post extraction.

After 6 months, significant decreases were measured in the Bone Ridge Buccal-Lingual Width and Aico-Coronal Height for the Allograft arm, along with decrease in New Bone Plus Graft Content. A significant increase in the buccal-lingual suture line gap was measured after 4 weeks.

Effect of Laser Use on Guided Tissue Regeneration in Treatment of Molar Teeth With Class 2 Furcation Affected by Periodontitis

Trial ID: NCT01522131

- 33 patients (< 18 years) in good general health with an O'Leary plaque score of 20% or less along with having class II furcation in the buccal of the maxillary molars or the buccal or lingual of the mandibular molars and lastly, tooth mobility not exceeding Class II were the inclusion criteria.
- The study aimed at comparing the clinical response of using bio-resorbable collagen membrane alone or defect debridement with erbium (Er) Laser irradiation in conjunction with bio-resorbable collagen membrane in

the treatment of Class II furcation defects in maxillary and mandibular teeth.

- The test group had debridement performed with the Er, Cr: YSGG (Erbium, chromium-doped yttrium, scandium, gallium and garnet) laser and ultrasonic cleansing, while the control group had hand instrumentation along with ultrasonic cleansing.
- The test group included 17 subjects while the control group had 16 subjects. Out of the 16 subjects, study was completed for 14 of them.
- **Change in clinical attachment (Loss) as well as Evidence of Regeneration of Class 2 Furcation Defects was higher in the test group as compared to the control group.**

Effect of Mucograft® Seal on Post-extraction Ridge Preservation Using Bone Allograft (Mucograft)

Trial ID: NCT02697890

Patients who were non-smokers, showed no evidence of acute periodontal infection, and had unsalvageable non-adjacent non-molar teeth scheduled for extraction were considered in the inclusion criteria. There were a total of 28 participants with the age group being 18 years and older. This trial suggests that the use of Mucograft® TM in periodontal plastic surgery may provide a viable source of grafting material as an alternative to autogenous and non-autogenous soft tissue graft materials. Participants were divided into 2 groups - Group A received FDBA and a Collagen Sponge (CS) while Group B received FDBA with Mucograft® seal. **In respect to the Changes in Alveolar Bone, Soft and Hard Tissues and in the Keratinized Tissue Width, Group B with Mucograft® showed much less change as compared to Group A with Collagen Sponge.**

A Volumetric Analysis of Soft and Hard Tissue Healing for Ridge Preservation and Socket Seal After Tooth Extraction

Trial ID: NCT02844569

24 participants ranging from 18-80 years of age in adequate periodontal health were selected in this trial to investigate the hard tissue vs soft tissue healing analysis. Subjects were recruited into 2 groups:

1. **Test** - Extraction treated with xenograft bone substitute (BioOss Collagen®) + collagen dressing (HeliPlug®),
 2. **Control** - Extraction treated with xenograft bone substitute (BioOss Collagen®) + 3D-collagen matrix (Mucograft Seal®), within a time frame of 6 months.
- **The change in Buccal Plate Thickness was 1.85mm in Test vs 1.25mm in Control group.**
 - **The change in Buccal Soft Tissue Volume was 68.6mm³ in Test vs 87.6mm³ in Control group.**
 - **The change in Buccal Plate Volume was 72.6mm³ in the Test vs 60.9mm³ in the Control group.**

Guided Bone Regeneration Around Immediate Implants

Trial ID: NCT01628367

32 patients (< 18 years) in good general health and having one or more anterior or premolar teeth with a hopeless prognosis, with adjacent and opposing teeth present were a part of this study, which investigated the effect of a non-resorbable polytetrafluoroethylene (PTFE) membrane on immediate implant placement in the aesthetic zone. The patients were divided into the test group and the Control (Collagen Plug) group. Sites in the test group received a high-density PTFE (d-PTFE) membrane over the socket while those in the control group received a collagen wound dressing over the socket.

After a year, the Mean changes in the thickness of Buccal Bone and Interproximal Bone Levels in the test group were 0.73mm and 1.38mm respectively, while the same measures for the Control group were 0.86mm and 1.42mm.

Comparison of Autogenous Periosteal Pedicle Graft and Collagen Membrane in Management of Periodontal Intra-bony Defects

Trial ID: NCT02248103

20 patients (35-50 years) suffering from advanced chronic periodontitis were included in this randomized controlled clinical trial. Each subject contributed matched pairs of two- or three-walled intra-bony defects. Each pair of periodontal defects were randomly assigned into the experimental group; periosteal pedicle graft guided tissue membrane or the positive control group; bioresorbable collagen guided tissue regeneration membrane.

The Clinical Attachment Level (or, CAL) level at the baseline was ~6 which fell to ~3 after 6 months. Additionally, at the baseline, CAL was higher in the experimental group compared to the positive group, however after 6 months, it was higher in the positive group. Both Pocket Depth levels and Bone Defect Area were high at baseline which halved after 6 months.

Evaluation of OSSIX-Plus Resorbable Collagen Membranes for Alveolar Ridge Preservation Following Exodontia (OSSIX)

Trial ID: NCT00639860

This study is designed to test the ability of OSSIX-Plus in promoting optimal bone healing following exodontia. 10 participants aged 18-80 years were included in this study and monitored for 12 weeks.

Mean Percentage of new bone formation of the alveolar bone core biopsies was found out to be 46.09%, while the mean change in Bone Gain or Loss (Stent to Apex) was 10.9mm and the mean Change in Bone Gain or Loss (Mesiodistal) was 4.6mm. Also, the Mean Change in Bone Gain or Loss (Bucco-palatal) was found to be 7.7mm

➤ *Collagen Trials On Post Menopausal Osteoporosis Patients*

A Study of Bone Turnover Markers in Post-Menopausal Women with Osteoporosis Treated with Monthly Boniva (Ibandronate)

Trial ID: NCT00303485

A total of 67 women with post-menopausal osteoporosis and in the group of above 65 years were chosen in this study to determine the rapidity of suppression of the bone resorption marker sCTX in postmenopausal women with osteoporosis. Patients will be randomised to either monthly Ibandronate 150mg or Placebo, in combination with vitamin D and calcium supplementation.

Relative Percent Change in Serum C-terminal Telopeptide of Type 1 Collagen (sCTX) Concentration from Baseline Over Time was measured which showed that in the first week of each month, the level was high and decreased significantly by the last week of each month. The measures and levels of Relative Percent Change in Bone Specific Alkaline Phosphatase (BSAP) Concentration as well as that of parathyroid Hormone from Baseline Over Time showed a significant decrease from baseline and thus greater response to therapy. However, one participant had to drop out due to dizziness from the Ibandronate group and 2 patients had to drop out from the placebo group due to Angina Unstable and Hypertension.

A Study of Ibandronate (Boniva) to Evaluate Bone Turnover Markers in Women with Treatment-Naive Postmenopausal Osteoporosis

Trial ID: NCT02598934

308 Females, ranging from children to older adults were a part of this study which evaluated if an early positive response to once-monthly oral ibandronate in treatment-naïve participants with postmenopausal osteoporosis is predictive of efficacy later in treatment, for 6 months. Patients were divided into 2 groups – 1 and 2, where both groups received a 6-month regimen with oral ibandronate, 150 mg once monthly. Group 1 received a physician consultation after 4 months of treatment to review bone turnover test results, which was not the case for group 2. 19 participants from group 1 and 22 participants from group 2 couldn't complete the trial due to various reasons.

68.8% of the Consult group participants responded that Ibandronate is effective in treating osteoporosis while only 51.9% of the Non-Consult group said so. When asked if it reduces the risk of breaking bones, the percentage was 64.9 and 50 respectively. The Percent Change in Serum CTX, NTX, P1NP, Serum osteocalcin and BSAP were 55.26%, 45.98%, 58.14%, 41.51% and 35.34% respectively FROM Baseline to Month No. 6.

A Double-blind Study to Assess the Efficacy and Safety of Denosumab Produced by Two Different Processes in Postmenopausal Women with Osteoporosis

Trial ID: NCT02157948

394 ambulatory postmenopausal women in the age range of 55 to 100 years were chosen to be a part of this study which compared the effect of denosumab produced by two different manufacturing processes – CP2 and CP4, on bone mineral density at the lumbar spine. 18 participants could not complete the study due to various reasons.

The mean percent change of Lumbar spine bone mineral density in the CP2 group was 5.78% as compared to the CP4 group which had 5.73%. The mean percent change of sCTX in CP2 group and CP4 group were 86.39% and 88.05% for Month 1, 76.46% and 79.48% for Month 6 and lastly, 71.34% and 75.44% for Month 12. Also, the mean percent change in P1NP in CP2 group and CP4 group were 29.59% and 29.86% for Month 1, 76.63% and 77.74% for Month 6 and lastly, 71.44% and 72.08% for Month 12.

Parathyroid Hormone (PTH) for Osteoporosis in Postmenopausal Women

Trial ID: NCT00086619

80 postmenopausal women in the age bracket of 46 to 85 years were a part of this study which tested whether increasing the daily dose of PTH sustains its ability to improve bone formation, and why PTH's effects on bone formation decline over time. Participants received synthetic human parathyroid hormone fragment 1-34 (hPTH 1-34) once-daily in a constant dose of 30 mcg/day, or in a dose that ascends at 6-month intervals (20-30-40 mcg/day). **Changes in Indices of Bone Turnover (in ng/ml) were measured which were –**

- **P1NP – 4418 (Constant) and 3696 (Ascending)**
- **Osteocalcin – 956 (Constant) and 822 (Ascending)**
- **CTX – 22 (Constant) and 19 (Ascending)**
- **Changes in Indices of Bone Mineral Density (in %) were measured which were –**
- **Femoral neck BMD – 1.7 (Constant) and 3.5 (Ascending)**
- **Spine BMD – 5.9 (Constant) and 7.4 (Ascending)**
- **Subtotal BMD - 1.6 (Constant) and -0.9 (Ascending)**
- **Total Hip – 1.4 (Constant) and 1.3 (Ascending)**

Assess the Safety, Efficacy, and Pharmacokinetics of Immediate and Delayed Release Weekly Risedronate

Trial ID: NCT00577720

181 Females in the age group of 45 – 80 years were chosen to compare the efficacy 50 mg delayed-release risedronate tablet, dosed immediately after breakfast, to a 35 mg immediate-release tablet, administered according to labelling instructions. Patients were divided into 4 arms - 35 mg IRBB, 35 mg DRFB, 50 mg DRFB and 50 mg DRBB and monitored for 13 weeks.

The values for the Percent change in serum CTX, Urine NTX/Cr and Serum BAP were calculated. It was found that the Least Squares Mean value was in the middle of the 95% confidence interval range.

A Study Comparing Oral Calcitonin to Nasal Spray Calcitonin in Postmenopausal Osteoporotic Women (ORACAL)

Trial ID: NCT00959764

The purpose of this study is to compare the effectiveness and tolerability of two medications, calcitonin nasal spray and a tablet containing calcitonin, in 565 postmenopausal women aged 45 years or older, with osteoporosis. Patients were divided into 3 arms - Oral Calcitonin: Patients who only received oral calcitonin as an active treatment, Nasal Calcitonin: Patients who only received nasal calcitonin as active treatment and, Placebo: Patients who did not receive any active treatment.

The Least Squares Mean Percent Increase from Baseline in Bone Mineral Density (BMD) of Axial Lumbar Spine was highest the Oral Calcitonin followed by Nasal Calcitonin and Placebo. The Least Squares Mean Percent Change in Plasma C-terminal Telopeptide of Collagen 1 (CTX-1) from baseline was also highest the Oral Calcitonin followed by Nasal Calcitonin and Placebo.

➤ *Collagen Trials On Rheumatoid Arthritis Patients*

Evaluation of the Role of Adalimumab on Extra Articular Manifestation - Bone Metabolism and Bone Mineral Density in Patients with Active Rheumatoid Arthritis

Trial ID: NCT01078155

131 Participants, all 18 years or older with active early and long-standing Rheumatoid Arthritis (RA) were included in this study to assess the prevention of generalized bone loss in patients with active RA treated with adalimumab (Humira®) in pragmatic prescribing situations. 44 Participants couldn't complete the trial due to various reasons. Proximal Femur T-score and Z-scores were measured and found to be in the normal bone density range throughout the course.

The duration of morning stiffness, tender joint count, Swollen Joint count, Visual Analogue Scale (VAS), Erythrocyte Sedimentation Rate (ESR) also reduced significantly during the course of treatment. Disease Activity Score in 28 joints (DAS28) also came down to the lower disease activity range from High RA disease activity.

Augment® Injectable Bone Graft Compared to Autologous Bone Graft as a Bone Regeneration Device in Hindfoot Fusions

Trial ID: NCT01305356

299 Participants all 18 years or older, diagnosed with degenerative joint disease (DJD) and requiring a hindfoot fusion procedure with supplemental bone graft/substitute were included in this study to evaluate a fully synthetic bone graft material to facilitate fusion in conditions or injuries requiring bone graft in a representative clinical fusion model and thus the opportunity to provide equivalent union rates as Autologous Bone Graft without necessitating an additional invasive procedure to harvest the graft. Patients were divided into 2 groups - Group I: Standard Rigid Fixation + Autologous Bone Graft Group II:

Standard Rigid Fixation + Augment® Injectable Bone Graft and monitored for 24 months after surgery.

After 52 weeks, both groups showed significant improvement in Pain on Weight Bearing as well as rapid decrease in Foot Function Index (FFI). AOFAS Hindfoot and Ankle Score increased significantly and Fusion site pain decreased. The improvements in the 2nd group were better as compared to the 1st group.

➤ *Collagen Trials On Patients With Spondylosis*

OsteoStrux™ Collagen Ceramic Scaffold in Instrumented Lumbar Spine Fusion

Trial ID: NCT01873586

The objective of this study was to prospectively evaluate the performance of Integra's OsteoStrux Collagen Ceramic Scaffold combined with bone marrow aspirate as an adjunct for instrumented posterolateral spine fusion, as compared to local autograft. The study was conducted in 29 patients aged 18 or older.

Number of Posterolateral Gutter That Have Evidence of Arthrodesis were measured up to 24 months and found to have increased linearly in the patients who received the OsteoStrux graft as compared to the local graft. When the EQ-5D Health State Visual Analog Scale (VAS) was measured, it increased after 6 months but slowly started to decrease later on. Oswestry Disability Index (ODI) also decreased significantly during the course.

➤ *Collagen Trials On Patients With Bone Degeneration*

Comparison of a PEG Membrane and a Collagen Membrane for the Treatment of Bone Dehiscence Defects at Bone Level Implants

Trial ID: NCT01012921

The study was performed to test the performance of Straumann® MembraGel (PEG Membrane) to act as a barrier for guided bone regeneration compared to that of a standard collagen membrane (BioGide®) in the bone regeneration. The study was conducted in 117 patients aged 18 – 80 and changes were measured in the yearly follow-up visit post-surgery.

The mean bone fill was assessed at 6 months after regenerative therapy and was found to be higher in the group with BioGide Membrane as compared to the MembraGel membrane

A Clinical Trial to Evaluate the Safety, Tolerability and Preliminary Effectiveness of Single Administration Intradiscal rhGDF-5 for the Treatment of Early Stage Lumbar Disc Degeneration

Trial ID: NCT01158924

The study was conducted in 40 participants aged 18 or older to show the safety, tolerability and preliminary effectiveness of Intradiscal rhGDF-5 in subjects with early lumbar disc degeneration. Patients were divided into 2 groups – where one group received 1.0mg of dosage(A) while the other group received 2.0mg of dosage(B).

Neurological Assessment for Motor Function and Reflexes/Sensory was done after 12 months where group A did not show any movement but group B showed Active movement when gravity was removed. Change in physical component summary of quality of life measure was assessed by short-form 36 at 12 Months from Baseline and found to be better in group A. Change in Pain was assessed by Visual Analog Scale (VAS) at 12 Months from Baseline and found to be higher in Group B.

➤ *Collagen Trials On Patients With Articular Cartilage Defects*

Superiority of MACI® Versus Microfracture Treatment in Patients with Symptomatic Articular Cartilage Defects in the Knee (SUMMIT)

Trial ID: NCT00719576

The objective of this trial was to demonstrate superior efficacy and safety of MACI compared with arthroscopic microfracture in the treatment of 144 patients (aged 18 to 55 years) with symptomatic articular cartilage defects of the knee. Patients were divided into 2 arms; where one received MACI and the other received Microfracture. Study results showed that Change from Baseline to Week 104 for the Participant's Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain and Function (Sports and Recreational Activities) Scores were higher for the MACI arm as compared to the Microfracture arm. Assessment of Defect Fill by MRI showed a higher percentage in the MACI arm as compared to the Microfracture arm. Also, a higher percentage of Microfracture patients had Treatment-Emergent Adverse Events than the MACI patients.

RCT of ChondroCelect® (in an ACI Procedure) vs Microfracture in the Repair of Cartilage Defects of the Knee (TIGACT01)

Trial ID: NCT00414700

This was a phase III, multicentre, open-label, randomized controlled trial of ChondroCelect® in an Autologous Chondrocyte Implantation (ACI) procedure compared to the procedure of microfracture (MF) in the repair of symptomatic cartilage lesions of the knee, done in 118 participants aged 18 – 50 years. Patients were divided into 2 arms; where one received ChondroCelect® and the other received Microfracture.

Study results showed a higher Least Squares Mean Ratio for ChondroCelect when measured for Histomorphometry Safranin-O + Anti-Collagen II Antibody Staining and, the Overall Histology Assessment on First Subscale of ICRS II Score was higher for ChondroCelect as well. Change from Baseline in Overall Knee Injury and Osteoarthritis Outcome Score (KOOS) at 12-18 Months (Average) was almost equal for both arms during the course duration.

➤ *Collagen Trials on Patients with Osteoporosis*

A Dose Selection Study of Oral Recombinant Salmon Calcitonin (rsCT) in Normal, Healthy, Postmenopausal Women

Trial ID: NCT00620854

This study compared the performance of different doses (0.15mg and 0.2mg) of oral recombinant salmon calcitonin (rsCT) with Fortical® nasal spray, as measured by a decrease in plasma C-terminal telopeptide of type I collagen (CTX-1). The Study involved 24 participants aged 45 – 70 years who were divided into 3 groups: rsCT-A (0.15mg), rsCT-B (0.2mg) and those with Fortical nasal spray.

Study results showed higher mean per cent Change in Baseline CTx-1 in rsCT-A, followed by rsCT-B and Fortical nasal spray.

Rosehip and Vitamin C for Musculoskeletal System Therapeutic Applications of Rose Hips from Different Rosa Species

This article discusses the therapeutic potential of these plants based on its antioxidant effects caused by or associated with its phytochemical composition, which includes **ascorbic acid**, phenolic compounds and healthy fatty acids among others. The medicinal interest in rose hips has increased as a consequence of recent research that has studied its potential application as a treatment for several diseases including skin disorders, hepatotoxicity, renal disturbances, diarrhoea, inflammatory disorders, arthritis, diabetes, hyperlipidaemia, obesity and cancer.

Rosehip, and in particular dog rose (*Rosa canina* L., Rosaceae) have traditionally been used for the prevention and therapy of rheumatoid arthritis. In particular, rosehip powder has been shown to reduce symptoms associated with rheumatoid inflammation in clinical trials. The inflammatory process triggered by rheumatoid arthritis has been also associated with an increased generation of reactive oxygen and nitrogen species (ROS/RNS), which contribute to tissue damage. In consequence, antioxidant nutrients such as vitamin C, vitamin E, carotenoids, polyphenols and antioxidant enzymes could play a significant role in the protection against the damaging effects of ROS/RNS produced in rheumatoid arthritis.

A standardized powder made from rosehips (*Rosa canina* L.) improves function and reduces pain and the consumption of rescue medication in osteoarthritis

The effect of a standardized powder made from rosehips on joint pain and stiffness in patients with osteoarthritis has been investigated in several clinical studies. Data derived from several different studies indicates that rosehip powder reduces pain and stiffness and improves ADL function in patients with osteoarthritis of various joints both in early and late stage osteoarthritis. The effect on pain seems to be of a sufficient magnitude to facilitate a reduction in the consumption of certain rescue medications normally used in osteoarthritis.

Vitamin C deficiency causes muscle atrophy and a deterioration in physical performance

The effect of Vitamin C aka L-Ascorbic acid (AsA) deficiency on skeletal muscle was examined using senescence marker protein-30 (SMP30)-knockout (KO) mice that are defective in AsA biosynthesis. SMP30-KO mouse models are similar to humans. Eight-week-old female SMP30-KO mice were divided into the two groups: an AsA-sufficient group [AsA (+)] that was administered 1.5g/L AsA and an AsA-deficient group [AsA (-)] that was administered tap (AsA-free) water. AsA is known to scavenge Reactive Oxygen Species (hydroxyl radicals, singlet oxygen, and superoxide radicals). The ROS level detected in the skeletal muscles of AsA (-) group was significantly higher than that AsA (+) group at the end of 8th week. The weight of major hind limb skeletal muscles of the AsA (-) group was significantly decreased by compared with the values in the AsA (+) group by the end of 12th week. Based on these results, AsA deficiency might induce skeletal muscle atrophy the expression levels of muscle atrophy-related genes were at 8, 12, and 16 weeks to examine the mechanism of skeletal muscle weight loss and fibre atrophy caused by AsA deficiency. These genes were found to be up-regulated in AsA (-) groups. As described above, muscle weight loss, muscle fibre atrophy, and decreased physical performance were observed in mice with AsA deficiency. AsA was administered to mice in the AsA (-) group beginning at 12 weeks, when all tested defects and muscle atrophy were observed, until 24 weeks to confirm that AsA deficiency caused these effects on skeletal muscle. Interestingly, the decrease in the AsA content elevated ROS level, and skeletal muscle weight loss caused by AsA deficiency for 12 weeks were restored by AsA supplementation for 12 weeks.

Rose hip herbal remedy in patients with rheumatoid arthritis - a randomised controlled trial

This study was conducted to investigate the effect of standardised powder made from rose-hip (*Rosa canina*) on the symptoms of patients suffering from rheumatoid arthritis. The results indicated that patients with RA may benefit from additional treatment with rose hip powder

Rosa canina – Rosehip pharmacological ingredients and molecular mechanics counteracting osteoarthritis

In this review article, relevant publications on pharmacological or mechanistic studies with relevance to osteoarthritis (e.g. studies examining anti-inflammatory activity) were studied. Furthermore, clinical osteoarthritis studies and reviews on *Rosa canina* and publications on *Rosa canina* pharmacologically active constituents were also considered relevant. A meta-analysis of some clinical studies demonstrated that it was twice as likely for an osteoarthritis patient receiving rose hip - compared to a placebo-patient - to respond to the therapy. This article also discusses the mechanism of action of Rosehip extract towards an inhibition of Osteoarthritis and one of them is the neutralization of RONS by antioxidative compounds.

The Effects of a Standardized Herbal Remedy Made from a Subtype of *Rosa canina* in Patients with Osteoarthritis: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial

This study was conducted to assess the impact of standardized rose-hip powder on the mobility of the hip and knee joints, activities of daily living, quality of life, and pain in patients with osteoarthritis.

In a 4-month double-blind placebo-controlled randomized study with 100 osteoarthritis patients, 5 g rosehip powder/day lead to a significant decrease in joint pain and a significant improvement of joint mobility – both compared to placebo. 64.6% of patients in the rosehip group reported at least some reduction of pain, compared to 43.8% of the placebo-treated patients. In this study population, it was concluded that standardized rose-hip powder reduced symptoms of osteoarthritis, as 64.6% of patients reported at least some reduction of pain while receiving treatment. The standardized rose-hip powder may improve hip flexion and reduce pain in patients with osteoarthritis.

A herbal remedy, Hymen Vital (stand. powder of a subspecies of *Rosa canina* fruits), reduces pain and improves general well being in patients with osteoarthritis—a double-blind, placebo-controlled, randomised trial.”

The double-blind, placebo-controlled, crossover study reported here examined the effect of Hymen Vital, a herbal remedy made from a subtype of *Rosa canina* on the symptoms of osteoarthritis. One hundred and twelve patients with osteoarthritis were randomly allocated to treatment with either Hyben Vital 5 g daily or an identical placebo for 3 months, followed immediately by the alternative treatment. The patients assessed changes in joint pain and stiffness after each treatment period on a 5-point categorical scale. General wellbeing, including mood, sleep quality and energy were also assessed and recorded in a personal diary. A 3-month response rate regarding the reduction of joint pain for 66% of the patients treated with 5 g rosehip powder/day compared to 36% of placebo-treated patients; the difference was statistically significant.

III. CLINICAL TRIALS ON ROSEHIP AND VITAMINS

Rose hips are pseudo-fruits from the plants of the *Rosa* genus in the Rosaceae family. *Rosa* genus contains around 100 species which are widely spread across Europe, the Middle East, Asia and North America. In Europe, the most abundant and most studied is the *Rosa canina* species which is a native shrub. The pseudo-fruits from *Rosa* species have been used both for alimentation and for medicinal purposes thanks to their high-level content of bioactive compounds. Reactive oxygen species (ROS) are generated as part of normal metabolism in mammalian cells. The majority of cellular ROS appear to be generated by mitochondria, but in phagocytic cells, NADPH oxidase systems additionally generate substantial amounts of ROS during activation. Skeletal muscle generates significant

amounts of oxidants during aerobic contractile activity. Rose hips are known to have a high level of antioxidant and antimicrobial action. Their antioxidant activity is due to their content in polyphenols, vitamins C, E, B and carotenoids and these compounds may have synergistic effects. Rose hips also have an anti-inflammatory action, as well as anti-diabetic and anticancer effects. Vitamin C (Ascorbic acid) is a water-soluble antioxidant that scavenges reactive oxygen species (ROS), such as hydroxyl radicals, singlet oxygen, and superoxide radicals. Many vertebrates have the ability to synthesize AsA. However, primates, including humans, and guinea pigs are unable to synthesize AsA since these organisms carry multiple mutations in the Gulo gene encoding L-gulonolactone oxidase, the last enzyme in the AsA biosynthesis pathway. Therefore, these animals contract scurvy unless they ingest AsA from food.

Improving Gait in Persons with Knee Related Mobility Limitations by Rosehips Food Supplement: A Randomized Double-blind Placebo-controlled Trial Trial ID: NCT01927848

In this study, the efficacy of specialized **rosehip** powder nutritional additives (Rosehips) on knee joint function during walking in subjects with knee-related walking limitations was evaluated. **100 participants**, 40 years and older with no usage of **Rosehip** nutritional supplements within the last 3 months and with self-reported knee-related walking limitations were **randomized (1:1)** to receive three capsules/day of either rosehip powder or identically appearing placebo capsules for **12 weeks**.

The resultant knee moment and in the peaks in the sagittal plane moments and kinematics during the stance phase of walking with the rosehip group exhibiting greater joint moments and more knee joint flexion during walking than the placebo group. **A daily intake of rosehip powder for 12 weeks improved important indices of knee joint function and dynamics during walking compared to placebo in persons with knee-related walking limitations.**

Rosehip Powder for Knee Osteoarthritis Trial ID: NCT01430481

A total of **150 patients, 40 years of age** with no usage of rosehip powder as a dietary supplement and with symptomatic knee osteoarthritis were randomly assigned to **three** combinations of preparations in a comparative trial program for 12-weeks on rosehip powder for knee Osteoarthritis.

- **Combination A:** 6 capsules of standardized hip powder of *Rosa canina* made from the seeds and husks of the fruits from a subtype of *R. canina* hip powder.
- **Combination B:** 6 capsules of modified hip powder of *Rosa canina* made from the seeds and husks of the fruits from a subtype of *R. canina* hip powder.
- **Combination C:** 3 capsules of modified hip powder of *Rosa canina* made from the seeds and husks of the fruits from a subtype of *R. canina* hip powder.

During the trial period the change in the primary outcome was comparable across groups. Combination C rosehip powder is at least as good, even taken as three capsules/day, as the original rosehip product for patients with symptomatic OA.

Does Vitamin C Reduce Finger Stiffness After Distal Radius Fractures?

Trial ID: NCT02216812

This study was done to evaluate the effect of vitamin C administration on the reduction of disproportionate pain and stiffness after distal radius fracture. 134 participants (age 18 or greater) were randomized to receive once-daily 500 mg vitamin C (67 participants) or placebo (67 participants) within 2 weeks after distal radius fracture.

Vitamin C does not seem to facilitate recovery after distal radius fracture, but amelioration of maladaptation to nociception (pain interference) merits greater attention.

Study of Vitamin C, Vitamin E and Their Combination to Treat Restless Legs Syndrome in Haemodialysis Patient

Trial ID: NCT01125033

This study was conducted to evaluate the efficacy of vitamins C and E and their combination in reducing the severity of RLS symptoms in haemodialysis patients in this randomized, double-blind, placebo-controlled, four-arm parallel trial. Sixty stable haemodialysis patients (18 Years to 75 Years) who had all four diagnostic criteria for RLS developed by the International Restless Legs Syndrome Group with no acute illness or history of renal stone were randomly allocated to four fifteen-patient parallel groups to receive vitamin C (200 mg) and vitamin E (400 mg), vitamin C (200 mg) and placebo, vitamin E (400 mg) and placebo, and double placebo daily for eight weeks. **Vitamins C and E and their combination are safe and effective treatments for reducing the severity of RLS in haemodialysis patients over the short-term.**

*Rose hips are a natural source of antioxidants with a potential use in disease prevention and treatment. Rosehip showed higher antioxidative properties than other well-known antioxidant fruits as rowanberry (*S. aucuparia*), hawthorn (*C. monogyna*), chokeberry (*A. melanocarpa*), blackcurrant (*R. nigrum*), and blueberry (*V. myrtillus*).*

The antioxidant and anti-inflammatory effects of Rosehip match its clinical action – especially considering new findings on the pharmacological disease pattern of OA. Considering the high content of bioactive molecules contained in Rosa genus, rosehip has an interesting potential for the treatment of different disorders related to oxidative stress or pro-inflammatory status. Further research is needed to elucidate how and in which manner single rosehip compounds interact with their molecular pharmacological targets.

IV. CONCLUSION

Chemical and in vitro cell studies have shown preventive properties of these compounds, being a potent antioxidant, against a variety of ROS and RNS. Also, the epidemiologic and immunopathological studies suggest that consumption of these compounds may lower multiple disease risk. Such potential benefits have been ascribed in part to high concentrations of compounds in nutraceutical treatments. However, these findings have yet only been supported by a small number of intervention trials. By defining the right population and combining antioxidant and immunopathological potentials of these compounds with vitamins and other bioactive plant compounds, the beneficial role of them in other diseases that could be better clarified in future studies.

REFERENCES

- [1]. Lee, J., Kim, J. & Kim, W. J. Photothermally Controllable Cytosolic Drug Delivery Based On Core-Shell MoS₂-Porous Silica Nanoplates. *Chem. Mater* **28**, 30 (2016).
- [2]. Chen, J. L. *et al.* Antiangiogenesis-Combined Photothermal Therapy in the Second Near-Infrared Window at Laser Powers Below the Skin Tolerance Threshold. *Nano-Micro Lett.* **11**, (2019).
- [3]. Yang, G. *et al.* Two-dimensional magnetic WS₂@Fe₃O₄ nanocomposite with mesoporous silica coating for drug delivery and imaging-guided therapy of cancer. *Elsevier*.
- [4]. Oh, J., Yoon, H. & Park, J.-H. Nanoparticle Platforms for Combined Photothermal and Photodynamic Therapy. *Biomed Eng Lett* **3**, 67–73 (2013).
- [5]. Chen, W. R. *et al.* Effect of Different Components of Laser Immunotherapy in Treatment of Metastatic Tumors in Rats I. *CANCER RESEARCH* vol. 62 <https://cancerres.aacrjournals.org/content/62/15/4295>. short (2002).
- [6]. Chenatbv, W. R., Adams, R. L., Carubell, R. & Nordqu&, R. E. Laser-photosensitizer assisted immunotherapy: a novel modality for cancer treatment. *Cancer Letters* vol. 115 <https://www.sciencedirect.com/science/article/pii/S0304383597047071> (1997).
- [7]. Fang, R. H., Kroll, A. V., Gao, W. & Zhang, L. Cell Membrane Coating Nanotechnology. *Advanced Materials* vol. 30 (2018).
- [8]. Chen, Q. *et al.* Photothermal therapy with immune-adjuvant nanoparticles together with checkpoint blockade for effective cancer immunotherapy. *Nat. Commun.* **7**, 13193 (2016).
- [9]. Guo, L. *et al.* A Comparative Study of Hollow Copper Sulfide Nanoparticles and Hollow Gold Nanospheres on Degradability and Toxicity. *ACS Publ.* **7**, 8780–8793 (2013).
- [10]. Guo, L. *et al.* Combinatorial Photothermal and Immuno Cancer Therapy Using Chitosan-Coated Hollow Copper Sulfide Nanoparticles. *ACS Publ.* **8**, 5670–5681 (2014).
- [11]. Martel-Pelletier, J. *et al.* Levels of serum biomarkers from a two-year multicentre trial are associated with treatment response on knee osteoarthritis cartilage loss as assessed by magnetic resonance imaging: An exploratory study. *Arthritis Res. Ther.* **19**, (2017).
- [12]. Pelletier, J. P. *et al.* Chondroitin sulfate efficacy versus celecoxib on knee osteoarthritis structural changes using magnetic resonance imaging: A 2-year multicentre exploratory study. *Arthritis Res. Ther.* **18**, (2016).
- [13]. Roman-Blas, J. A. *et al.* Combined Treatment With Chondroitin Sulfate and Glucosamine Sulfate Shows No Superiority Over Placebo for Reduction of Joint Pain and Functional Impairment in Patients With Knee Osteoarthritis: A Six-Month Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Arthritis Rheumatol.* **69**, 77–85 (2017).
- [14]. Hochberg, M., Martel-Pelletier, J., ... J. M.-A. of the & 2016, undefined. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. *ard.bmj.com*.
- [15]. Hochberg, M., Martel-Pelletier, J., ... J. M.-A. of the & 2014, undefined. Intervention Study with Sysadua (MOVES): Effects of Combined Glucosamine Hydrochloride and Chondroitin Sulfate VS Celecoxib for Painful Knee Osteoarthritis. *ard.bmj.com*.
- [16]. journal, B. M.-B. medical & 1952, undefined. Collagen/chondroitin sulphate ratio of human articular cartilage related to function. *ncbi.nlm.nih.gov*.
- [17]. Chondroitin sulfate reduces both cartilage volume... - Google Scholar. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Chondroitin+sulfate+reduces+both+cartilage+volume+loss+and+bone+marrow+lesions+in+knee+osteoarthritis+patients+starting+as+early+as+six+months+after+initiation+of+therapy%3A+a+randomized%2C+double-blind%2C+placebo-controlled+pilot+study+using+MRI&btnG=.
- [18]. Wandel, S. *et al.* Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *bmj.com*.
- [19]. medicine, R. L.-C. therapies in & 2009, undefined. Chondroitin sulphate: a complex molecule with potential impacts on a wide range of biological systems. *Elsevier*.
- [20]. Pelletier, J. P. Chondroitin for osteoarthritis of the knee or hip [2]. *Annals of Internal Medicine* vol. 147 883–884 (2007).
- [21]. Zhu, X., Sang, L., Wu, D., Rong, J. & Jiang, L. Effectiveness and safety of glucosamine and chondroitin for the treatment of osteoarthritis: A meta-analysis of randomized controlled trials. *Journal of Orthopaedic Surgery and Research* vol. 13 (2018).
- [22]. Franz, B. & Karl, L. A metaanalysis of chondroitin sulfate in the treatment of osteoarthritis. *Article in The Journal of Rheumatology* <https://www.researchgate.net/publication/12666617> (2000).
- [23]. Gregori, D. *et al.* Association of Pharmacological Treatments With Long-term Pain Control in Patients With Knee Osteoarthritis A Systematic Review and Meta-analysis Supplemental content CME Quiz at

- jamanetwork.com/learning and CME Questions page 2595. *JAMA* **320**, 2564–2579 (2018).
- [24]. rheumatology, J. J.-I. journal of & 2011, undefined. Effects of glucosamine and chondroitin sulfate on cartilage metabolism in OA: outlook on other nutrient partners especially omega-3 fatty acids. *hindawi.com*.
- [25]. Hansen, M. *et al.* Effects of estrogen replacement and lower androgen status on skeletal muscle collagen and myofibrillar protein synthesis in postmenopausal women. *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* **67 A**, (2012).
- [26]. Hansen, M. *et al.* Effect of administration of oral contraceptives in vivo on collagen synthesis in tendon and muscle connective tissue in young women. *J. Appl. Physiol.* **106**, (2009).
- [27]. Doessing, S. *et al.* Growth hormone stimulates the collagen synthesis in human tendon and skeletal muscle without affecting myofibrillar protein synthesis. *J. Physiol.* **588**, (2010).
- [28]. DePhillipo, N. N. *et al.* Efficacy of Vitamin C Supplementation on Collagen Synthesis and Oxidative Stress After Musculoskeletal Injuries: A Systematic Review. *Orthopaedic Journal of Sports Medicine* vol. 6 (2018).
- [29]. Alexopoulos, L. G., Youn, I., Bonaldo, P. & Guilak, F. Developmental and osteoarthritic changes in Col6a1-knockout mice: Biomechanics of type VI collagen in the cartilage pericellular matrix. *Arthritis Rheum.* **60**, (2009).
- [30]. Heikkinen, A., Tu, H. & Pihlajaniemi, T. Collagen XIII: A type II transmembrane protein with relevance to musculoskeletal tissues, microvessels and inflammation. *International Journal of Biochemistry and Cell Biology* vol. 44 (2012).
- [31]. Van De Lest, C. H. A., Brama, P. A. J., Van El, B., Degroot, J. & Van Weeren, P. R. Extracellular matrix changes in early osteochondrotic defects in foals: A key role for collagen? *Biochim. Biophys. Acta - Mol. Basis Dis.* **1690**, (2004).
- [32]. Relini, A. *et al.* Collagen plays an active role in the aggregation of β 2- microglobulin under physiopathological conditions of dialysis-related amyloidosis. *J. Biol. Chem.* **281**, (2006).
- [33]. Gistelink, C. *et al.* Loss of Type I Collagen Telopeptide Lysyl Hydroxylation Causes Musculoskeletal Abnormalities in a Zebrafish Model of Bruck Syndrome. *J. Bone Miner. Res.* **31**, (2016).
- [34]. Franchi, M., Trirè, A., Quaranta, M., Orsini, E. & Ottani, V. Collagen structure of tendon relates to function. *TheScientificWorldJournal* vol. 7 (2007).
- [35]. Kwatra, B. A REVIEW ON POTENTIAL PROPERTIES AND THERAPEUTIC APPLICATIONS OF GRAPE SEED EXTRACT. *World J. Pharm. Res.* **9**, 2519–2540 (2020).
- [36]. Kwatra, B. A REVIEW ON POTENTIAL PROPERTIES AND THERAPEUTIC APPLICATIONS OF BRANCHED CHAIN AMINO. *WORLD J. Pharm. Pharm. Sci.* **9**, 561–588 (2020).
- [37]. Kwatra, B. & Arora, C. The Studying Of Movements Resonant the Pendulum Elastic. *Indian J. Appl. Res.* **10**, 1–2 (2020).
- [38]. Kwatra, B. COLLAGEN SUPPLEMENTATION : THERAPY FOR SKIN DISORDERS : A REVIEW. *World J. Pharm. Res.* **9**, 2504–2518 (2020).
- [39]. Kwatra, B. A REVIEW ON POTENTIAL PROPERTIES AND THERAPEUTIC APPLICATIONS OF LYCOPENE. *Int. J. Med. Biomed. Stud.* **4**, 33–44 (2020).
- [40]. Kwatra, B. & Mudgil, M. LIGHT ASSISTED TIO₂-BASED NANOCOMPOSITE SYSTEMS: A NOVEL TREATMENT FOR CANCER. *Int. J. Med. Biomed. Stud.* **4**, 28–32 (2020).
- [41]. Kwatra, B. A Review on Potential Properties and Therapeutic Applications of Vitamin D. *Int. J. Sci. Res.* **9**, 682–691 (2020).
- [42]. Kwatra, B. HYDROQUINONE: A novel growth inhibitor and apoptosis inducer in U-251 MG CELLS. *Int. J. Med. Biomed. Stud.* **3**, 15–16 (2019).
- [43]. Kwatra, B. HACKING THE BLOOD-BRAIN BARRIER. *Eur. J. Biol. Med. Sci. Res.* **5**, 10–13 (2017).
- [44]. Kwatra, B. EXPRESSION AND CHARACTERIZATION IN PICHIA PASTORIS BY CLONING OF DELTA 4 DESATURASE FROM ISOCHRYSIS GALBANA. *Indian J. Appl. Res.* **9**, 1–2 (2019).
- [45]. Kwatra, B. CALCIUM AND IRON ABSORPTION: INVITRO STUDIES. *Int. J. Med. Biomed. Stud.* **3**, 59–61 (2019).
- [46]. Kwatra, B. Allicin-An After Digestion Antimicrobial Agent. *ACTA Sci. Microbiol.* **2**, 48–51 (2019).
- [47]. Kwatra, B. LOCATOR THEORY FOR ELEMENTS IN PERIODIC TABLE 'LEPT'. *Glob. J. Pure Appl. Chem. Res.* **5**, 9–10 (2017).
- [48]. Kwatra, B. & A, A. UTERINE CANCER: SEX DOMINANT CHARACTER. *Int. J. Adv. Res.* **08**, 663–667 (2020).
- [49]. Kwatra, B. Studies on People Employed in High Risk Workplace: Between Genetic Polymorphism for Tumor Necrosis Factor (TNF- A) and Blood Pressure. *Int. J. Innov. Res. Technol.* **6**, 268–270 (2020).
- [50]. Kwatra, B. & Arora, C. Investigation of Conductance Quantization with Magnetic Field Control and Application of Biosensor. *Int. J. Innov. Res. Technol.* **6**, 271–272 (2020).
- [51]. Kwatra, B. Candidate genes of OCD interacts with human retrovirus to form new link in inflammatory hypothesis. *Int. J. Sci. Appl. Res.* **7**, 1–2 (2020).
- [52]. Kwatra, B. COLLAGEN SUPPLEMENTATION : THERAPY FOR THE PREVENTION AND TREATMENT OF OSTEOPOROSIS AND OSTEOARTHRITIS: A REVIEW. *WORLD J. Pharm. Pharm. Sci.* **9**, 589–604 (2020).
- [53]. Kwatra, B. & Arora, C. THE UNEXPLAINED SIMILARITY BETWEEN THE ATOMIC AND GRAVITATIONAL MODELS. *Int. J. Adv. Res.* **8**, 1099–1107 (2020).
- [54]. Kwatra, B. A Review on Potential Properties and Therapeutic Applications of DHA and EPA. *ijppr.humanjournals* **16**, 140–176 (2019).

- [55]. Kwatra, B. Tinospora Crispa As A Future Cure For Obesity/Cholesterol. *Int. J. Sci. Technol. Res.* **6**, 340–341 (2017).
- [56]. Bharat Kwatra. Procuring Natural Dye for Solar Cell Using Leaf Waste. *Int. J. Sci. Eng. Res.* **7**, 46–47 (2019).
- [57]. Kwatra, B. THE SIMVASTATIN AND DMXAA ON THE CO-CULTURE OF B16.F10 MELANOMA CELLS AND MACROPHAGES SHOWS ANTITUMOR ACTIVITY. *World J. Pharm. Res.* **8**, 1318–1319 (2019).
- [58]. Kwatra, B. Bioactive-Compounds: alternative to control Candida spp. *Int. J. Sci. Res. Rev.* **8**, 221–223 (2019).
- [59]. Kwatra, B. Effects of Mineral Separation by Time and Enteric Coating Mechanism for Calcium and Iron Absorption in Mammalia. *Int. J. Sci. Res.* **8**, 1265–1270 (2019).
- [60]. Kwatra, B. Maprovit 3, 6, 9: Perfect Companion of your Immune System to Fight Corona Virus Hit. *Int. J. Sci. Res.* **9**, 241–241 (2020).
- [61]. Kwatra, B. & Mudgil, M. Untangling the Mathematical Relation Between Natural Selection and Adaptive Radiation Using Macromolecules and Microevolutionary Forces. *Int. J. Sci. Res. Sci. Technol. IJSRST / 7*, 313–339 (2020).
- [62]. Chaitanya Arora¹, B. K. Mathematical and Statistical Approach to Define Past Present Future Events. *Int. J. Sci. Res.* **8**, 261–263 (2019).
- [63]. Kwatra, B. MECHANISMS OF PATTERN FORMATION OF FBP17 IN MAST CELLS. *Int. J. Adv. Res.* **7**, 413–414 (2019).
- [64]. Mudgil¹, M. & Kwatra², B. Mosquito Menace Aim: Observing the life cycle of Aedes aegypti mosquito and understanding its behavior towards different natural oils for encouraging natural methods of repellence. *Int. J. Sci. Res.* **8**, 1314–1315 (2019).
- [65]. Kwatra, B. A REVIEW ON POTENTIAL PROPERTIES AND THERAPEUTIC APPLICATIONS OF BROMELAIN. *www.wjpps.com* **8**, 488–500 (2019).
- [66]. Kwatra, B. Holothuroidea (Sea Cucumber): Key to Anti-Aging. *Int. J. Sci. Res.* **8**, 884–884 (2019).
- [67]. Kwatra, B. & Mudgil, M. PROTONATED CRAB SHELL WASTE AS FUNGAL INHIBITOR. *Int. J. Med. Biomed. Stud.* **3**, 111–116 (2019).
- [68]. Willich, S. N. *et al.* Rose hip herbal remedy in patients with rheumatoid arthritis - a randomised controlled trial. *Phytomedicine* **17**, (2010).
- [69]. Winther, K. A standardized powder made from rosehips (*Rosa canina* L.) improves function and reduces pain and the consumption of rescue medication in osteoarthritis. *Osteoarthr. Cartil.* **16**, (2008).
- [70]. Warholm, O., Skaar, S., Hedman, E., Mølmen, H. M. & Eik, L. The effects of a standardized herbal remedy made from a subtype of *Rosa canina* in patients with osteoarthritis: A double-blind, randomized, placebo-controlled clinical trial. *Curr. Ther. Res. - Clin. Exp.* **64**, (2003).
- [71]. Rein, E., Kharazmi, A. & Winther, K. 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, randomised trial. *Phytomedicine* **11**, (2004).
- [72]. Gruenwald, J., Uebelhack, R. & Moré, M. I. *Rosa canina* – Rose hip pharmacological ingredients and molecular mechanics counteracting osteoarthritis – A systematic review. *Phytomedicine* **60**, (2019).
- [73]. Takisawa, S. *et al.* Vitamin C deficiency causes muscle atrophy and a deterioration in physical performance. *Sci. Rep.* **9**, (2019).
- [74]. Mármol, I., Sánchez-De-Diego, C., Jiménez-Moreno, N., Ancín-Azpilicueta, C. & Rodríguez-Yoldi, M. Therapeutic applications of rose hips from different *Rosa* species. *International Journal of Molecular Sciences* vol. 18 (2017).