

## BÖLÜM 5

# KAS VE İSKELET SİSTEMİ HASTALIKLARININ PROFİLAKSİ ve TEDAVİSİNDE YARARLI OLABİLECEK DOĞAL ÜRÜN SEÇENEKLERİ



Erdem YEŞİLADA

### GİRİŞ

Kas ve İskelet Sistemi hastalıkları (KİSH), genel anlamı ile insan vücudunda hareket veya kas iskelet sistemini (kaslar, tendonlar, ligamentler, sinirler, diskler, kan damarları vd.) olumsuz olarak etkileyen yaralanma, ağrı ve hastalıklar olarak tanımlanır. Tüm dünyada en yaygın görülen hastalıklardan biri olarak sadece bireylerin yaşam kalitesini olumsuz etkilemekle kalmayıp, işgücü kaybı ve tedavi harcamaları ile ülkelerin ekonomisine de büyük yük getirmesi bakımından en önemli sağlık sorunları arasında gösterilmektedir.

Hemen tüm hastalıkların etiyojisinde olduğu gibi KİSH oluşumunda da hasar oluşturan etkene karşı vücudun iltihaplanma cevabı başlıca neden olarak kabul edilmektedir. KİSH oluşumunda otoimmün cevap (romatoid), enfeksiyon, bazı ilaçlar, metabolik tepki (gut) gibi etkenlerin yanı sıra ilerleyen yaş, genetik yatkınlık, obezite, ağır sporlar ya da aşırı zorlayıcı hareketler (biyomekanik yük; mesleki, ayakta dikili durmak, yük taşıma vb.) en sık nedenler arasında yer almaktadır. KİSH semptomları kişisel farklılıklar göstermekle beraber genel olarak ağrı, şişme, iltihaplanma ve hareket güçlüğü başlıca ortak şikâyetler olarak tanımlanabilir. Dolayısıyla uygulanan tedavilerde öncelikle hastanın şikâyetlerini gidererek yaşam kalitesinin artırılması, hasarın ilerlemesinin önlenmesi amaçlanmaktadır. Bu amaçla kilo kontrolü, güçlendirme egzersizleri, fizik tedavi ve rehabilitasyon uygulamaları ve kaplıca tedavisi gibi yardımcı tedavilerin yanı sıra ağrı ve iltihaplanmanın giderilmesine yönelik uygulanan farmakoterapinin (kortikosteroidler, non steroid antiinflamatuar ajanlar “NSAEİ” ve analjezikler)

makalenin kalitesine bakılmaksızın ücret karşılığı makale yayımlandığı göz önüne alınmalıdır. Bir başka önemli husus ise doğal ürünler genel olarak etkinliklerini hafif ve orta derecede semptomlar üzerinde gösterebilmektedir. Bu bakımdan ilgili çalışmada uygulama yapılan hasta grubunun semptom şiddetinin değerlendirilmesi önemlidir.

Hiç şüphesiz, KİSH şikâyetleri üzerinde etkili olabilecek doğal ürün seçenekleri bu bölümde belirtilen örnekler ile sınırlı değildir. Avokado yağı (*Persea americana*), hodan tohumu yağı (*Borago officinalis*), Evening primrose yağı (*Oenothera biennis*) gibi yağların enflamatuvar yolda rol oynayan lipit ve protein mediyatörleri üzerindeki inhibitör etkisi ile KİSH üzerinde etkili olabildiği bildirilmektedir. Halk arasında artrit şikâyetleri üzerinde etkinliği ile bilinen ve sık olarak kullanılan ısırğan yaprağı (*Urtica dioica*) gibi çeşitli bitkisel ilaçlar bulunmaktadır. Ancak bu konularda bilimsel formatta ayrıntılı deneysel ve klinik araştırma bulgularına ihtiyaç duyulmaktadır.

Bir diğer önemli husus ise, özellikle eklemlerde meydana gelen hasarın onarımının bütün çabalara rağmen her zaman yeterli şekilde sağlanamaması nedeniyle yüksek risk gruplarında; obezler, 50 yaş üzeri bireyler, sporcular ve spora tutkulu sağlıklı yaşam uygulayıcılarının kürler halinde bu tip ürünleri profilaktik olarak kullanmaları önerilmelidir.

## KAYNAKLAR

1. McAlindon TE, Driban JB, Henrotin Y et al., OARSI Clinical Trials Recommendations: Design, conduct, and reporting of clinical trials for knee osteoarthritis. *Osteoarthritis Cartilage*. 2015;23(5):747-60.
2. Sengupta K, Alluri KV, Satish AR, et al. A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin. *Arthritis Res Ther* 2008;10:R85.
3. Sengupta K, Krishnaraju AV, Vishal AA et al., Comparative efficacy and tolerability of 5-Loxin and Aflapin against osteoarthritis of the knee: a double blind, randomized, placebo controlled clinical study. *Int J Med Sci* 2010;7:366-77.
4. Vishal AA, Mishra A, Raychaudhuri SP. A double-blind, randomized, placebo controlled clinical study evaluates the early efficacy of aflapin in subjects with osteoarthritis of knee. *Int J Med Sci* 2011;8:615-22.
5. Chopra A, Saluja M, Tillu G et al. Ayurvedic medicine offers a good alternative to glucosamine and celecoxib in the treatment of symptomatic knee osteoarthritis: a randomized, double-blind, controlled equivalence drug trial. *Rheumatology (Oxford)* 2013;52(8):1408-17.
6. Kizhakkedath R. Clinical evaluation of a formulation containing Curcuma longa and Boswellia serrata extracts in the management of knee osteoarthritis. *Mol Med Rep* 2013;8(5):1542-8.
7. Sontakke S, Thawani V, Pimpalkhute S et al., Open, randomized, controlled clinical trial of Boswellia serrata extract as compared to valdecoxib in osteoarthritis of knee. *Indian Journal of Pharmacology* 2007;39:27-9.
8. Bartels EM, Folmer VN, Bliddal H et al. Efficacy and safety of ginger in osteoarthritis patients: a meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Cartilage* 2015;23(1):13-21.

9. Leach MJ, Kumar S. The clinical effectiveness of ginger (*Zingiber officinale*) in adults with osteoarthritis. *Int J Evid Based Health* 2008;6:311-20.
10. Terry R, Posadzki P, Watson LK et al. The use of ginger (*Zingiber officinale*) for the treatment of pain: a systematic review of clinical trials. *Pain Med* 2011;12:1808-18.
11. Wigler I, Grotto I, Caspi D, et al. The effects of Zintona EC (a ginger extract) on symptomatic gonarthrosis. *Osteoarthritis Cartilage* 2003;11:783-9.
12. Haghghi M, Khalva A, Toliat T et al. Comparing the effects of ginger (*Zingiber officinale*) extract and ibuprofen on patients with osteoarthritis. *Arch Iran Med* 2005;8:267-71.
13. Paramdeep G. Efficacy and tolerability of ginger (*Zingiber officinale*) in patients of osteoarthritis of knee. *Indian J Physiol Pharmacol* 2013;57(2):177-83.
14. Drozdov VN, Kim VA, Tkachenko EV et al. Influence of a specific ginger combination on gastropathy conditions in patients with osteoarthritis of the knee or hip. *J Alt Compl Med* 2012;18:583-8.
15. Black CD, Herring MP, Hurley DJ, et al. Ginger (*Zingiber officinale*) reduces muscle pain caused by eccentric exercise. *J Pain* 2010;11:894-903.
16. Black CD, O'Connor PJ. Acute effects of dietary ginger on muscle pain induced by eccentric exercise. *Phytother Res* 2010;24:1620-6.
17. Belcaro G, Cesarone MR, Dugall M, et al. Efficacy and safety of Meriva, a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. *Alt Med Rev* 2010;15:337-4.
18. Matsumura MD, Zavorsky GS, Smoliga JM. The effects of pre-exercise ginger supplementation on muscle damage and delayed onset muscle soreness. *Phytother Res.* 2015;29(6):887-93.
19. Madhu K, Chanda K, Saji MJ. Safety and efficacy of *Curcuma longa* extract in the treatment of painful knee osteoarthritis: a randomized placebo-controlled trial. *Inflammopharmacology* 2013;21(2):129-36.
20. Nakagawa Y, Mukai S, Yamada S et al. Short-term effects of highly-bioavailable curcumin for treating knee osteoarthritis: a randomized, double-blind, placebo-controlled prospective study. *J Orthop Sci.* 2014;19(6):933-9.
21. Kuptniratsaikul V, Dajpratham P, Taechaarpornkul W et al. Efficacy and safety of *Curcuma domestica* extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. *Clin Interv Aging* 2014;9:451-8.
22. Pinsornsak P, Niempoog S. The efficacy of *Curcuma Longa L.* extract as an adjuvant therapy in primary knee osteoarthritis: a randomized control trial. *J Med Assoc Thai* 2012;95 Suppl 1:S51-8.
23. Haroyan A, Mukuchyan V, Mkrtchyan N et al. Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study. *BMC Complement Altern Med.* 2018;18(1):7.
24. Sterzi S, Giordani L, Morrone M, Lena E et al. The efficacy and safety of a combination of glucosamine hydrochloride, chondroitin sulfate, and bio-curcumin with exercise in the treatment of knee osteoarthritis: a randomized, double-blind, placebo-controlled study. *Eur J Phys Rehabil Med.* 2016;52(3):321-30.
25. Karlapudi V, Prasad Mungara AVV, Sengupta K et al. A placebo-controlled double-blind study demonstrates the clinical efficacy of a novel herbal formulation for relieving joint discomfort in human subjects with osteoarthritis of knee. *J Med Food.* 2018;21(5):511-520.
26. Belcaro G, Dugall M, Luzzi R et al. *Phytoproflex*: supplementary management of osteoarthritis: a supplement registry. *Minerva Med.* 2018;109(2):88-94.
27. Amalraj A, Varma K, Jacob J et al. A novel highly bioavailable curcumin formulation improves symptoms and diagnostic indicators in rheumatoid arthritis patients: A randomized, double-blind, placebo-controlled, two-dose, three-arm, and parallel-group study. *J Med Food.* 2017;20(10):1022-1030.

28. Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phytother Res* 2012;26:1719-25.
29. Walker AF, Bundy R, Hicks SM. Bromelain reduces mild acute knee pain and improves well-being in a dose-dependent fashion in an open study of otherwise healthy adults. *Phytomedicine* 2002;9:681-6.
30. Kasemsuk T, Saengpetch N, Sibmooh N et al. Improved WOMAC score following 16-week treatment with bromelain for knee osteoarthritis. *Clin Rheumatol.* 2016;35(10):2531-40.
31. Brien S, Lewith G, Walker AF et al. Bromelain as an adjunctive treatment for moderate-to-severe osteoarthritis of the knee: a randomized placebo-controlled pilot study. *QJM* 2006;99:841-50.
32. Klein G, Kullich W. Short-term treatment of painful osteoarthritis of the knee with oral enzymes. *Clin Drug Invest* 2000;19:15-23.
33. Bolten WW, Glade MJ, Raum S et al. The safety and efficacy of an enzyme combination in managing knee osteoarthritis pain in adults: a randomized, double-blind, placebo-controlled trial. *Arthritis.* 2015;251521.
34. Conrozier T, Mathieu P, Bonjean M et al. A complex of three natural anti-inflammatory agents provides relief of osteoarthritis pain. *Altern Ther Health Med.* 20 Suppl 2014;1:32-7.
35. Cohen A, Goldman J. Bromelains therapy in rheumatoid arthritis. *Pa Med J.* 1964;67:27-30.
36. Rein E, Kharazmi A, Thamsborg G et al. Herbal remedy made from a subspecies of rose-hip *Rosa canina* reduces symptoms of knee and hip osteoarthritis. *Osteoarthr Cartil* 2004;12(Suppl 2):80.
37. Warholm O, Skaar S, Hedman E et al. The effects of a standardized herbal remedy ade from a subtype of *Rosa canina* in patients with osteoarthritis: a double-blind, randomized, placebo-controlled clinical trial. *Curr Ther Res* 2003;64(1):21-31.
38. Winther K, Kharazmi A. A powder prepared from seeds and shells of subtype of rose-hip *Rosa canina* reduces pain in patients with osteoarthritis of the hand-a double blind, placebo-controlled study. *Osteoarthr Cartil* 2004;12(Suppl 2):145.
39. Winther K, Apel K, Thamsborg G. A powder made from seeds and shells of a rose-hip subspecies (*Rosa canina*) reduces symptoms of knee and hip osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial. *Scand J Rheumatol.* 2005;34(4):302-308.
40. Willich SN, Rosnagel K, Roll S et al. Rose hip herbal remedy in patients with rheumatoid arthritis - a randomised controlled trial. *Phytomedicine* 2010;17:87-93.
41. Chrubasik S, Zimpfer C, Schutt U et al. Effectiveness of *Harpagophytum procumbens* in treatment of acute low back pain. *Phytomedicine* 1996;3(1):1-10.
42. Chrubasik S, Schmidt A, Junck H et al. Effectiveness and economy of *Harpagophytum* extract in the treatment of acute low back pain - first results of a therapeutic cohort study. *Forsch Komplementarmed* 1997;4:332-336.
43. Chrubasik S, Junck H, Breitschwerdt H et al. Effectiveness of *Harpagophytum* extract WS 1531 in the treatment of exacerbation of low back pain: a randomized, placebo-controlled, double-blind study. *Eur.J Anaesthesiol.* 1999;16(2):118-129.
44. Chrubasik S, Thanner J, Kunzel O et al. Comparison of outcome measures during treatment with the proprietary *Harpagophytum* extract doloteffin in patients with pain in the lower back, knee or hip. *Phytomedicine* 2002;9:181-94.
45. Chrubasik S, Model A, Black A et al. A randomized double-blind pilot study comparing Doloteffin® and Vioxx® in the treatment of low back pain. *Rheumatology* 2003;42:141-148.
46. Gagnier JJ, Chrubasik S, Manheimer E. *Harpagophytum procumbens* for osteoarthritis and low back pain: a systematic review. *BMC Complement Altern Med* 2004;4:13.
47. Gobel H, Heinze A, Ingwersen M. Effects of *Harpagophytum procumbens* LI 174 (devil's claw) on sensory, motor und vascular muscle reagibility in the treatment of unspecific back pain. *Schmerz.* 2001;15(1):10-18.

48. Laudahn D, Walper A. Efficacy and tolerance of Harpagophytum extract LI 174 in patients with chronic non-radicular back pain. *Phytother.Res.* 2001;15(7):621-624.
49. Leblan D, Chantre P, Fournie B. Harpagophytum procumbens in the treatment of knee and hip osteoarthritis. Four-month results of a prospective, multicenter, double-blind trial versus diacerhein. *Joint Bone Spine* 2000;67(5):462-467.
50. Wegener T, Lupke NP. Treatment of patients with arthrosis of hip or knee with an aqueous extract of devil's claw (Harpagophytum procumbens DC). *Phytother Res* 2003;17:1165-72.
51. Chantre P, Cappelaere A, Leblan D et al. Efficacy and tolerance of Harpagophytum procumbens versus diacerhein in treatment of osteoarthritis. *Phytomedicine* 2000;7:177-83.
52. Menghini L, Recinella L, Leone S et al. Devil's claw (Harpagophytum procumbens) and chronic inflammatory diseases: A concise overview on preclinical and clinical data. *Phytother Res.* 2019; Jul 4. doi: 10.1002/ptr.6395.
53. Chrubasik S, Eisenberg E, Balan E, et al. Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. *Am J Med* 2000;109:9-14.
54. Nieman DC, Shanely RA, Luo B et al. A commercialized dietary supplement alleviates joint pain in community adults: a double-blind, placebo-controlled community trial. *Nutr J* 2013;12(1):154.
55. Schmid B, Ludtke R, Selbmann HK et al. Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: randomized placebo-controlled, double blind clinical trial. *Phytother Res* 2001;15:344-50.
56. Beer AM, Wegener T. Willow bark extract (Salicis cortex) for gonarthrosis and coxarthrosis--results of a cohort study with a control group. *Phytomedicine.* 2008;15(11):907-13.
57. Biegert C, Wagner I, Ludtke R et al. Efficacy and safety of willow bark extract in the treatment of osteoarthritis and rheumatoid arthritis: results of 2 randomized double-blind controlled trials. *J Rheumatol* 2004;31:2121-30.
58. Nandhakumar J. Efficacy, tolerability, and safety of a multicomponent antiinflammatory with glucosamine hydrochloride vs glucosamine sulfate vs an NSAID in the treatment of knee osteoarthritis--a randomized, prospective, double-blind, comparative study. *Integr Med Clin J* 2009;8(3):32-38.
59. Eriksen P, Bartels EM, Altman RD, et al. Risk of bias and brand explain the observed inconsistency in trials on glucosamine for symptomatic relief of osteoarthritis: a meta-analysis of placebo-controlled trials. *Arthritis Care Res (Hoboken)* 2014;66(12):1844-55.
60. Poolsup N, Suthisisang C, Channark P et al. Glucosamine long-term treatment and the progression of knee osteoarthritis: systematic review of randomized controlled trials. *Ann Pharmacother* 2005;39:1080-7.
61. Bruyere O, Pavelka K, Rovati LC et al. Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. *Osteoarthritis Cartilage* 2008;16:254-60.
62. Reginster JY, Deroisy R, Rovati LC et al. Long-term effects of glucosamine sulfate on osteoarthritis progression: a randomised, placebo-controlled trial. *Lancet* 2001;357:251-6.
63. Lee YH, Woo JH, Choi SJ et al. Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. *Rheumatol Int* 2010;30(3):357-363.
64. Wilkens P, Scheel IB, Grundnes O et al. Effect of glucosamine on pain-related disability in patients with chronic low back pain and degenerative lumbar osteoarthritis: a randomized controlled trial. *JAMA* 2010;304(1):45-52.
65. Rovati LC, Giacobelli G, Annefeld N et al. A large, randomized, placebo-controlled, double-blind study of glucosamine sulfate vs piroxicam and vs their association on the kinetics of the symptomatic effect in knee osteoarthritis. *Osteoarth Cartilage* 1994;2(suppl 1):56.
66. Cibere J, Kopec JA, Thorne A et al. Randomized, double-blind, placebo-controlled glucosamine discontinuation trial in knee osteoarthritis. *Arthritis Rheum* 2004;51:738-45.

67. Reichelt A. Efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee. A randomised, placebo-controlled, double-blind study. *Arzneimittelforschung* 1994;44:75-80.
68. Theodosakis J. A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. *J Rheumatol* 2004;31:826.
69. Fransen M, Agaliotis M, Nairn L et al. LEGS study collaborative group. Glucosamine and chondroitin for knee osteoarthritis: a double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. *Ann Rheum Dis* 2015;74(5):851-8.
70. Singh JA, Noorbaloochi S, MacDonald R et al. Chondroitin for osteoarthritis. *Cochrane Database Syst Rev.* 2015;28;1:CD005614.
71. Reginster JY, Dudler J, Blicharski T et al. Pharmaceutical-grade Chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the ChONDroitin versus CElecoxib versus Placebo Trial (CONCEPT). *Ann Rheum Dis.* 2017;22. pii: annrheumdis-2016-210860.
72. Morreale P, Manopulo R, Galati M et al. Comparison of the anti-inflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. *J Rheumatol* 1996;23:1385-91.
73. Hochberg MC, Zhan M, Langenberg P. The rate of decline of joint space width in patients with osteoarthritis of the knee: a systematic review and meta-analysis of randomized placebo-controlled trials of chondroitin sulfate. *Curr.Med.Res.Opin.* 2008;24(11):3029-3035.
74. Hochberg MC. Structure-modifying effects of chondroitin sulfate in knee osteoarthritis: an updated meta-analysis of randomized placebo-controlled trials of 2-year duration. *Osteoarthritis Cartilage.* 2010;18 Suppl 1:S28-S31.
75. Hochberg MC, Martel-Pelletier J, Monfort J et al. Combined chondroitin sulfate and glucosamine for painful knee osteoarthritis: a multicentre, randomised, double-blind, non-inferiority trial versus celecoxib. *Ann Rheum Dis* 2016;75(1):37-44.
76. Das A Jr, Hammad TA. Efficacy of a combination of FCHG49 glucosamine hydrochloride, TRH122 low molecular weight sodium chondroitin sulfate and manganese ascorbate in the management of knee osteoarthritis. *Osteoarthritis Cartilage* 2000;8:343-50.
77. Oliviero U, Sorrentino GP, De Paola P et al. Effects of the treatment with matrix on elderly people with chronic articular degeneration. *Drugs Exp Clin Res* 1991;7(1):45-51.
78. Greenlee H, Crew KD, Shao T et al.. Phase II study of glucosamine with chondroitin on aromatase inhibitor-associated joint symptoms in women with breast cancer. *Support Care Cancer* 2013;21(4):1077-87.
79. Garcia-Coronado JM, Martinez-Olvera L, Elizondo-Omana RE et al. Effect of collagen supplementation on osteoarthritis symptoms: a meta-analysis of randomized placebo-controlled trials. *Int Orthopaedics* 2019;43:531-538.
80. Lugo JP, Saiyed ZM, Lane NE. Efficacy and tolerability of an undenaturated type II collagen supplement in modulating knee placebo-controlled symptoms: a multicentered randomized, double-blind, placebo-controlled study. *Nutr J* 2016;15:14.
81. Schaus AG, Stenehjem J, Park J et al. Effect of the novel low molecular weight hydrolyzed chicken sternal cartilage extracts, biocell collagen, on improving osteoarthritis-related symptoms: a randomized, double-blind, placebo controlled trial. *J Agric Food Chem* 2012;60:4096-4101.
82. Kumar S, Sugihara F, Suzuki K et al., A double-blind, placebo-controlled, randomized, clinical study on the effectiveness of collagen peptide on osteoarthritis. *J Sci Food Agric* 2014;95:702-707
83. Benito-Ruiz P, Camacho-Zambrano MM, Carillo-Arcenales JN et al. A randomized controlled trial on the efficacy and safety of a food ingredient, collagen hydrolysate, for improving joint comfort. *Int J Food Sci Nutr* 2009;60:99-113.



84. McAlindon TE, Nuite M, Krishnan N et al. Change in knee osteoarthritis cartilage detected by delayed gadolinium enhanced magnetic resonance imaging following treatment with collagen hydrolysate: a pilot randomized controlled trial. *Osteoarthritis Cartilage* 2011;19:399-405.
85. Trentham DE, Dinesius-Trentham RA, Orav EJ et al. Effects of oral administration of type II collagen on rheumatoid arthritis. *Science* 1993;261(5129):1727-1730.
86. McKown KM, Carbone LD, Kaplan SB et al. Lack of efficacy of oral bovine type II collagen added to existing therapy in rheumatoid arthritis. *Arthritis Rheum* 1999;42(6):1204-1208.
87. Zhang LL, Wei W, Xiao F et al. A randomized, double-blind, multicenter, controlled clinical trial of chicken type II collagen in patients with rheumatoid arthritis. *Arthritis Rheum* 2008;59(7):905-910.
88. Ruff KJ, Winkler A, Jackson RW, et al. Eggshell membrane in the treatment of pain and stiffness from osteoarthritis of the knee: a randomized, multicenter, double-blind, placebo-controlled clinical study. *Clin Rheumatol* 2009;28:907-914.
89. Ruff KJ, DeVore DP, Leu MD, et al. Eggshell membrane: A possible new natural therapeutic for joint and connective tissue disorders. Results from two open-label human clinical studies. *Clin Interv Aging* 2009;4:235-240.
90. Bradley JD, Flusser D, Katz BP et al. A randomized, double blind, placebo controlled trial of intravenous loading with S-adenosylmethionine (SAM) followed by oral SAM therapy in patients with knee osteoarthritis. *J Rheumatol* 1994;21:905-11.
91. Brien S, Prescott P, Bashir N et al. Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis. *Osteoarthritis Cartilage*. 2008;16:1277-88.
92. Debbi EM, Agar G, Fichman G et al. Efficacy of methylsulfonylmethane supplementation on osteoarthritis of the knee: a randomized controlled study. *BMC Complement Altern Med*. 2011;27:11:50.
93. Usha PR, Naidu MU. Randomised, Double-Blind, Parallel, Placebo-Controlled Study of Oral Glucosamine, Methylsulfonylmethane and their Combination in Osteoarthritis. *Clin Drug Investig*. 2004;24(6):353-63.
94. Lubis AMT, Siagian C, Wonggokusuma E et al. Comparison of glucosamine-chondroitin sulfate with and without methylsulfonylmethane in grade I-II knee osteoarthritis: a double blind randomized controlled trial. *Acta Med Indones*. 2017;49(2):105-11.
95. Notarnicola A, Maccagnano G, Moretti L et al. Methylsulfonylmethane and boswellic acids versus glucosamine sulfate in the treatment of knee arthritis: randomized trial. *Int J Immunopathol Pharmacol*. 2016;29(1):140-6.
96. Xie Q, Shi R, Xu G et al. Effects of AR7 Joint Complex on arthralgia for patients with osteoarthritis: results of a three-month study in Shanghai, China. *Nutr J*. 2008;27:7:31.
97. Barmaki S, Bohlooli S, Khoshkharesh F, et al. Effect of methylsulfonylmethane supplementation on exercise - induced muscle damage and total antioxidant capacity. *J Sports Med Phys Fitness*. 2012;52:170-4.
98. Withee ED, Tippens KM, Dehen R et al. Effects of methylsulfonylmethane (MSM) on exercise-induced oxidative stress, muscle damage, and pain following a half-marathon: a double-blind, randomized, placebo-controlled trial. *J Int Soc Sports Nutr*. 2017;21:14:24.