



Epimedium brevicornum Maxim.

None

Epimedium brevicornum Maxim. is a genus of flowering plants endemic native to China. Its bioactive component, icariin, is a flavonoid glycoside demonstrating various antioxidant and anti-inflammatory benefits^[1]. Numerous in vitro cell culture studies showed that icariin has the potential to suppress inflammatory pathways involved in OA (Osteoarthritis)^[2-7]. In rodent OA models, joint injection of icariin for 32 and 84 days was found to protect the articular cartilage from degeneration^{[4][8]}. One randomized, placebo-controlled study reported pain reduction and functionality improvement in knee OA patients ≥ 40 years old after a 6-month supplementation of Xianlinggubao (3 g/day), a traditional herbal formula containing 70 wt% Epimedium extract (2.1 g/day)^[9]. The same study also demonstrated that the supplementation is both safe and well tolerated in knee OA patients^[9].

[1] Fang J, Zhang Y. (2017). *Icarin, an Anti-atherosclerotic Drug from Chinese Medicinal Herb Horny Goat Weed*. *Front Pharmacol*, 8:734. doi:10.3389/fphar.2017.00734.

[2] Chen SR, Xu XZ, Wang YH, Chen JW, Xu SW, Gu LQ, Liu PQ. (2010). *Icarin derivative inhibits inflammation through suppression of p38 mitogen-activated protein kinase and nuclear factor-κappaB pathways*. *BiolPharm Bull*, 33(8):1307-13. doi:10.1248/bpb.33.1307.

[3] Liu MH, Sun JS, Tsai SW, Sheu SY, Chen MH. (2010). *Icarin protects murine chondrocytes from lipopolysaccharide-induced inflammatory responses and extracellular matrix degradation*. *Nutrition research*, 30(1):57-65. doi:10.1016/j.nutres.2009.10.020.

[4] Zu Y, Mu Y, Li Q, Zhang ST, Yan HJ. (2019). *Icarin alleviates osteoarthritis by inhibiting NLRP3-mediated pyroptosis*. *J Orthop Surg Res*, 14(1):307. doi:10.1186/s13018-019-1307-6.

[5] Yan N, Wen DS, Zhao YR, Xu SJ. (2018). *Epimedium sagittatum inhibits TLR4/MD-2 mediated NF- κappaB signaling pathway with anti-inflammatory activity*. *BMC Complement Altern Med*, 18(1):303. doi:10.1186/s12908-018-2363-x.

[6] Wang P, Zhang F, He Q, Wang J, Shiu HT, Shiu Y, Tsang WP, Liang S, Zhao K, Wan C. (2016). *Flavonoid Compound Icarin Activates Hypoxia Inducible Factor-1alpha in Chondrocytes and Promotes Articular Cartilage Repair*. *PLoS One*, 11(2): e0148372. doi:10.1371/journal.pone.0148372.

[7] Pan L, Zhang Y, Chen N, Yang L. (2017). *Icarin Regulates Cellular Functions and Gene Expression of Osteoarthritis Patient-Derived Human Fibroblast-Like Synoviocytes*. *Int J Mol Sci*, 18(12). doi:10.3390/ijms18122656.

[8] Luo Y, Zhang Y, Huang Y. (2018). *Icarin Reduces Cartilage Degeneration in a Mouse Model of Osteoarthritis and is Associated with the Changes in Expression of Indian Hedgehog and Parathyroid Hormone-Related Protein*. *Med Sci Monit*, 24:6695-706. doi:10.12659/MSM.910983.

[9] Wang F, Shi L, Zhang Y, Wang K, Pei F, Zhu H, Shi Z, Tao T, Li Z, Zeng P, et al. (2018). *A Traditional Herbal Formula Xianlinggubao for Pain Control and Function Improvement in Patients with Knee and Hand Osteoarthritis: A Multicenter, Randomized, Open-Label, Controlled Trial*. *Evid Based Complement Alternat Med*, 2018:1827528. doi:10.1155/2018/1827528.

[10] Ou-Yang SH, Jiang T, Zhu L, Yi T. (2018). *Dioscorea nipponica Makino: a systematic review on its ethnobotany, phytochemical and pharmacological profiles*. *Chem Cent J*, 12(1):57. doi:10.1186/s13065-018-0423-4.

[11] Junchao Y, Zhen W, Yuan W, Liying X, Libin J, Yuanhong Z, Wei Z, Rulin C, Lu Z. (2017). *Anti-trachea inflammatory effects of diosgenin from Dioscorea nipponica through interactions with glucocorticoid receptor alpha*. *J Int Med Res*, 45(1):101-13. doi:10.1177/0300060516676724.

[12] Zhao X, Yin L, Fang L, Xu L, Sun P, Xu M, Liu K, Peng J. (2016). *Protective effects of dioscin against systemic inflammatory response syndrome via adjusting TLR2/MyD88/NFκappab signal pathway*. *Int Immunopharmacol*, 65:458-69. doi:10.1016/j.intimp.2016.05.036.

[13] Ma S, Zhang D, Lou H, Sun L, Ji J. (2016). *Evaluation of the anti-inflammatory activities of tanshinones isolated from Salvia miltiorrhiza var. alba roots in THP-1 macrophages*. *J Ethnopharmacol*, 188:193-9. doi:10.1016/j.jep.2016.05.018.

[14] Bai B, Li Y. (2016). *Danshen prevents articular cartilage degeneration via antioxidation in rabbits with osteoarthritis*. *Osteoarthritis Cartilage*, 24(3):514-20. doi:10.1016/j.joca.2015.10.004.

[15] Xu X, Lv H, Li X, Su H, Zhang X, Yang J. (2017). *Danshen attenuates osteoarthritis-related cartilage degeneration through inhibition of NF-κappaB signaling pathway in vivo and in vitro*. *Biochem Cell Biol*, 95(6):644-51. doi:10.1139/bcb-2017-0025.

[16] Xu X, Lv H, Li X, Su H, Zhang X, Yang J. (2018). *Danshen attenuates cartilage injuries in osteoarthritis in vivo and in vitro by activating JAK2/STAT3 and AKT pathways*. *Exp Anim*, 67(2):127-37. doi:10.1538/expanim.17-0062.



Dioscorea nipponica Makino

None

Dioscorea nipponica Makino is a genus of flowering plants commonly used in traditional Chinese medicine, mainly for treating bone-related conditions, such as OA (Osteoarthritis)^[10]. *Dioscorea* extract contains two major bioactive compounds, diosgenin and dioscin, both of which are found to have a protective role against systemic inflammation in vitro^{[11][12]}. Numerous pre-clinical studies have also demonstrated the anti-inflammatory and analgesic properties of *Dioscorea* extract in rodent models with induced arthritis^[10]. Furthermore, two human studies indicated that *Dioscorea* extract is an effective treatment for knee OA by orally given decoction and external application.



Salvia miltiorrhiza Bunge.

None

Salvia miltiorrhiza Bunge. is sustainably cultivated from a special ecosystem in Shandong Province, China. Tanshinones, the main bioactive components isolated from *S.miltiorrhiza* extract, can significantly inhibit expression of pro-inflammatory cytokines in vitro^[13]. In rabbit models of OA, supplementation of *S. miltiorrhiza* extract attenuated cartilage injury by lowering oxidative stress^[14] and reducing chondrocyte apoptosis via regulation of various signaling pathways^{[15][16]}.