REGENAPEP

Creating Moments in Motion

REGENAPEP is a new TGA-certified anti-inflammatory supplement that acts as an advanced reliever of musculoskeletal, rheumatic and arthritic pain, and a preventive system against potential future onset of arthritis by alleviating conditions associated with early-stage musculoskeletal and joint inflammation through pro-inflammatory cytokine regulation induced by IL1RA-enriched (interleukin-1 receptor antagonist peptides) colostrum, and a combination of purified botanical extracts.

Principal Indication.
REGENAPEP supports: (1) the relief of musculoskeletal, rheumatic and arthritic pain (Pain Management), (2) the preventive care for non-arthritic patients against potential onset of arthritis and other form of musculoskeletal inflammation (Anti-Inflammatory Preventive System), (3) the safe and accessible adjuvant to existing first-line treatments to delay and manage the progression of early to mid-stage arthritis and other musculoskeletal inflammatory conditions (Adjuvant Therapy).

Recommended Users.
REGENAPEP is recommended for patients with early to mid-stage arthritis, and non-arthritic adults seeking to maintain a good musculoskeletal and joint health.

Other Potential Indications (Developmental Pipeline).
REGENAPEP is formulated with ingredients that may be used for injury prevention and recovery in sports medicine. IL1RA peptides (enriched in REGENAPEP's colostrum) address chronic 'hidden' inflammation that may potentially extend the therapeutic effects of REGENAPEP to non-musculoskeletal inflammatory conditions.

Composition.

Dosage Form:	Powdered Tablets		
Therapeutic Use:	Dietary Supplement		
Recommended Intake:	2 tablets/day (maximum daily dose 6 tablets)		
Composition: 60 tablets/pack	Colostrum Powder	50mg	The colostrum used in REGENAPEP formula is enriched and purified for interleukin-1 receptor antagonist (IL1RA) peptides. Colostrum contains a variety of cytokines with immune-modulatory properties[1]. IL1RA peptide is a key neutralizing agent of the pro-inflammatory cytokine interleukin-1, which has a significant body of experimental evidence implicating it in the pathogenesis of arthritis. In both rheumatoid arthritis and osteoarthritis, IL-1 leads to tissue destruction by inhibiting matrix synthesis and increasing production of matrix degradation proteinase by cells in the synovium and by chondrocytes in the adjacent articular cartilage[2]. IL1RA peptide suppresses specific IL-1 pro-inflammatory cytokines to impede the progression of arthritic disease, provide secondary pain reduction effect and allow for better regenerative conditions to the cartilage and synovium. Studies suggest that the IL1RA peptide production may be relatively deficient or inadequate in patients with rheumatoid arthritis.[3] In one instance, patients with rheumatic profile treated with recombinant human IL1RA for six months exhibited improvements in clinical parameters and in radiographic evidence of joint damage[4].
	Curcuma Longa (rhizome) • *Concentration of 20:1 equiv. to Curcuma Longa dry*	50mg *1g*	Curcuma longa (turmeric) rhizome extract has anti-rheumatic[5] and anti-inflammatory[6] effects as demonstrated by a number of clinical studies. Other effects such as anti-depression and osteogenic differentiation of mesenchymal stem cells have also been observed. Turmeric extract inhibits multiple pro-inflammatory pathways primarily due to the active component, curcumin, which is a potent blocker of NF-κB activation[7], matrix metalloproteinases (MMPs) upregulation in primary chondrocytes[8] and prostaglandin E2 production[9]. Recent study has demonstrated that the ability of turmeric extract to suppress the secretion of COX-2 is relatively similar to diclofenac sodium (voltaren)[10]. Curcumin has also displayed natural and lasting antidepressant effect by increasing brain derived neurotrophic factor (BDNF) in hippocampus[11], which may assist in targeting depression symptomatically associated with arthritis. Curcumin can potently induce heme oxygenase-1 (HO-1) expression, which ultimately promotes mesenchymal stem cell osteoblast differentiation and inhibits adipocyte differentiation[12].

[1] Hagiwara K, Kataoka S, Yamanaka H, Kirisawa R, Iwai H. Detection of cytokines in bovine colostrum. Vet Immunol Immunopathol. 2000 Oct 31;76(3-4):183-90. PubMed PMID: 11044552.
[2] Phillips KL, Jordan-Mahy N, Nicklin MJ, Le Maitre CL. Interleukin-1 receptor antagonist deficient mice provide insights into pathogenesis of human intervertebral disc degeneration. Ann Rheum Dis. 2013 Feb 9. [Epub ahead of print] PubMed PMID: 23396662.
[3] Chikanza IC, Roux-Lombard P, Dayer J-M, Panayi GS. 1995. Dysregulation of the in vivo production of interleukin-1 receptor antagonist in patients with rheumatoid arthritis. *Arthritis Rheum.* 38:642-48.
[4] William P. Arend, Mark Malyak, Carla J. Guthridge, and Cem Gabay. Interleukin-1 Receptor Antagonist: Role in Biology. *Annual Review of Immunology.* 1998; 16: 27-55.
[5] Aggarwal BB, Harikumar KB (2009) Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol 41: 40–59.
[6] Klawitter M, Quero L, Klasen J, Gloess AN, Klopprogge B, Hausmann O, Boos N, Wuertz K. Curcuma DMSO extracts and curcumin exhibit an anti-inflammatory and anti-catabolic effect on human intervertebral disc cells, possibly by influencing TLR2 expression and JNK activity. J Inflamm (Lond). 2012 Aug 21;9(1):29. doi: 10.1186/1476-9255-9-29. PubMed PMID: 22909087; PubMed Central PMCID: PMC3506446.
[7] Singh S, Aggarwal BB. Activation of transcription factor NF- kappa B is suppressed by curcumin (diferuloylmethane) [corrected]. *J Biol Chem* 1995;270:24995-25000.
[8] Onodera S, Kaneda K, Mizue Y, Koyama Y, Fujinaga M, Nishihira J. Macrophage migration inhibitory factor up-regulates expression of matrix metalloproteinases in synovial fibroblasts of rheumatoid arthritis. J Biol Chem. 2000 Jan 7;275(1):444-50. PubMed PMID: 10617637.
[9] Park C, Moon DO, Choi IW, Choi BT, Nam TJ, Rhu CH, Kwon TK, Lee WH, Kim GY, Choi YH. Curcumin induces apoptosis and inhibits prostaglandin E(2) production in synovial fibroblasts of patients with rheumatoid arthritis. Int J Mol Med. 2007;20:365–372.
[10] Kertia N, Asdie AH, Rochmah W, Marsetyawan. Ability of curcuminoid compared to diclofenac sodium in reducing the secretion of cycloxygenase-2 enzyme by synovial fluid's monocytes of patients with osteoarthritis. Acta Med Indones. 2012 Apr;44(2):105-13. PubMed PMID: 22745140.
[11] Hurley LL, Akinfiresoye L, Nwulia E, Kamiya A, Kulkarni AA, Tizabi Y. Antidepressant-like effects of curcumin in WKY rat model of depression is associated with an increase in hippocampal BDNF. Behav Brain Res. 2013 Feb 15;239:27-30. doi: 10.1016/j.bbr.2012.10.049. Epub 2012 Nov 8. PubMed PMID: 23142609; PubMed Central PMCID: PMC3525727.
[12] Gu Q, Cai Y, Huang C, Shi Q, Yang H. Curcumin increases rat mesenchymal stem cell osteoblast differentiation but inhibits adipocyte differentiation. Pharmacogn Mag. 2012 Jul;8(31):202-8. doi: 10.4103/0973-1296.99285. PubMed PMID: 23060694; PubMed Central PMCID: PMC3466455.

	Salix Alba (stem bark) • *Concentration of 25:1 equiv. to Salix Alba fresh*	0.33g *8.25g*	Salix alba (white willow) stem bark extract is capable of alleviating inflammation by reducing IL-6 and TNF-α production[13]. Salicin, the active extract of white willow improves pain in the short-term[14]. Recent study demonstrated that white willow extract could also stimulate new cartilage formation by exerting anabolic effects on articular chondrocyte in animal models[15].
	Harpagophytum Procumbens (root) • *Concentration of 6:1 equiv. to Harpagophytum Procumbens dry*	50mg *300mg*	Harpagoside, the primary active constituent of harpagophytum procumbens (devil's claw) root extract exhibits anti-inflammatory, chondroprotective and analgesic activities. Harpagoside is capable of inhibiting inducible nitric oxide (iNOS) and cyclooxygenase-2 (COX-2) expression by suppressing nuclear factor kappaB (NF-κB), which ultimately reduces inflammation[16]. Human research has demonstrated decreased pain in knee and hip osteoarthritis and non-specific low-back pain after ingestion of devil's claw extract containing harpagoside[17]. Devil's claw extract has a role in reducing cartilage degradation through the inhibition of matrix metalloproteinase (MMPs) and elastase[18].
	Boswellia Serrata (gum oleoresin) • *Concentration of 6:1 equiv. to Boswellia Serrata fresh*	230mg *1.38g*	Boswellic serrata gum oleoresin extract is a nutraceutical agent with potent anti-inflammatory, anti-arthritic and analgesic effects[19]. Animal studies have shown ingestion of boswellia serrata extract decreased polymorphonuclear leukocyte infiltration and migration, and decreased primary antibody synthesis[20]. One of the key phytochemical constituents, acetyl-11-keto-β-boswellic acid is a potent and specific inhibitor of 5-lipoxygenase, an enzyme responsible for inflammation.[21]
	Zingiber Officinale (rhizome) • *Concentration of 10:1 equiv. to Zingiber Officinale fresh*	100mg 1g	Zingiber officinale (ginger) rhizome extract has been prescribed as an analgesic for arthritis pain in traditional medicine. Ginger extract also possesses a significant anti-inflammatory effect, with recent studies demonstrating equal potency to glucocorticoid steroid drug such as betamethasone[22]. It suppresses the production of prostaglandin E-2 and nitric oxide, and the activation of macrophages in animal models[23].
	Manganese Sulphate Monohydrate • *Equiv. to Manganese*	10mg *3.25mg*	Manganese is one of the key trace minerals needed to build cartilage and maintain a normal skeletal growth[24].
	Inactive ingredients: Crospovidone, Cellulose – microcrystalline, Silica – colloidal anhydrous, Maltodextrin, Magnesium stearate, Calcium hydrogen phosphate.		

Biological Mechanisms.
Interleukin-1 Inhibition (*IL1RA-enriched colostrum*); Inhibition of NF-κB (*curcuma longa, harpagophytum procumbens*); Matrix Metalloproteinase and Elastase Inhibition (*curcuma longa, harpagophytum procumbens*); Inhibition of Prostaglandin E2 Production (*curcuma longa, zingiber officinale*); Selective COX-2 Inhibition (*curcuma longa, harpagophytum procumbens*); Reduced Production of Interleukin-6 and TNF-α (*salix alba*); 5-lipoxygenase Inhibition (*boswellia serrata*); Stimulation of Osteoblast Differentiation through Elevated HO-1 Expression (*curcuma longa*); Trace Mineral Supplementation (*manganese sulphate*); Anabolic Effects on Articular Chondrocytes (*salix alba*); Increased Brain Derived Neurotrophic Factor for Anti-Depression (*curcuma longa*);

Competitive Analysis. Current approaches for the pathophysiological treatment and pain relief of patients with musculoskeletal and arthritic conditions can be classified as: (1) Therapeutic biologics: anti-TNF monoclonal antibodies and anti B-cell proteins, (2) Corrective invasive surgery: arthroplasty and osteotomy, (3) Lubrication injections: synvisc, orthovisc and corticosteroids, and (4) Oral medications: COX-2 selective inhibitors, NSAIDs and non-narcotic analgesics. There are reservations towards the effectiveness of current pharmacological approaches to target inflammation and impede the progression and pathological manifestations of arthritis. The more promising class of therapeutic biologics poses considerable long-term risks such as lymphoma and other malignancies (anti-TNF drugs), and is expensive and less accessible by consumers globally. The osteoarthritic supplement market is saturated with a large number of brands offering similar glucosamine chondroitin, with no guarantee of satisfactory quality and therapeutic effects. Joint supplements comprising glucosamine and chondroitin have a significant effect in short term pain reduction, and exhibit few side reactions. However, glucosamine and chondroitin do not address the underlying inflammatory disorder associated with musculoskeletal, rheumatic and arthritic conditions, so joint retardation and progression of the disease does not stop. When used alone, NSAIDs are not sufficient to address musculoskeletal and arthritic conditions.

Precaution.
Use in children under 12 years is not recommended except on professional health advice. If symptoms persist consult your healthcare practitioner. If you are pregnant or breast feeding, seek the advice of a healthcare professional before taking REGENAPEP. This product contains colostrum powder that may contain lactose. This product should not be taken with high alcohol intake. This product is meant to supplement and not to replace primary treatments or advice from your doctor or healthcare provider.

Storage.
Store in cool and dry condition.

For Additional Information, Enquiries or Updates, visit the website myopep.lab-rms.com or contact info@lab-rms.com.

[13] Drummond EM, Harbourne N, Marete E, Martyn D, Jacquier J, O'Riordan D, Gibney ER. Inhibition of Proinflammatory Biomarkers in THP1 Macrophages by Polyphenols Derived From Chamomile, Meadowsweet and Willow bark. Phytother Res. 2012 Jun 18. doi: 10.1002/ptr.4753. [Epub ahead of print] PubMed PMID: 22711544.
[14] Gagnier JJ, van Tulder MW, Berman B, Bombardier C. Herbal medicine for low back pain: a Cochrane review. Spine (Phila Pa 1976). 2007 Jan 1;32(1):82-92. Review. Erratum in: Spine. 2007 Aug 1;32(17):1931.. PubMed PMID: 17202897.
[15] Shakibaei M, Allaway D, Nebrich S, Mobasheri A. Botanical extracts from Rosehip (Rosa canina), Willow Bark (Salix alba), and Nettle Leaf (Urtica dioica) suppress IL-1beta-induced NF-kappaB activation in Canine Articular Chondrocytes. Evid Based Complement Alternat Med. 2012;2012:509383. doi: 10.1155/2012/509383.
[16] Huang TH, Tran VH, Duke RK, et al. Harpagoside suppresses lipopolysaccharide-induced iNOS and COX-2 expression through inhibition of NF-kappa B activation. J Ethnopharmacol 2006;104:149-155.
[17] 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;17:1165-1172.
[18] Fiebich BL, Heinrich M, Hiller KO, Kammerer N. Inhibition of TNF-alpha synthesis in LPS-stimulated primary human monocytes by Harpagophytum extract SteiHap 69. Phytomedicine 2001;8:28-30.
[19] Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee--a randomized double blind placebo controlled trial. Phytomedicine. 2003 Jan;10(1):3-7. PubMed PMID: 12622457.
[20] Sharma ML, Khajuria A, Kaul A, et al. Effects of salai guggal ex-Boswellia serrata on cellular and humoral immune responses and leukocyte migration. *Agents Actions* 1988;24:161-164.
[21] Siddiqui MZ. Boswellia serrata, a potential antiinflammatory agent: an overview. Indian J Pharm Sci. 2011 May;73(3):255-61. doi: 10.4103/0250-474X.93507. PubMed PMID: 22457547; PubMed Central PMCID: PMC3309643.
[22] Ribel-Madsen S, Bartels EM, Stockmarr A, Borgwardt A, Cornett C, Danneskiold-Samsøe B, Bliddal H. A synoviocyte model for osteoarthritis and rheumatoid arthritis: response to Ibuprofen, betamethasone, and ginger extract-a cross-sectional in vitro study. Arthritis. 2012;2012:505842. doi: 10.1155/2012/505842. Epub 2012 Dec 31. PubMed PMID: 23365744; PubMed Central PMCID: PMC3546442.
[23] Shimoda H, Shan SJ, Tanaka J, Seki A, Seo JW, Kasajima N, Tamura S, Ke Y, Murakami N. Anti-inflammatory properties of red ginger (Zingiber officinale var. Rubra) extract and suppression of nitric oxide production by its constituents. J Med Food. 2010 Feb;13(1):156-62. doi: 10.1089/jmf.2009.1084. PubMed PMID: 20136450.
[24] Chang Li and Hai-Meng Zhou, "The Role of Manganese Superoxide Dismutase in Inflammation Defense," Enzyme Research, vol. 2011, Article ID 387176, 6 pages, 2011. doi:10.4061/2011/387176