

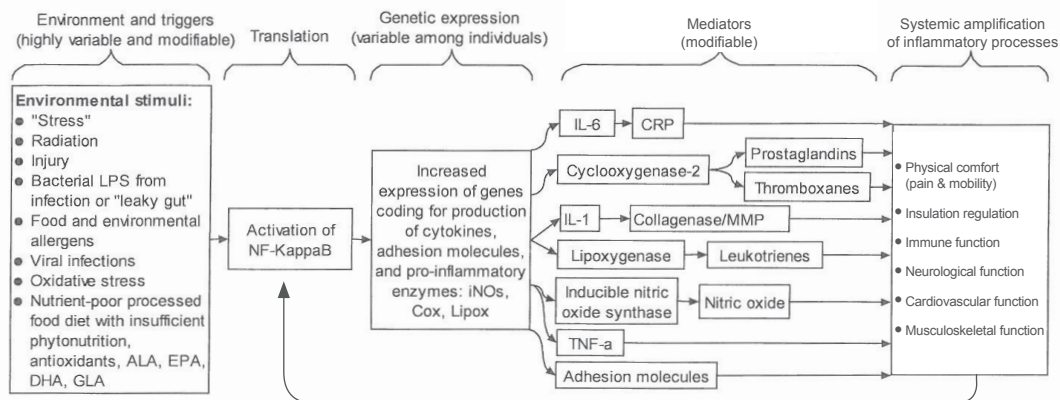
# KappArest™

## Nutritional Support for a Healthy Inflammatory Response NF-kappaB Downregulator



**KappArest™** is a proprietary blend of nutrients designed to downregulate inflammatory pathways, primarily through the inhibition of nuclear transcription factor-kappaB (NF-kappaB), a protein complex found in each cell that controls transcription of DNA, cytokine production, immune response and cell survival. NF-kappaB signaling is primarily regulated by inhibitor kappaB (IkappaB) proteins and the IkappaB kinase complex through two major pathways: the canonical (mediates inflammatory responses) and non-canonical (immune cell maturation) NF-kappaB pathways.<sup>(1)</sup> Because of the interdependencies between the two, most view the NF-kappaB complex as a single signaling system.<sup>(2)</sup>

Triggered by environmental stimuli, such as stress, radiation, injury, infection or oxidative stress, NF-kappaB becomes activated and acts as an intracellular 'amplifier' promoting the production of the direct mediators of inflammation such as cytokines, prostaglandins, leukotrienes, nitric oxide and free radicals. NF-kappaB can play a protective role, protecting from acute injurious situations. However, dysregulated NFkB activity is often observed and may link to a failed feedback mechanism, which may result in defective communication between the cells and the host organism.<sup>(3)</sup> Understanding and regulating the NF-kappaB signaling pathway is critical to overall health.



While individual ingredients within combination nutritional formulas are often well-studied, rarely is the formula itself, comprised of varied vitamins, minerals, antioxidant enzymes, botanical extracts and carotenoids put through the rigor of research as a complex. The formula, **KappArest™**, however, is the exception to this rule, as there are two such studies that have evaluated its ability to decrease the inflammatory response.<sup>(4,5)</sup>



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These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

One study evaluated the effects of **KappArest™** on cyclooxygenase (COX) enzyme activity, and also immune responsiveness of RAW264.7 macrophages, a key cell population involved in inflammation. **KappArest™** was found to selectively inhibit COX-2. It also decreased the lipopolysaccharide (LPS)-stimulated macrophages, as well as decreased the LPS-induced production of nitric oxide (NO) and interleukin-6 (IL-6), suggesting its protective effect in chronic inflammatory disorders.<sup>(4)</sup>

A second study evaluated **KappArest™** for its immunomodulatory effects on dendritic cells (DCs) due to their preferential inhibition of COX-2 in an initial screening assay. **KappArest™** was found to be selective for COX-2 inhibition. It also inhibited the release of NO, IL-6 and TNF- $\alpha$  by LPS activated bmDCs. In summary, the data suggests **KappArest™** may act as an effective anti-inflammatory product with little to no risk of toxicity.<sup>(5)</sup>

**KappArest™** supplies a broad array of antioxidants and phytonutrient components, demonstrated to suppress the activation of NF-kappaB and associated kinases, including AP-1. The following ingredients found in **KappArest™** have documented activity in suppressing NF-kappaB.

### **Curcumin:**

**KappArest™** has been newly formulated to include 50% **CurcumRx®**, an emulsified Curcuma longa root extract, prepared using a non-chemical process that creates an excellent dual-phase, polar/non-polar emulsion for transport through the lipid membrane. This specialized technology results in increased bioavailability without the use of nanotechnology, including the use of “tweens” and other surfactants that may damage lipid membranes and result in leaky gut.

**CurcumRx®** supplies a nutrient-dense turmeric complex that not only contains curcumin, bisdemethoxycurcumin and demethoxycurcumin, it contains more than 200 additional compounds of nutritional interest, including phenolic compounds, sesquiterpenes, sterols, fatty acids, and more. Turmeric and its curcuminoid constituents have been shown to be an effective inhibitor to the activation and release of NF-kappaB.<sup>(6,7)</sup> In-vitro results suggest that curcumin most likely inhibits cell proliferation, cell-mediated cytotoxicity, and cytokine production by inhibiting NF-kappaB target genes involved in induction of these immune responses.<sup>(8)</sup>

### **Boswellia serrata:**

In one animal study, acetyl-11-keto- $\beta$ -boswellic acid (AKBA), an agent obtained from the gum resin of *Boswellia serrata* was found to significantly inhibit active NF-kappaB and suppress the NF-kappaB regulating gene expression.<sup>(9)</sup> AKBA produced significant decreases in the expression of NF-kappaB regulating genes in tissues.<sup>(10)</sup> In evaluating its activity, one study demonstrated that *Boswellia serrata* significantly improved the comfort levels compared to the placebo.<sup>(11)</sup>

### **Propolis:**

Propolis, a sticky resin honeybees produce by mixing saliva and beeswax, is used as a sealant in the bee hive. It has also traditionally been used in folk medicine as a “drink” to support healthy inflammation pathways. Propolis contains caffeic acid. Both propolis and caffeic acid are strong antioxidants, which have been found to suppress LPS-induced signaling pathways, namely p38 MAPK, JNK1/2 and NF-kappaB, without inducing hepatotoxicity.<sup>(12)</sup>

### **Green Tea:**

The ability of tea polyphenols to prevent NF-kappaB activation has been evaluated in a number of studies. One study demonstrated the antioxidant activity of green tea extract in subjects with nonalcoholic steatohepatitis (NASH) where it was determined that green tea extract improved glutathione status, contributing to the inhibition of the inflammatory response mediated by NF-kappaB.<sup>(13)</sup> Also, another study suggests that early use of green tea helps regulate NF-kappaB activity in regenerating muscle fibers.<sup>(14)</sup>

### **Ginger:**

Ginger, a plant with an abundance of phytochemicals yielding antioxidant effects, has been found to support healthy inflammatory pathways. In one study, 1-dihydro-[10]-gingerdione (D10G), a constituent of ginger, was found to “mediate the suppression of NF-kappaB-regulated expression of inflammatory genes linked to toll-like receptor (TLR)-mediated innate immunity”.<sup>(15)</sup> Ginger was also shown to support healthy insulin levels by reducing NF-kappaB.<sup>(16)</sup>

## Rosemary:

Carnosol, a naturally-occurring phytopolyphenol, is the key antioxidant in rosemary studied for its ability to downregulate NF-kappaB. Carnosol decreases high concentrations of nitric oxide (NO) that can be produced by inducible NO synthase (iNOS), and also reduced NF-kappaB subunits translocation and NF-kappaB DNA binding activity. By inhibiting NF-kappaB activation, carnosol suppresses the NO production and iNOS gene expression.<sup>(17)</sup>

## Celery:

Intake of apigenin (4',5,7-trihydroxyflavone), a plant flavone found in celery blocks phosphorylation and degradation of Ikb $\alpha$  by inhibiting IKK activation, which in turn led to suppression of NF- $\kappa$ B activation.<sup>(18)</sup>

## Alpha-Lipoic Acid:

In an animal model, alpha-lipoic acid (ALA), a powerful antioxidant, was found to significantly support cartilage health and function. ALA not only provided strong antioxidant support and increased levels of collagen, it also inhibited the activation of NF-kappaB.<sup>(20)</sup>

## Trans-Resveratrol:

Resveratrol has also been found to support healthy inflammation pathways through its suppression of NF-kappaB and JAK/STAT signaling pathways. In one study, the effect of resveratrol on the lipopolysaccharide (LPS)-induced inflammatory response in RAW264.7 murine macrophages and results confirmed that resveratrol decreased expression of inducible nitric oxide synthase (iNOS) and interleukin-6 (IL-6), thus suppressing production of nitric oxide (NO). By modulating NF-kappaB, resveratrol supports healthy inflammatory pathways.<sup>(19)</sup>

**Phytolens**<sup>®</sup>, a Biotics Research patented extract from lentil, has also demonstrated superior antioxidant properties and displays potent free-radical scavenging ability, resulting in marked benefits. In addition to its antioxidant potency, **Phytolens**<sup>®</sup> exhibited great inhibitory effect on both COX-1 and COX-2 activity in one study where it modulated the production of inflammatory mediators by DC2.4 cells.<sup>(5)</sup>

Oftentimes, the mechanisms underlying disease processes are a result of a chronic inflammatory state. Much damage can occur when there is an uncontrolled host inflammatory response. **KappArest**<sup>™</sup> provides the effective blend of nutrients proven to downregulate inflammatory pathways, primarily through the inhibition of NF-kappaB.

**KappArest**<sup>™</sup> is available in a 180-count bottle (#7855).



| Supplement Facts  |                    |
|---|--------------------|
| Serving Size: 3 Capsules                                      |                    |
| Servings Per Container: 60                                    |                    |
|   | Amount Per Serving |
| Proprietary Blend   | 1,150 mg           |
| Curcuma Longa (emulsified root extract† and rhizome power)*   |                    |
| Boswellia (Boswellia serrata) (gum) (extract) *               |                    |
| Propolis *  |                    |
| Green Tea (Camellia sinensis) (leaf) (extract) *              |                    |
| Ginger (Zingiber officinale) (rhizome) (extract) *            |                    |
| Rosemary (Rosmarinus officinalis) (aerial part) (extract) *   |                    |
| Celery (Apium graveolens) (seed) (extract) *                  |                    |
| Alpha-Lipoic Acid *   |                    |
| Trans-Resveratrol *   |                    |
| Phytolens <sup>®</sup> (Lens esculenta) (extract) (husk) †† * |                    |
| Bioperine <sup>®</sup> (Piper nigrum) (extract) (fruit) ††† * |                    |

\* Daily Value not established

**Other ingredients:** Capsule shell (gelatin and water), cellulose, silica and magnesium stearate (vegetable source).

† Emulsified Curcuma longa root extract is prepared using a non-chemical process which creates an excellent dual-phase, polar/non-polar emulsion for transport through the lipid membrane.

†† **Phytolens**<sup>®</sup> is a registered trademark of Biotics Research Corporation, U.S. Patent # 5,762,936

††† **Bioperine**<sup>®</sup> is a registered trademark of Sabinsa Corporation.

**This product is gluten and dairy free.**

**RECOMMENDATION:** Three (3) capsules two (2) times each day as a dietary supplement or as otherwise directed by a healthcare professional.

**CAUTION:** Not recommended for pregnant or lactating women.

**KEEP OUT OF REACH OF CHILDREN**

Store in a cool, dry area.  
Sealed with an imprinted safety seal for your protection.

Product # 7855 Rev. 01/18

## References

1. Gilmore TD. "Introduction to NF-kappaB: players, pathways, perspectives". *Oncogene*. 2006 Oct 30;25(51):6680-4.
2. Vincent Feng-Sheng Shih, Rachel Tsui, Andrew Caldwell, and Alexander Hoffmann. "A single NFkB system for both canonical and non-canonical signaling". *Cell Res*. 2011 Jan; 21(1): 86–102.
3. Vlahopoulos SA. "Aberrant control of NF-kB in cancer permits transcriptional and phenotypic plasticity, to curtail dependence on host tissue: molecular mode". *Cancer Biol Med*. 2017 Aug;14(3):254-270. doi: 10.20892/j.issn.2095-3941.2017.0029.
4. Jenna M. Benson , BA, Andrea K. Miller , BS, Natalie Cooper, Dave N. Muanza , PhD, Jerry R. Smith , PhD & David M. Shepherd , PhD. Anti-Inflammatory Effects of Natural Product Formulations on Murine Macrophages. *Journal of Dietary Supplements*, Vol 7, 2010 – Issue 3
5. Andrea K. Miller, BS, Jenna M. Benson, BA, Dave N. Muanza, PhD, Jerry R. Smith, PhD, and David M. Shepherd, PhD. Anti-inflammatory effects of natural product formulations on murine dendritic cells. *J Diet Suppl*. 2011 Mar; 8(1): 19–33.
6. Parodi FE, et al. "Oral administration of diferuloylmethane (curcumin) suppresses proinflammatory cytokines and destructive connective tissue remodeling in experimental abdominal aortic aneurysms". *Ann Vasc Surg* 2006; 20(3): 360-368.
7. Sing S, Aggarwal BB. "Activation of transcription factor NF-kB is suppressed by curcumin (diferuloylmethane)". *J Biological Chem*. 1995 270 (42): 24995-25000.
8. Gao X, et al. "Immunomodulatory activity of curcumin suppression of lymphocyte proliferation, development of cell-mediated cytotoxicity, and cytokine production in vitro". *Biochemical Pharmacology*. 1 July 2004. 68(1): 51-61.
9. Byoungduck Park, Bokyung Sung, Vivek R. Yadav, Sung-Gook Cho, Mingyao Liu, and Bharat B. Aggarwal.. "Acetyl-11-keto-β-Boswellic Acid Suppresses Invasion of Pancreatic Cancer Cells Through the Downregulation of CXCR4 Chemokine Receptor Expression". *Int J Cancer*. 2011 Jul 1; 129(1): 23–33.
10. Park B, Prasad S, Yadav V, Sung B, Aggarwal BB. "Boswellic acid suppresses growth and metastasis of human pancreatic tumors in an orthotopic nude mouse model through modulation of multiple targets". *PLoS One*. 2011;6(10):e26943.
11. Prabhavathi K, Chandra US, Soanker R, Rani PU. *Indian J Pharmacol*. "A randomized, double blind, placebo controlled, cross over study to evaluate the analgesic activity of *Boswellia serrata* in healthy volunteers using mechanical pain model". 2014 Sep-Oct;46(5):475-9. doi: 10.4103/0253-7613.140570.
12. Buffalo MC, et al. "Propolis and its constituent caffeic acid suppress LPS-stimulated pro-inflammatory response by blocking NF-kappaB andMAPK activation in macrophages." *J Ethnopharmacol*. 2013.
13. Park HJ, Lee JY, Chung MY, Park YK, Bower AM, Koo SI, Giardina C, Bruno RS. "Green tea extract suppresses NFkB activation and inflammatory responses in diet-induced obese rats with nonalcoholic steatohepatitis". *J Nutr*. 2012 Jan;142(1):57-63.
14. Evans NP, Call JA, Bassaganya-Riera J, Robertson JL, Grange RW. "Green tea extract decreases muscle pathology and NF-kappaB immunostaining in regenerating muscle fibers of mdx mice". *Clin Nutr*. 2010 Jun;29(3):391-8.
15. Lee HY, Park SH, Lee M, Kim HJ, Ryu SY, Kim ND, Hwang BY, Hong JT, Han SB, Kim Y. 1-Dehydro-[10]-gingerdione from ginger inhibits IKKβ activity for NF-kB activation and suppresses NF-kB-regulated expression of inflammatory genes. *Br J Pharmacol*. 2012 Sep;167(1):128-40.
16. Honarvar, Niaz Mohammadzadeh. "Effects of Ginger Supplementation on NF-KB in Peripheral Blood Mononuclear Cells in Type 2 Diabetes Mellitus". *Tehran University of Medical Sciences*. XXX
17. Lo AH, Liang YC, Lin-Shiau SY, Ho CT, Lin JK. "Carnosol, an antioxidant in rosemary, suppresses inducible nitric oxid synthase through down-regulating nuclear factor-kappaB in mouse macrophages". *Carcinogenesis*. 2002 Jun;23(6):983-91.
18. Sanjeev Shukla, Eswar Shankar, Pingfu Fu, Gregory T. MacLennan, Sanjay Gupta. "Suppression of NF-kB and NF-kB-Regulated Gene Expression by Apigenin through IκBα and IKK Pathway in TRAMP Mice. *PLOS*. September 17, 2015.
19. Ma C, Wang Y, Dong L, Li M, Cai W. Anti-inflammatory effect of resveratrol through the suppression of NF-kB and JAK/STAT signaling pathways. *Acta Biochim Biophys Sin (Shanghai)*. 2015 Mar;47(3):207-13.
20. Wang J, Sun H, Fu Z, Liu M. Chondroprotective effects of alpha-lipoic acid in a rat model of osteoarthritis. *Free Radic Res*. 2016 Jul;50(7):767-80.

To place your order for **KappArest™**, or for additional information, please contact us below.



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