

Synergistic inhibition of NF-kappaB as an underlying scientific basis for phytonutritional supplementation and dietary modification:

a final common pathway to explain some of the clinical benefits of vitamin D, DHEA, resveratrol, curcumin, garlic, lipoic acid, Green tea extract, Ginger, Celery seed, Rosemary, Black pepper (for piperine), grape seed extract, N-acetyl cysteine, Resveratrol, Lipoic acid, soy isoflavones, the bee product propolis, and the so-called “alternative therapies” of dietary restriction and therapeutic fasting.

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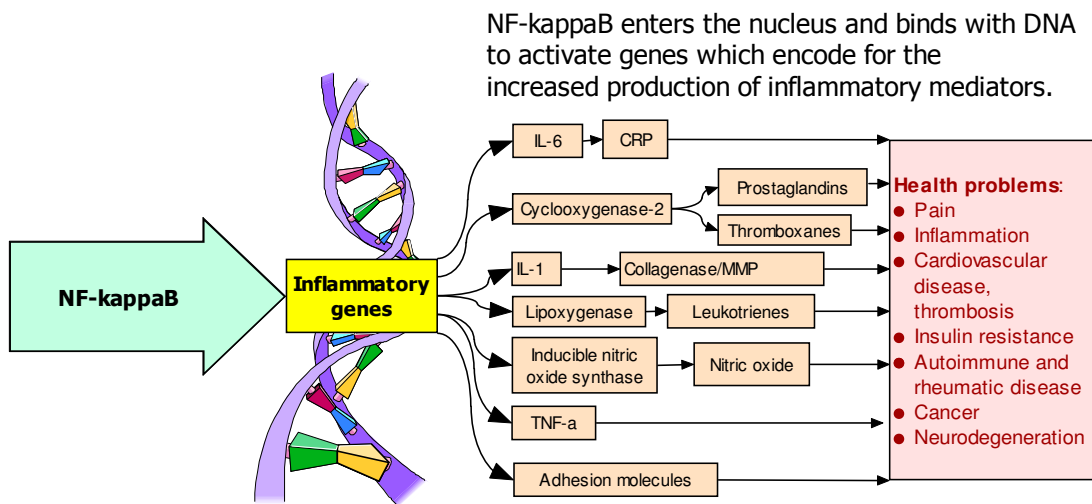
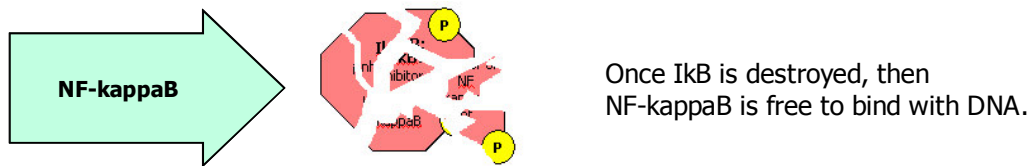
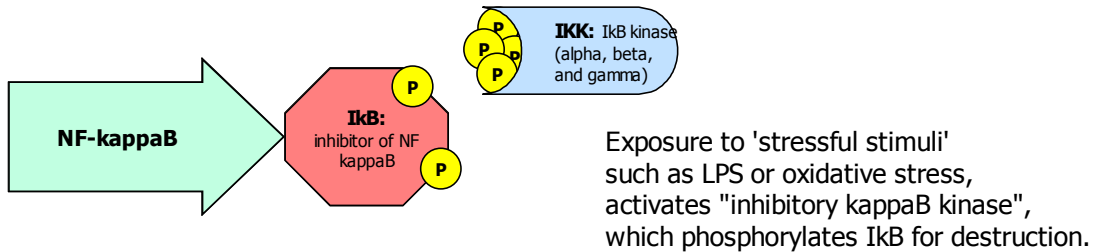
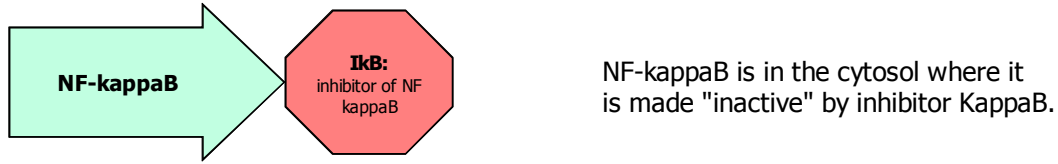
What doctors need to know:

1. NF-kappaB is a molecule inside each cell that becomes activated to stimulate the production of inflammatory chemicals that promote pain, inflammation, and variety of diseases such as cancer, arthritis, heart disease, and autoimmune diseases such as lupus and rheumatoid arthritis.
2. Inhibition of NF-kappaB is emerging as a primary clinical goal for the reduction of pain and inflammation.
3. Several natural products safely and effectively inhibit NF-kappaB, and they can be used in combination to help doctors attain improved outcomes in their patients.
4. **Clinical application of this research is simple:**
 - a. low-fat, low-sugar diet
 - b. daily use of
 - i. **Bio-D-Mulsion Forte**: 1-2 drops per day
 - ii. **KappArest**: 4 caps 2 times per day
 - iii. **Optimal EFAs**: 1-3 servings per day



These products work together to promote optimal health.

New research is showing that many disease conditions are associated with inappropriate activation of **nuclear transcription factor kappaB**, generally referred to as **NF-kappaB**. Inhibition of NF-kappaB is now a major therapeutic goal in the treatment and prevention of a wide range of illnesses, including cancer, arthritis, autoimmune diseases, and neurologic illnesses such as Alzheimer's and Parkinson's disease.¹



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Integrative Orthopedics

Increased production of inflammatory mediators - such as cytokines, prostaglandins, leukotrienes - promotes cellular dysfunction and tissue destruction.

¹ D'Acquisto F, May MJ, Ghosh S. Inhibition of Nuclear Factor Kappa B (NF- κ B): An Emerging Theme in Anti-Inflammatory Therapies. *Mol Interv.* 2002 Feb;2(1):22-35 <http://molinterv.aspetjournals.org/cgi/content/full/2/1/22>

Natural interventions that inhibit NF-kappaB

Bio-D-Mulsion Forte	Quote/example from the research literature
vitamin D	<ul style="list-style-type: none"> • “1Alpha,25-dihydroxyvitamin D3 (1,25-(OH)₂-D₃), the active metabolite of vitamin D, can inhibit NF-kappaB activity in human MRC-5 fibroblasts, targeting DNA binding of NF-kappaB but not translocation of its subunits p50 and p65.”² • “Thus, 1,25(OH)₂D₃ may negatively regulate IL-12 production by downregulation of NF-κB activation and binding to the p40-κB sequence.”³ • Clinical studies in patients with critical illness and multiple sclerosis have shown an anti-inflammatory benefit from vitamin D.

KappArest	Quote/example from the research literature
Turmeric-curcumin (requires piperine for absorption)	<ul style="list-style-type: none"> • “Curcumin, EGCG and resveratrol have been shown to suppress activation of NF-kappa B.”⁴
Lipoic acid	<ul style="list-style-type: none"> • “ALA reduced the TNF-alpha-stimulated ICAM-1 expression in a dose-dependent manner, to levels observed in unstimulated cells. Alpha-lipoic acid also reduced NF-kappaB activity in these cells in a dose-dependent manner.”⁵
Green tea extract	<ul style="list-style-type: none"> • “In conclusion, EGCG is an effective inhibitor of IKK activity. This may explain, at least in part, some of the reported anti-inflammatory and anticancer effects of green tea.”⁶
Rosemary	<ul style="list-style-type: none"> • “These results suggest that carnosol suppresses the NO production and iNOS gene expression by inhibiting NF-kappaB activation, and provide possible mechanisms for its anti-inflammatory and chemopreventive action.”⁷
Grape seed extract	<ul style="list-style-type: none"> • “Constitutive and TNFalpha-induced NF-kappaB DNA binding activity was inhibited by GSE at doses > or =50 microg/ml and treatments for > or =12 h.”⁸
Propolis	<ul style="list-style-type: none"> • “Caffeic acid phenethyl ester (CAPE) is an anti-inflammatory component of propolis (honeybee resin). CAPE is reportedly a specific inhibitor of nuclear factor-kappaB (NF-kappaB).”⁹
Resveratrol	<ul style="list-style-type: none"> • “Resveratrol's anticarcinogenic, anti-inflammatory, and growth-modulatory effects may thus be partially ascribed to the inhibition of activation of NF-kappaB and AP-1 and the associated kinases.”¹⁰ • “Both resveratrol and quercetin inhibited NF-kappaB-, AP-1- and CREB-dependent transcription to a greater extent than the glucocorticosteroid, dexamethasone.”¹¹
Phytolens (Biotics exclusive; patented)	<ul style="list-style-type: none"> • Phytolens is Biotics' patented polyphenolic extract from lentils. Published experimental research has documented the in vivo antioxidant activity against superoxide other free radicals.¹²

² Harant H, Wolff B, Lindley IJ. 1Alpha,25-dihydroxyvitamin D3 decreases DNA binding of nuclear factor-kappaB in human fibroblasts. *FEBS Lett.* 1998 Oct 9;436(3):329-34

³ D'Ambrosio D, Cipitelli M, Cocciolo MG, Mazzeo D, Di Lucia P, Lang R, Sinigaglia F, Panina-Bordignon P. Inhibition of IL-12 production by 1,25-dihydroxyvitamin D3. Involvement of NF-kappaB downregulation in transcriptional repression of the p40 gene. *J Clin Invest.* 1998 Jan 1;101(1):252-62

⁴ Surh YJ, Chun KS, Cha HH, Han SS, Keum YS, Park KK, Lee SS. Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: down-regulation of COX-2 and iNOS through suppression of NF-kappa B activation. *Mutat Res.* 2001 Sep 1;480-481:243-68

⁵ Lee HA, Hughes DA. Alpha-lipoic acid modulates NF-kappaB activity in human monocytic cells by direct interaction with DNA. *Exp Gerontol.* 2002 Jan-Mar;37(2-3):401-10

⁶ Yang F, Oz HS, Barve S, de Villiers WJ, McClain CJ, Varilek GW. The green tea polyphenol (-)-epigallocatechin-3-gallate blocks nuclear factor-kappa B activation by inhibiting I kappa B kinase activity in the intestinal epithelial cell line IEC-6. *Mol Pharmacol.* 2001 Sep;60(3):528-33

⁷ Lo AH, Liang YC, Lin-Shiau SY, Ho CT, Lin JK. Carnosol, an antioxidant in rosemary, suppresses inducible nitric oxide synthase through down-regulating nuclear factor-kappaB in mouse macrophages. *Carcinogenesis.* 2002 Jun;23(6):983-91

⁸ Dhanalakshmi S, Agarwal R, Agarwal C. Inhibition of NF-kappaB pathway in grape seed extract-induced apoptotic death of human prostate carcinoma DU145 cells. *Int J Oncol.* 2003 Sep;23(3):721-7

⁹ Fitzpatrick LR, Wang J, Le T. Caffeic acid phenethyl ester, an inhibitor of nuclear factor-kappaB, attenuates bacterial peptidoglycan polysaccharide-induced colitis in rats. *J Pharmacol Exp Ther.* 2001 Dec;299(3):915-20

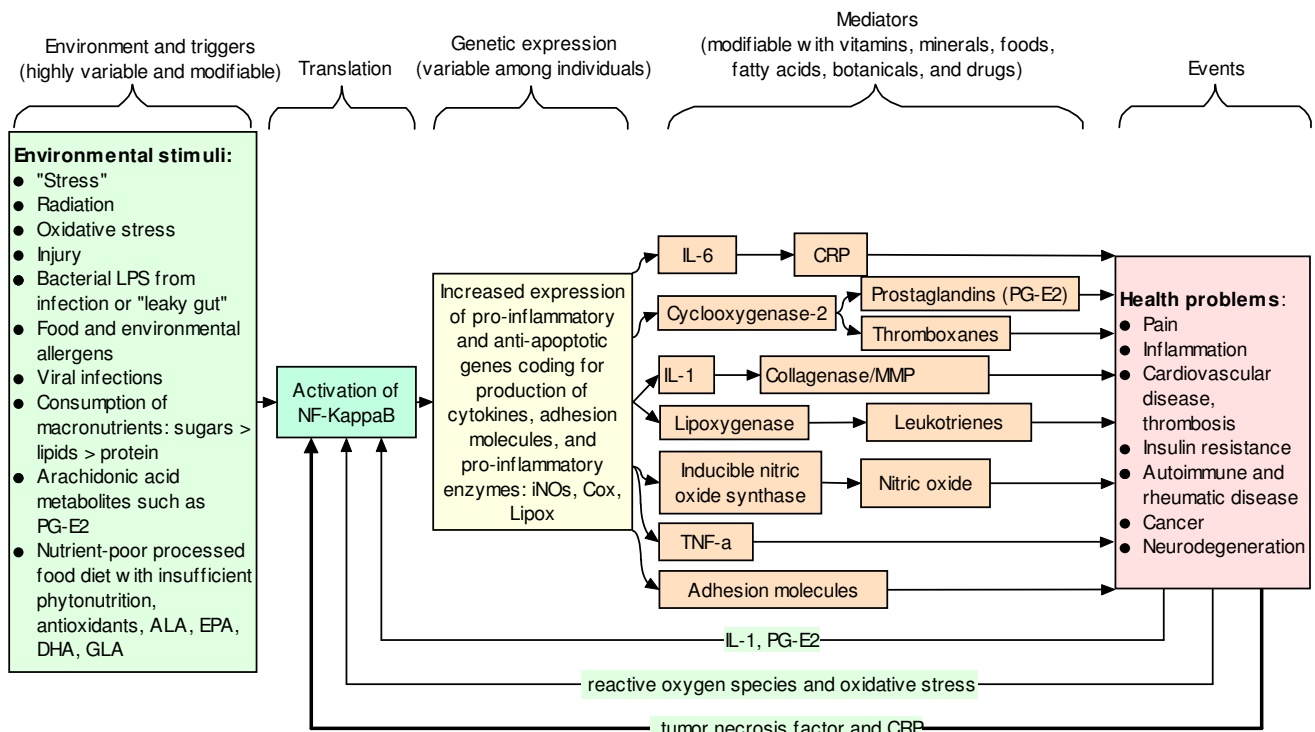
¹⁰ Manna SK, Mukhopadhyay A, Aggarwal BB. Resveratrol suppresses TNF-induced activation of nuclear transcription factors NF-kappa B, activator protein-1, and apoptosis: potential role of reactive oxygen intermediates and lipid peroxidation. *J Immunol.* 2000 Jun 15;164(12):6509-19

¹¹ Donnelly LE, Newton R, Kennedy GE, Fenwick PS, Leung RH, Ito K, Russell RE, Barnes PJ. Anti-inflammatory Effects of Resveratrol in Lung Epithelial Cells: Molecular Mechanisms. *Am J Physiol Lung Cell Mol Physiol.* 2004 Jun 4 [Epub ahead of print]

¹² Sandoval M, Ronzio RA, Muanza DN, Clark DA, Miller MJ. Peroxynitrite-induced apoptosis in epithelial (T84) and macrophage (RAW 264.7) cell lines: effect of legume-derived polyphenols (phytolens). *Nitric Oxide.* 1997;1(6):476-83

Optimal EFAs	Findings from the research literature
ALA	<ul style="list-style-type: none"> “CONCLUSIONS: Dietary supplementation with ALA for 3 months decreases significantly CRP, SAA and IL-6 levels in dyslipidaemic patients. This anti-inflammatory effect may provide a possible additional mechanism for the beneficial effect of plant n-3 polyunsaturated fatty acids in primary and secondary prevention of coronary artery disease.”¹³
EPA and DHA	<ul style="list-style-type: none"> Reduce the incidence and severity of cardiovascular disease, depression, sudden death, and joint pain and inflammation via their anti-inflammatory effects and through improvement of gene expression: “The recent GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)-Prevention study of 11,324 patients showed a 45% decrease in risk of sudden cardiac death and a 20% reduction in all-cause mortality in the group taking 850 mg/d of omega-3 fatty acids.”
GLA	<ul style="list-style-type: none"> Significant anticancer effect and anti-inflammatory benefit is well-proven: “GLA treatment is associated with clinical improvement in patients with RA, as evaluated by duration of morning stiffness, joint pain and swelling, and ability to reduce other medications.”^{14,15}

Inflammation is a destructive and self-perpetuating process.



Using these natural treatments *in combination* helps to safely reduce inflammation and the activity of NF-kappaB and thus promotes the restoration of homeostasis.

¹³ Rallidis LS, et al. Dietary alpha-linolenic acid decreases C-reactive protein, serum amyloid A and interleukin-6 in dyslipidaemic patients. *Atherosclerosis*. 2003 Apr;167(2):237-42

¹⁴ Rothman D, DeLuca P, Zurier RB. Botanical lipids: effects on inflammation, immune responses, and rheumatoid arthritis. *Semin Arthritis Rheum*. 1995 Oct;25(2):87-96

¹⁵ O'Keefe JH Jr, Harris WS. From Inuit to implementation: omega-3 fatty acids come of age. *Mayo Clin Proc*. 2000 Jun;75(6):607-14