

Kaprex®

Tetrase™-Based Softgels by Oral Administration. Dietary Supplement Dispensed by Healthcare Practitioner Recommendation.

(U.S. Patents 7,195,785 and 7,205,151.)

INDICATIONS AND USAGE

Kaprex is indicated for individuals with minor pain. Kaprex offers a safer approach and has been recommended for daily use with no serious adverse events reported.*

Established protein and genomic testing technologies and clinical evaluations demonstrate that Kaprex ingredients offer a high level of comparable efficacy with a leading competitor. These ingredients have been shown to be active in target tissues (e.g., joint) while exhibiting minimal activity in non-target tissues (e.g., gastrointestinal), making it an effective approach with a reduced risk of adverse events. It works by interfering with signals in the body that initiate the production of compounds that may negatively impact cartilage and other joint tissues.*

DESCRIPTION

Kaprex (in a dark, oblong softgel delivery form) is a dietary supplement formulated with a modified hops extract that has been demonstrated to modulate specific kinases associated with minor pain. Kinases function to chemically modify other proteins and help regulate eicosanoids (e.g., COX-2, PGE₂), cytokines (e.g., TNF-α), reactive oxygen species (nitric oxide), and other mediators (e.g., NF-κB) that may negatively impact the body both locally and systemically. Research suggests kinase modulation is an attractive approach to target the origins of minor pain.*¹⁻³

Kaprex effectively calms the body's eicosanoid cascade by modulating enzyme formation in cells associated with minor pain. It does so without directly blocking constitutive (housekeeping) cyclooxygenase (COX) enzyme activity, a mechanism known to cause adverse effects with long-term use in some individuals. Instead, Kaprex indirectly modulates induced COX-2 proteins activated in response to stimuli.*

Kaprex and its primary active ingredients have been the subjects of proprietary cell proteomic research, safety evaluations, human ex vivo research, and human clinical research to help determine efficacy, bioavailability, and predicted safety.[‡] Clinical experience and tolerance tests demonstrate Kaprex to be well-tolerated.*

Each softgel supplies:

A proprietary blend of: 350 mg

- Tetrase™ (tetrahydro-iso-alpha acids complex, from hops, *Humulus lupulus L.*)

- Oleonic Acid (from olive leaf extract, *Olea europaea*)
- Rosemary Leaf Extract (*Rosmarinus officinalis*)

Other Ingredients: Soybean oil, gelatin, glycerin, lecithin (soy), water, beeswax, and sodium copper chlorophyllin. Contains: soy.

Formulated to Exclude: Wheat, gluten, yeast, dairy products, nuts, tree nuts, fish, shellfish, or artificial colors, sweeteners, or preservatives.[†]

Structure of Tetrase

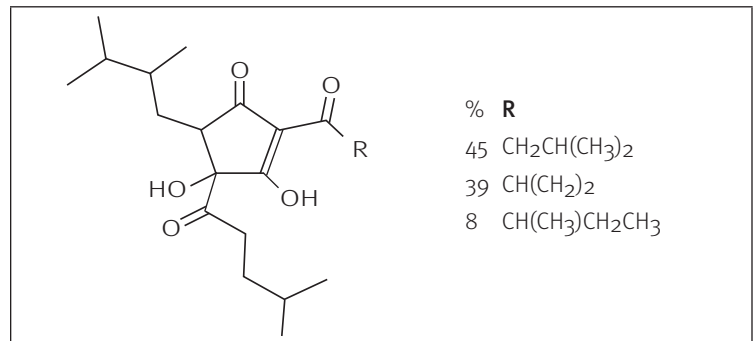


Figure 1. Chemical structures of substituted 1, 3-cyclopentadiones present in Tetrase.¹

FORMULA MECHANISM OF ACTION

Selective kinase modulation

Unlike other approaches, Kaprex addresses the eicosanoid cascade upstream from COX-2 activity—specifically modulating kinases that influence signal transduction in the NF-κB pathway. NF-κB plays a critical role in the regulation of the eicosanoid cascade by activating transcription of genes, enzymes, and cytokines, including COX-2, TNF-α, and nitric oxide. Modulating kinases associated with the NF-κB signaling pathway has been demonstrated to provide tissue specificity for an effective but safer approach.*¹⁻³

In vitro research with Tetrase, the key active ingredient in Kaprex (see “KEY INGREDIENT MECHANISM OF ACTION”), demonstrated the following:*^{1,4}

- Modulation of kinases in NF-κB pathway—including BTK, SyK, BMX, PI3K (α,β,δ), PDK1, PKB (α,β,δ), GSK3 (α,β,δ), IRAK (-1,-4), TAB-1, TAK-1, and IKK (α,β)
- Inhibition of NF-κB activation (Figure 2) and related downstream events:
 - Luciferase activity
 - TNF-α activation
 - Nitric oxide production
 - COX-2 protein expression (Figure 3)
 - PGE₂ production (Figure 4)
- Minimal effect on constitutive COX-2 and PGE₂ biosynthesis (Figure 5) associated with housekeeping functions (also see “SAFETY EVALUATIONS”)

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Human clinical research demonstrates Tetrase bioavailability in plasma (see “BIOAVAILABILITY”). And related ex vivo PBMC data suggests that Tetrase concentration in the blood could effectively relieve minor pain based on inhibition of lipopolysaccharide (LPS)-stimulated IL-6 and TNF- α production in a dose-dependent manner. Researchers noted that these results can be directly correlated with LPS-stimulated macrophage tests and several in vitro kinase assays.¹

KEY INGREDIENT MECHANISM OF ACTION

Tetrase (THIAA)

Selective kinase response modulators (SKRMs)

Hop extracts have been suggested by earlier third-party in vitro and animal research to inhibit COX-2 protein induction at or prior to the step of transcription.^{5,6} Proprietary in vitro and ex vivo research demonstrates that iso-alpha acid derivatives from hops such as tetrahydro iso-alpha acids (THIAA) act as SKRMs to favorably modulate important kinases associated with cascade proliferation that can lead to minor pain.^{1,4,7-20}

*May support maintenance of cartilage**

Preliminary in vitro and animal research suggests that Tetrase may support maintenance of cartilage and joints, differentiating it from certain conventional approaches.^{*4} (Figure 6)

Oleanolic Acid

*Promotes healthy eicosanoid balance**

Oleanolic acid is an isomer of ursolic acid. Both triterpenoids have been the subject of over 700 research articles, including toxicity studies and clinical use.²¹ Natural ursolic acid has been shown in cell research to favorably modulate eicosanoid (e.g., PGE₂) synthesis.²² In vivo research with natural oleanolic acid has demonstrated a marked improvement in adjuvant-induced cascade response in animals.^{*23}

Rosemary Extract

*Promotes inhibition of NF- κ B, COX-2, and nitric oxide**

In vitro studies demonstrate that rosemary constituents inhibit NF- κ B activation and associated nitric oxide production through its effects on kinase pathways.²⁴⁻²⁶ Additional cell research with a rosemary extract suggests this same kinase pathway modulation was responsible for a reduction of induced COX-2 activity.^{*27}

Bioavailability

Oral supplementation in human subjects showed that Tetrase is bioavailable (up to 10 μ g/ml) in the serum. Tetrase was detected in the plasma of 4 human subjects within 1 h following a single oral dose of 940 mg; peak levels were observed in 3 of the 4 subjects at 4 h. While inter-subject variability was evident, C_{max} ranged from 4–15 μ g/ml and T_{max} from 2–4 h (Figure 7). In the absence of data from systemic administration of Tetrase, it was not possible to determine the absolute bioavailability, but the area-under-the-curve (AUC_{0–8 h}) ranged from 15–98 μ g h/ml when normalized to a dose of 10 mg/kg.^{1,4}

SAFETY EVALUATIONS

Constitutive PGE₂ and COX-2 Biosynthesis

Constitutive COX enzymes (1 & 2) and PGE₂ are vital to important housekeeping functions in the body—maintaining healthy blood pressure, renal flow, and gastrointestinal (GI) cellular maintenance and health. No significant effect on constitutive PGE₂ or COX-2 enzyme synthesis was observed through in vitro and ex vivo research with iso-alpha acids or a combination of iso-alpha acids, oleanic acid, and rosemary extract. This suggests a higher degree of predicted safety.^{*7-12}

Blood Pressure (BP)

Clinical testing with a combination of iso-alpha acids, oleanic acid, and rosemary extract demonstrated no significant effect on systolic or diastolic BP in 50 human subjects over 8 weeks. A second randomized, placebo-controlled trial of 32 subjects lasting 6 weeks yielded similar results.⁸ Pooled data from these independent trials was examined to determine effects on hypertensive subjects; no significant difference was observed in systolic or diastolic BP.^{*7,9}

Kidney & Liver Function

No measurable effect in kidney function markers or electrolytes was observed in 2 short-term clinical studies (total n=82, see “Blood Pressure”) with a combination of iso-alpha acids, oleanic acid, and rosemary extract. These studies also showed that markers of liver function remained within reference ranges.^{*8,9}

Cardiovascular Homeostasis: Urinary Prostanoid Excretion

Urinary prostanoid excretion of PGI₂ (vasodilator) and TXA₂ (vasoconstrictor) are indicators of cardiovascular homeostasis, though neither is stable for detection. Instead, levels of PGI-M and TXB₂ were measured in two clinical studies (total n=8) with urine samples collected over 8 h in a comparison study that included administration of an iso-alpha acids/rosemary/oleanolic acid combination. Results were combined for analysis, which showed no significant increase in either biomarker with the nutritional supplement. Another approach, however, yielded a decrease in PGI-M (indicating a negative influence) and was in agreement with the suggestions of third-party research.^{*7,9}

Gastrointestinal Homeostasis: Fecal Calprotectin

Some approaches can significantly increase fecal calprotectin, which has been shown to be a reliable biomarker of adverse influence on the intestinal lining. Tetrase supplementation in human subjects (n=11) did not increase fecal calprotectin, a protein secreted by the GI immune system as a consequence of the cascade response.⁴ Two additional clinical studies with iso-alpha acids (total n=9) also displayed no significant effect on fecal calprotectin.⁷ A larger, 2-week, randomized, crossover study of 21 subjects that were administered an iso-alpha acids/rosemary extract/oleanolic acid combination demonstrated no significant changes in fecal calprotectin.^{9,13-14} Separately, 8 subjects taking an iso-alpha acids/rosemary/oleanolic acid combination (along with other medications and/or nutritional supplements)

Inhibition of NF- κ B

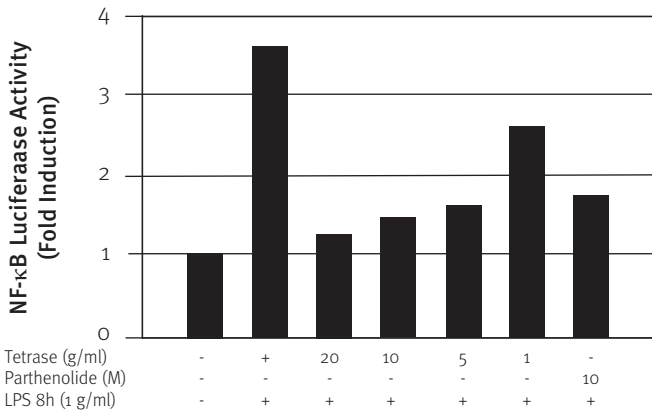


Figure 2. Cells were transiently transfected with NF- κ B firefly luciferase construct for 2 days followed by 1 h pre-incubation with test compounds and 8 h LPS (1 μ g/ml) stimulation. NF- κ B luciferase activity was normalized with constitutively expressed Renilla luciferase. Data representative (mean \pm SEM) from 3 experiments. * $p < 0.05$ compared with LPS stimulation.¹

Minimal Effect on Constitutive PGE₂

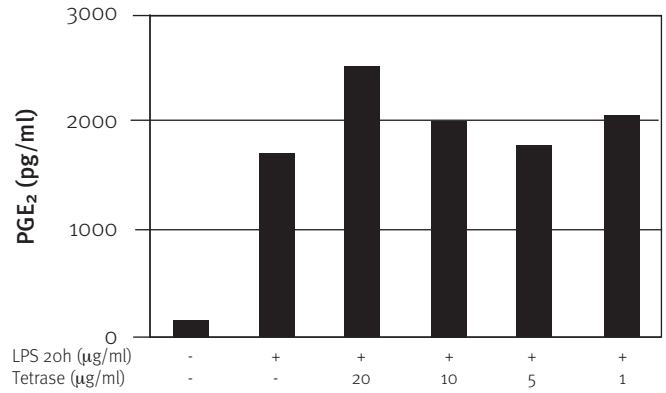


Figure 5. To evaluate the effect on constitutive (housekeeping) COX-2 activity, cells were LPS-stimulated for 20 h, followed by 1 h incubation with test compound. After PBS wash, compounds with LPS were added and incubated for 1 h and PGE₂ (produced by induced COX-2 activity) in the medium was determined.¹

Inhibition of Induced COX-2

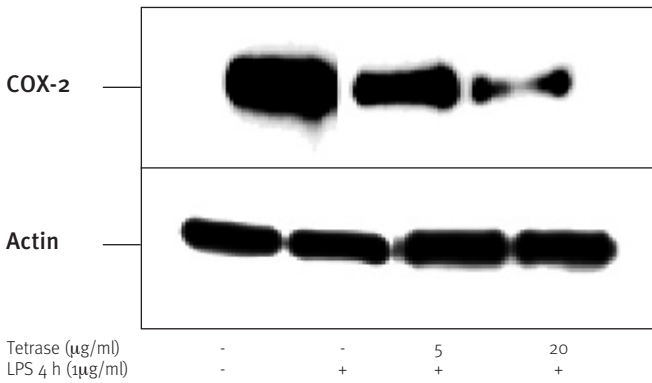


Figure 3. Cells were pre-incubated with 1-20 μ g/ml Tetrase for 1 h and stimulated with LPS for 16 h for measurement of COX-2 with western blot.¹

Cartilage Maintenance

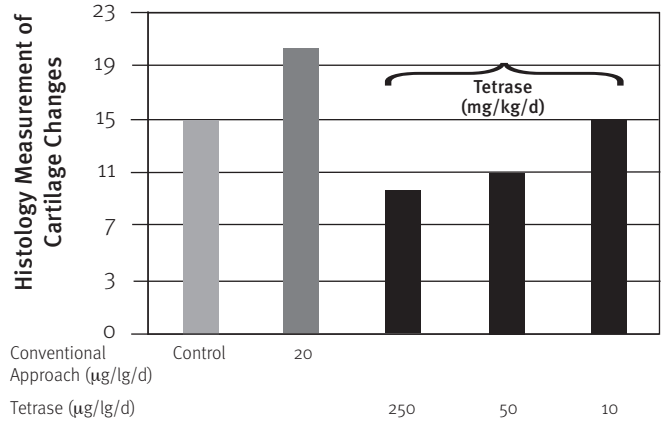


Figure 6. In a mouse model, Tetrase was shown to promote maintenance of cartilage better than a leading conventional approach.⁴⁴

Inhibition of Induced PGE₂

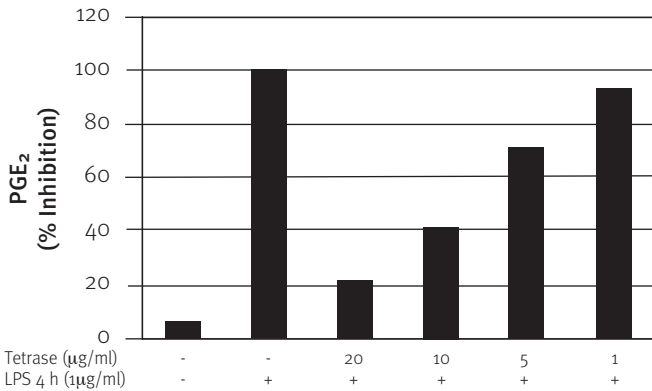


Figure 4. Cells were pre-incubated with 1-20 μ g/ml Tetrase for 1 h and stimulated with LPS for 4 h for measurement of PGE₂.¹

Bioavailability

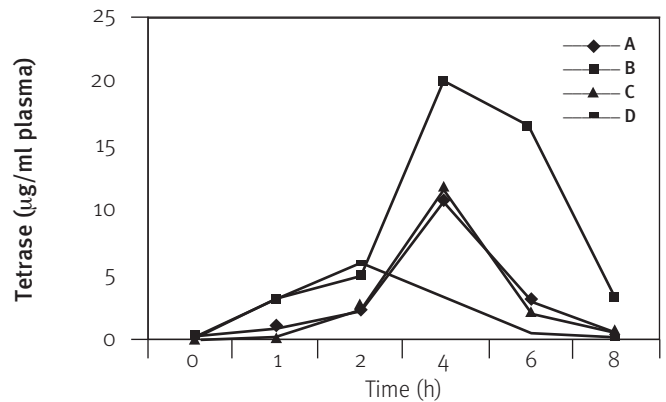


Figure 7. After oral administration of 940 mg Tetrase by 4 healthy human volunteers, plasma was measured over an 8 h period. Peak levels were observed in 3 of the 4 subjects at 4 h.¹

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were followed by a healthcare practitioner for 3 years at the Functional Medicine Research Center[†]; samples at random intervals also showed no significant changes in fecal calprotectin levels.*⁹

Platelet Function

No direct effect on platelet function, coagulation, or complete blood counts was observed in 2 clinical studies (total n=82, see “Blood Pressure”) with a combination of iso-alpha acids, oleanic acid, and rosemary extract.*^{8-9,11}

CAUTIONS

General

Patients with a hypersensitivity to ingredients in Kaprex should avoid use.

Pregnancy and Nursing

Due to a lack of testing in these individuals, Kaprex is not recommended for pregnant or nursing women.

Children

This product is not recommended for use in children.

ADVERSE REACTIONS

No serious adverse events reported as of April 2009.

POTENTIAL DRUG/NUTRIENT INTERACTIONS

Anti-Coagulants (Warfarin, Heparin)

Theoretically, concomitant use with anticoagulants can cause addictive therapeutic and potential adverse effects.

STORAGE: Keep tightly closed in a cool, dry place.

DOSAGE AND ADMINISTRATION: One softgel with food two times daily or as directed.

HOW SUPPLIED: 20 and 60 Softgel Bottles

REFERENCES

1. Desai A, Hall A, Konda VR, Darland G, et al. METo60 inhibits multiple kinases in the NF- κ B pathway and suppresses LPS-mediated inflammation in vitro and ex vivo. *Inflamm Res*. 2009;58:1-6.
2. Pine PR, Chang B, Schoettler N, et al. Inflammation and bone erosion are suppressed in models of rheumatoid arthritis following treatment with a novel Syk inhibitor. *Clin Immunol*. 2007;124(3):244-257.
3. Wong BR, Grossbard EB, Payan DG, Masuda ES. Targeting syk as a treatment for allergic and autoimmune disorders. *Expert Opin Investig Drugs*. 2004;13(7):743-762.
4. Konda VR, Darland G, Desai A, et al. 1, 3-cyclopentadienes with a history of safe use in humans are selective multi-target protein kinase inhibitors with anti-inflammatory efficacy in vitro and in vivo. *Proprietary Clinical Research Report*. Gig Harbor, WA: Functional Medicine Research Center; 2008.
5. Yamamoto K, Wang J, Yamamoto S, et al. Suppression of cyclooxygenase-2 gene transcription by humulon of beer hop extract studied with reference to glucocorticoid. *FEBS Lett*. 2000;465:103-106.

6. Lee JC, Kundu JK, Hwang DM, Na HK, Surh YJ. Humulone inhibits phorbol ester-induced COX-2 expression in mouse skin by blocking activation of NF-kappaB and AP-1: IkappaB kinase and c-Jun-N-terminal kinase as respective upstream targets. *Carcinogenesis*. 2007;28(7):1491-1498.
7. Hall A, Babish JG, Darland GK, et al. Safety, efficacy and anti-inflammatory activity of rho iso-alpha-acids from hops. *Phytochemistry*. 2008;69(7):1534-1547.
8. Liska D, Darland G, Tripp M. *Proprietary Clinical Research Report*. Gig Harbor, WA: Functional Medicine Research Center; 2004.
9. Minich DM, Bland JS, Katke J, et al. Clinical safety and efficacy of NG440: a novel combination of rho iso-alpha acids from hops, rosemary, and oleanolic acid for inflammatory conditions. *Can J Physiol Pharmacol*. 2007;85:872-883.
10. Tripp M, Babish J, Darland G, et al. Hop and modified hop extracts have potent in vitro anti-inflammatory properties. Published Proceedings from 1st International Symposium on Humulus. Editors K.E. Hummer and J.A. Henning *Acta Horticulturae* 668, ISHS 2005.
11. Tripp M, Darland G, Lerman RH, et al. Development of Metao50, a natural anti-inflammatory targeting inhibition of cyclooxygenase gene induction instead of direct cyclooxygenase enzyme inhibition, resulting in an anti-inflammatory with low-predicted GI toxicity. Presented at: *Fed Am Soc Experimental Biol*. 2003; April.
12. Lerman RH, Babish J, Lucakzer D, et al. Ex vivo clinical study of the anti-inflammatory activity of a proprietary synergistic blend of hops extract, rosemary, and oleanolic acid. Presented at: *Fed Am Soc Experimental Biol*. 2003; April.
13. Lukaczer D, Lerman RH, Tripp M, et al. A randomized cross-over study to assess the effects of a proprietary reduced iso-alpha acid (RIAA), rosemary extract, and oleanolic acid supplement on gastrointestinal integrity using the fecal calprotectin assay. *Proprietary Clinical Research Report*. Gig Harbor, WA: Functional Medicine Research Center; 2004.
14. Liska DJ, Tripp M, Lukaczer D, et al. Randomized cross-over study of RIAA, rosemary extract, and oleanic acid on gastrointestinal integrity using fecal calprotectin. Presented at: *Fed Am Soc Experimental Biol*. 2005; April.
15. Konda VR, et al. Unpublished results. MetaProteomics, Inc.
16. Lukaczer D, Lerman RH, Darland G, et al. Effects of a reduced iso-alpha acids (RIAA), rosemary extract, and oleanolic acid supplement on pain in subjects with osteoarthritis (OA). *Proprietary Clinical Research Report*. Gig Harbor, WA: Functional Medicine Research Center; 2004.
17. Lerman RH, Liska D, Tripp M, et al. Summary of effects of a reduced iso-alpha acids (RIAA), rosemary extract, and oleanolic acid supplement on parameters of cardiovascular health. *Proprietary Clinical Research Report*. Gig Harbor, WA: Functional Medicine Research Center; 2008.
18. Lerman RH, Liska D, Tripp M, et al. Clinical trial evaluating the effect of Metao50 on parameters of platelet function and blood coagulation. *Proprietary Clinical Research Report*. Gig Harbor, WA: Functional Medicine Research Center; 2004.
19. Lucakzer D, Lerman RH, Darland G, et al. Benefits of a proprietary reduced iso-alpha acids (hops), rosemary extract, and oleanolic acid supplement on pain in patients with osteoarthritis. Presented at: *Fed Am Soc Experimental Biol*. 2004; April.20. Hall AJ, Tripp M, Howell T, Darland G, Bland JS, Babish JG. Gastric mucosal call model for estimating relative gastrointestinal toxicity of non-steroidal anti-inflammatory drugs. *Prostaglandins Leukot Essent Fatty Acids*. 2006;57:9-16.
21. Liu J. Oleanic acid and ursolic acid: research perspectives. *J Ethnopharmacol*. 2005;100(1-2):92-94.
22. Najid A, Simon A, Cook J, et al. Characterization of ursolic acid as a lipoxygenase and cyclooxygenase inhibitor using macrophages, platelets, and differentiated HL60 leukemic cells. *FEBS Lett*. 1992;299(3):213-217.
23. Kapil A, Sharma S. Effect of oleanolic acid on complement in adjuvant- and carrageenan-induced inflammation in rats. *J Pharm Pharmacol*. 1995;47(7):585-587.
24. Huang SC, Ho CT, Lin-Shiau SY, Lin JK. Carnosol inhibits the invasion of B16/F10 mouse melanoma cells by suppressing metalloproteinase-9 through down-regulating nuclear factor-kappa B and c-Jun. *Biochem Pharmacol*. 2005;69(2):221-232.
25. 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;23(6):983-991.
26. Ai-Hsiang Lo, Yu-Chih L, Shoei-Yn L, et al. Carnosol, an antioxidant in rosemary, suppresses inducible nitric oxide synthase through down regulation of nuclear factor κ B in mouse macrophage. *Carcinogenesis*. 2002;23(6):983-991.
27. Schechel KA, Degner SC, Romagnolo DF. Rosmarinic acid antagonizes activator protein-1-dependent activation of cyclooxygenase-2 expression in human cancer and nonmalignant cell lines. *J Nutr*. 2008;138(11):2098-2105.

[†] This product is manufactured in a facility that produces products containing soy, dairy, nuts, tree nuts, fish, and shellfish.

[‡] At MetaProteomics, Inc. and the Functional Medicine Research CenterSM, the research arms of Metagenics, Inc.



Kaprex is part of a select group of novel formulations that set a new standard of clinical certainty in natural products by demonstrating efficacy, bioavailability, and a high level of predicted safety.*

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Metagenics is committed to using only environmentally-friendly papers and inks.

