

**Anti-catabolic/Healing** (surgery, injury, aging and overtraining)  
**Pain-Relief** (chronic and acute)

### Indications

Significant antioxidant and anti-catabolic benefits indicate Recovery<sup>®</sup> may be used to reduce spasm and pain and improve rate and quality of post-trauma recovery.

age-related decline, breathing issues, digestive issues, hoof health, pain (back, hock, leg, neck, stifle, etc.), skin and coat issues, trauma rehabilitation, wound healing

The ability to decrease catabolism of cell structures associated with trauma and degenerative disease is what gives Recovery<sup>®</sup> a potentially broad-spectrum indication profile. Results observed by clinicians over the last 10 years warrant further research for the treatment of chronic skin, respiratory, gastrointestinal and "autoimmune" issues.

### Pathophysiology

#### Trauma, Catabolism and "Dis-ease"

When oxygen is utilized by the body, destructive "exhaust" called reactive oxygen species (ROS) result. ROS include hydroxyl radicals, superoxides, hypochlorite and hydrogen peroxide, etc. Minimal amounts of ROS, play necessary roles in metabolism; whereas, when ROS production increases and the cell's ability to neutralize ROS decreases, tissues are damaged (aging and "dis-ease"). (1-4)

Increased production of ROS is linked to damage, spasm, inflammation, pain and loss of physiological function throughout the body. (5-7)

ROS react with cells initiating chain reactions that result in tissue damage causing inflammation, spasm, pain and disease. (1, 3)

Antioxidants, such as Coenzyme Q10, alpha lipoic acid and NADH (nicotinamide adenine dinucleotide) and anti-catabolic enzymes, such as glutathione peroxidase, superoxide dismutase and catalase minimize the damage due to ROS. Younger healthy cells produce larger quantities of protective substances. (3, 5)

Aging and disease result in diminished cell production of protective compounds leading to increased damage to cell membranes; inevitably, damage to membranes diminishes cellular ability to repair damaged tissue. (1, 7)

Membrane and extra-cellular matrix damage leads to decreased ideal first-intention healing involving parenchyma. (8-10)

#### Cell damage leads to:

##### 1. Dehydration and Loss of Cell Function

Decreased long chain glycosaminoglycans (GAG's) with an increase in shorter chain GAG's, leads to tissue dehydration and loss of membrane function (9, 11, 12)

##### 2. Loss of Membrane Receptivity to Growth Factors

Cell membrane desensitization to growth factors (somatomedins, insulin, etc.) necessary for cell repair, maintenance, protection and communication (13-15, 41)

##### 3. Sclerosing of Tissue

Deposition of heavily glycosylated, compact & inflexible collagen V & VI (12, 16-22)

##### 4. Compromised Ability to Heal

Increased granulomatous second intention healing involving stromal elements (i.e. development of scar tissue) resulting in loss of cell/tissue function (9, 42)

#### Consequences:

Loss of cell and tissue function results in further inability to repair damage, leading to increased tendency to bruising, excessive inflammation, spasm, joint stiffness, digestive abnormalities and respiratory distress. (7, 9, 15, 20, 21, 23, 24)

\* Insulin shuttles amino acids, glucose, fatty acids, glucosamine and other precursors into the cell so that the cell may synthesize required structures for tissue repair.

### Mechanism of Action

Recovery<sup>®</sup> is designed to halt damage & pain at the "root". (43, 44)

Nutricol<sup>®</sup>, a potent proprietary bioflavonoid complex containing EGCG, proanthocyanidins, theaflavin and resveratrol from grapes and tea, is the primary active ingredient in Recovery<sup>®</sup>.

Nutricol<sup>®</sup> reinforces membrane and matrix structure (helps to halt damage that initiates inflammatory and spasmodic reactions) (26, 27, 31, 45, 46)

Nutricol<sup>®</sup> increases membrane receptivity to hormones such as insulin, IGF and thyroxine (required for anabolic repair/healing) (13, 14)

#### Site of Action

Nutricol<sup>®</sup> embeds in the cell membrane and matrix. (43, 44, 48)

#### Mechanism of Action

The significant water and fat soluble antioxidant actions of Nutricol<sup>®</sup> produce the following anti-catabolic and inflammation-modulating effects:

1. Stabilize collagen aldimine reducible cross-links to reinforce the strength and elasticity of connective tissues such as cartilage, synovium, ligaments, tendons, fascia, bone, blood vessel walls and the dermis of the skin.
2. Neutralize ROS and catabolic enzymes decreasing their negative impact on cellular and extra-cellular structure and function; this improves membrane receptivity to growth factors such as insulin, somatomedins and thyroxine required for anabolic repair and cell maintenance (4, 10, 13, 28-30, 35, 49)
3. Decrease excess production of catabolic substances such as collagenase, elastase, hyaluronidase, TNF, NOS and xanthine oxidase\*; these substances are released from immune, microbial and damaged cells and cause damage to connective and epithelial tissue, resulting in joint pain, inflammation, capillary fragility and other soft-tissue damage (4, 25, 31-35)
4. Prevent the release of inflammation promoters such as histamine, serine proteases, prostaglandins and leukotrienes by non-competitively inhibiting the release of the pro-inflammatory enzymes cyclo-oxygenase, lipoxygenase and phosphodiesterase (33, 36)
5. Improve protective epithelial mucosal surface integrity (digestive, respiratory & genitourinary tract) (37-40)

\*Xanthine oxidase - enzyme that produces ROS. (4, 50)

### Ingredients Recovery<sup>®</sup> EQ-Extra Strength

Nutricol <sup>®</sup>	1,000mg
methyl sulfonyl methane	10,000mg
glucosamine hydrochloride (vegan-source)	10,000mg
trimethylglycine (TMG)	1,000mg
vitamin C	1,400mg
magnesium (elemental)	525mg
vitamin E (natural d-alpha tocopheryl)	750iu
hyaluronic acid (vegan-source)	100mg

\*serving = 1 scoop/26 grams/1 oz/2 tablespoons

### Dosage and Administration

#### Suggested use:

Introduce gradually over a two week period to a concentrated dose of ½ scoop per 300 lbs body weight. Mix with food. After 30 - 60 days it may be possible to reduce intake to ¼ scoop per 300lbs body weight.

\*Increasing the dose too rapidly may result in temporary loose stool, fatigue and hypersensitivity at previous trauma sites.

## Summary

By implementing Recovery<sup>®</sup> (a Biostructural<sup>®</sup> Medicine), health care professionals can safely modulate inflammatory conditions, prevent tissue damage and improve the quality and rate of healing.

Recovery<sup>®</sup> is believed to decrease trauma (from disease, surgery and injury) by increasing membrane receptivity to growth factors and stabilizing cell structures.

We believe Recovery<sup>®</sup> should be used to halt damage and pain and promote healing.

## Safely Combining with Drugs

Due to its antioxidant, inflammation-modulating and anti-catabolic action, combining Recovery<sup>®</sup> with drugs can lead to reduced drug toxicity and side effects:

### Anti-inflammatory (NSAIDs/cox-2 inhibitors)

Most conventional NSAIDs interfere with cyclo-oxygenase and prostaglandins. Cell damage still continues because:

1. Oxidation of membranes remains unblocked
2. With standard NSAIDs, the production of PG1 and PG3, normally involved in repair, are also blocked

Recovery<sup>®</sup> benefits alone or combined with NSAIDs include:

1. Inhibiting the inflammatory cascade or "domino effect" by increasing a cell's ability to neutralize lysosomal enzymes and ROS released from neighboring damaged cells - reducing trauma.
2. Increasing delivery of certain hormones, neurochemicals and nutrients into the cell and enhancing waste transport out of the cell - improving cell communication.

Studies demonstrate that the addition of Recovery<sup>®</sup> ingredients with Sulindac (NSAID) results in a reduction in GI side-effects that accompany Sulindac usage (Ohishi et al. Cancer Lett 2002, 177(1):49-56)

### Corticosteroids

Corticosteroids mimic cortisol, which reduces inflammation; however, corticosteroids inhibit immune response and ability to repair, predisposing individuals to risk of infection and accelerated rate of tissue breakdown.

Excessive levels of nitric oxide synthase (NOS), an enzyme that produces nitric oxide, are involved in the initiation and progression of cancer and inflammation. Studies have shown higher levels of nitric oxide in various inflammatory bowel diseases, and that corticosteroids have no effect on reducing NOS. (N Leonard, et. al. J. Clin. Pathology: 1998, 51: (10) 750-753)

Recovery<sup>®</sup> may compliment corticosteroids as it can normalize levels of NOS (Yu-Li Lin et.al. Molecular Pharm: 1997 (52):465-472).

### Acetaminophen

Recovery<sup>®</sup> ingredients reduce acetaminophen-induced kidney and liver toxicity (Res Commun Mol Pathol Pharmacol 2000; 107(1-2):137-66), (Ray S.D., Arch Biochem Biophys 1999 Sep 1; 369(1):42-58).

Many cases have demonstrated Recovery<sup>®</sup> may be superior to acetaminophen for chronic pain relief. Recovery<sup>®</sup> decreases the need for acetaminophen

### Antibiotics

2 studies report anti-bacterial action was enhanced when Recovery<sup>®</sup> ingredients were combined with ampicillin/sulbactam, benzylpenicillin, oxacillin, methacillin, cephalixin (Journal of Antimicrobial Chemotherapy, 2001, (48), 361-364), (Antimicrobial Agents and Chemotherapy, 2001, 45, (6), 1737-1742).

### Anti-coagulants

Since 1998, there have been observations with several patients on warfarin and Recovery<sup>®</sup>. There were no changes in prothrombin time reported, nor any signs of increased bleeding. Recovery<sup>®</sup> may have anti-platelet activity related to normalizing excessive platelet adhesiveness. (Kang WS., Thromb Res 1999 Nov 1; 96(3):229-37)

### Amiodarone, Doxorubicin, Idarubicin, 4-HC

The ingredients in Recovery<sup>®</sup> reduce organ and serum toxicity induced by these drugs (Bagchi D., Drugs Exp Clin Res 2001; 27(1): 3-15), (Res Commun Mol Pathol Pharmacol 2000; 107(1-2): 137-66)

## Safety Data

Recovery<sup>®</sup> has significant benefits with very low risk. All Recovery<sup>®</sup> ingredients are naturally-occurring and non-toxic.

Nutricol<sup>®</sup> constituents have been clinically observed to possess health-promoting properties in the liver, lung, breast, pancreas, bladder, prostate, skin and most of the gastrointestinal system (Fujiki. (1999) J. Cancer Res Clin Oncol.125:589-97).

### Effects on Liver Function

Due to anti-catabolic and anti-oxidative actions, Recovery<sup>®</sup> may aid in the proper elimination and metabolism of drugs and other toxins by supporting 4 Phase II liver pathways (glutathione conjugation, taurine conjugation, methylation, and sulfation).

## Drug and Food Interactions

Mixing Nutricol<sup>®</sup> with dairy inhibits absorption.

## Side effects and precautions

Recovery<sup>®</sup> contains hypoallergenic ingredients; however, the introduction of any new food or drug may result in an allergy.

## Toxicology Data

### Nutricol<sup>®</sup>

#### EGCG (epigallocatechin gallate)

The LD50 in male rats is greater than 5g/kg and 3g/kg in female rats. The rats were Sprague-Dawley rats (Yamane et al. (1995) Cancer 7:1662-7). Found to be non-toxic for Rodents and Humans (Fujiki et al. 1998).

#### Procyanidolic oligomers, resveratrol

The LD50\* found to be greater than 5g/kg body weight in a single oral intubation to fasted male and female albino rats. (Bagchi et al. (2000) Toxicology 148:87-197)

### Glucosamine (2-amino-2-deoxy-alpha-D-glucose)

No mortalities in mice or rats at very high levels. LD50 is greater than 5g/kg of body weight orally. (Pharmatherapeutica 1982; 3(3):157-68) Theoretically, long-term use of very high-doses of glucosamine may result in hyperglycemia.

\*Recovery<sup>®</sup> has demonstrated blood sugar regulating effects. Nutricol<sup>®</sup> increases membrane insulin sensitivity. Recovery<sup>®</sup> is safe to administer to stable Type II diabetics.

### MSM (methyl sulfonyl methane)

MSM has very low toxicity, with an LD50 in rats that exceeds 20g/kg body weight per day. In dogs, no toxicity was reported in a 30-day test receiving 3g/kg body weight per day, administered both orally and intravenously. There was a drop in hematocrit in the later stages of the high dose intravenous study that returned to normal post-treatment. (Metcalf, J.W. (1986) MSM status report, Eq. Vet. Data 7:332-334).

### TMG (trimethylglycine)

Safety studies show TMG to be very safe, with an acute LD50 in rats of over 11,000 mg/kg body weight. (Life Science Research 1990).

### Disclaimer

Administering natural products should be a decision based on personal research and understanding of the role food-derived components play in health and wellbeing.

The information contained within this document is for informational purposes only and is not intended as a substitute for advice from a veterinarian or other health care professional, and should not be used for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. A health care professional should be consulted before starting any diet, exercise or supplementation program, before administering any medication, or if you suspect a health problem. Do not discontinue any other medical treatments without first consulting a veterinarian.

## Clinical References

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## Bioflavonoids & Osteoarthritis

Singh R, Ahmed S, Malemud CJ, Goldberg VM, Haqqi TM, J Orthop Res 2003 Jan;21(1):102-9 **Epigallocatechin-3-gallate selectively inhibits interleukin-1beta-induced activation of mitogen activated protein kinase subgroup c-jun N-terminal kinase in human osteoarthritis chondrocytes.**

Activation of mitogen activated protein kinases (MAPK) is a critical event in pro-inflammatory cytokine-induced signalling cascade in synoviocytes and chondrocytes that lead to the production of several mediators of cartilage damage in an arthritic joint. Green tea (*Camellia sinensis*) is a widely consumed beverage and we earlier showed that polyphenols present in green tea (GTP) inhibit the development of inflammation and cartilage damage in an animal model of arthritis. In this study we evaluated the role of epigallocatechin-3-gallate (EGCG), a green tea polyphenol which mimics its anti-inflammatory effects, in modulating the IL-1beta-induced activation of MAPKs in human chondrocytes. We discovered that EGCG inhibited the IL-1beta-induced phosphorylation of c-Jun N-terminal kinase (JNK) isoforms, accumulation of phospho-c-Jun and DNA binding activity of AP-1 in osteoarthritis (OA) chondrocytes. Also IL-1beta, but not EGCG, induced the expression of JNK p46 without modulating the expression of JNK p54 in OA chondrocytes. In immunocomplex kinase assays, EGCG completely blocked the substrate phosphorylating activity of JNK but not of p38-MAPK. EGCG had no inhibitory effect on the activation of extracellular signal-regulated kinase p44/p42 (ERKp44/p42) or p38-MAPK in OA chondrocytes. EGCG or IL-1beta did not alter the total non-phosphorylated levels of either p38-MAPK or ERKp44/p42 in OA chondrocytes. **Conclusion:** These are novel findings and indicate that EGCG may be of potential benefit in inhibiting IL-1beta-induced catabolic effects in OA chondrocytes that are dependent on JNK activity.

Ahmed S, Rahman A, Hasnain A, Lalonde M, Goldberg VM, Haqqi TM, Free Radic Biol Med 2002 Oct 15;33 (8):1097-105 **Green tea polyphenol epigallocatechin-3-gallate inhibits the IL-1 beta-induced activity and expression of cyclooxygenase-2 and nitric oxide synthase-2 in human chondrocytes.**

We have previously shown that green tea polyphenols inhibit the onset and severity of collagen II-induced arthritis in mice. In the present study, we report the pharmacological effects of green tea polyphenol epigallocatechin-3-gallate (EGCG), on interleukin-1 beta (IL-1 beta)-induced expression and activity of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in human chondrocytes derived from osteoarthritis (OA) cartilage. Stimulation of human chondrocytes with IL-1 beta (5 ng/ml) for 24 h resulted in significantly enhanced production of nitric oxide (NO) and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) when compared to untreated controls ( $p < .001$ ). Pretreatment of human chondrocytes with EGCG showed a dose-dependent inhibition in the production of NO and PGE<sub>2</sub> by 48% and 24%, respectively, and correlated with the inhibition of iNOS and COX-2 activities ( $p < .005$ ). In addition, IL-1 beta-induced expression of iNOS and COX-2 was also markedly inhibited in human chondrocytes pretreated with EGCG ( $p < .001$ ). Parallel to these findings, EGCG also inhibited the IL-1 beta-induced LDH release in chondrocytes cultures. **Conclusion:** Overall, the study suggests that EGCG affords protection against IL-1 beta-induced production of catabolic mediators NO and PGE<sub>2</sub> in human chondrocytes by regulating the expression and catalytic activity of their respective enzymes. Furthermore, our results also indicate that EGCG may be of potential therapeutic value for inhibiting cartilage resorption in arthritic joints.

Singh R, Ahmed S, Islam N, Goldberg VM, Haqqi TM, Arthritis Rheum 2002 Aug; 46 (8):2079-86 **Epigallocatechin gallate inhibits interleukin-1beta-induced expression of nitric oxide synthase and production of nitric oxide in human chondrocytes: suppression of nuclear factor kappaB activation by degradation of the inhibitor of nuclear factor kappaB.**

Human chondrocytes were derived from OA cartilage and were treated with EGCG (100 microM) and IL-1beta (2 ng/ml) for different periods, and inducible nitric oxide synthase (iNOS) messenger RNA and protein expression was determined by real-time quantitative reverse transcriptase-polymerase chain reaction and Western blotting, respectively. Production of NO was determined as nitrite in culture supernatant. Activation and translocation of nuclear factor kappaB (NF-kappaB), levels of inhibitor of nuclear factor kappaB (IkpappaB), and NF-kappaB DNA binding activity were determined by Western blotting and a highly sensitive and specific enzyme-linked immunosorbent assay. Activity of IkappaB kinase was determined using in vitro kinase assay. Human chondrocytes cotreated with EGCG produced significantly less NO compared with chondrocytes stimulated with IL-1beta alone ( $P < 0.005$ ). The inhibition of NO production correlated with the suppression of induction and expression of NF-kappaB-dependent gene iNOS. EGCG inhibited the activation and translocation of NF-kappaB to the nucleus by suppressing the degradation of its inhibitory protein IkappaBalpha in the cytoplasm.

**Conclusion:** Our results indicate that EGCG inhibits the IL-1beta-induced production of NO in human chondrocytes by interfering with the activation of NF-kappaB through a novel mechanism. Our data further suggest that EGCG may be a therapeutically effective inhibitor of IL-1beta-induced inflammatory effects that are dependent on NF-kappaB activation in human OA chondrocytes.

Takita H, Kikuchi M, Sato Y, Kuboki Y, Connect Tissue Res 2002;43(2-3):520-3 **Inhibition of BMP-induced ectopic bone formation by an antiangiogenic agent (epigallocatechin gallate)**

Epigallocatechin gallate (EGCG), which is one of the components of green tea, was recently shown to inhibit endothelial cell growth in vitro and angiogenesis in vivo [5]. We have previously shown that bone and cartilage formation by bone morphogenetic protein (BMP) is highly dependent on the geometry of the carrier (vasculature-inducing or -inhibiting geometry [2]). To verify the function of angiogenesis in the BMP induction system, we examine in this article whether inhibition of angiogenesis enhances chondrogenesis and suppresses osteogenesis. Fibrous glass membrane used as a BMP carrier was mixed with 1.2 micrograms rhBMP-2 and 1-10 micrograms of EGCG and was implanted into rats subcutaneously. As the dose of EGCG increased, alkaline phosphatase activity and calcium content were decreased, whereas the type II collagen content was increased. **Conclusion:** The results clearly indicated that inhibition of vascularization enhanced chondrogenesis and suppressed osteogenesis.

Chen PC, Wheeler DS, Malhotra V, Odoms K, Denenberg AG, Wong HR, Inflammation 2002 Oct; 26 (5):233-41 **A green tea-derived polyphenol, epigallocatechin-3-gallate, inhibits IkappaB kinase activation and IL-8 gene expression in respiratory epithelium.**

Interleukin-8 (IL-8) is a principle neutrophil chemoattractant and activator in humans. There is interest in developing novel pharmacological inhibitors of IL-8 gene expression as a means for modulating inflammation in disease states such as acute lung injury. Herein we determined the effects of epigallocatechin-3-gallate (EGCG), a green tea-derived polyphenol, on tumor necrosis factor-alpha (TNF-alpha)-mediated expression of the IL-8 gene in A549 cells. EGCG inhibited TNF-alpha-mediated IL-8 gene expression in a dose response manner, as measured by ELISA and Northern blot analysis. This effect appears to primarily involve inhibition of IL-8 transcription because EGCG inhibited TNF-alpha-mediated activation of the IL-8 promoter in cells transiently transfected with an IL-8 promoter-luciferase reporter plasmid. In addition, EGCG inhibited TNF-alpha-mediated activation of IkappaB kinase and subsequent activation of the IkappaB alpha/NF-kappaB pathway. **Conclusion:** We conclude that EGCG is a potent inhibitor of IL-8 gene expression in vitro. The proximal mechanism of this effect involves, in part, inhibition of IkappaB kinase activation.

Adcocks C, Collin P, Buttle DJ, J Nutr 2002 Mar; 132 (3):341-6 **Catechins from green tea (*Camellia sinensis*) inhibit bovine and human cartilage proteoglycan and type II collagen degradation in vitro.**

Polyphenolic compounds from green tea have been shown to reduce inflammation in a murine model of inflammatory arthritis, but no studies have been undertaken to investigate whether these compounds are protective to joint tissues. We therefore investigated the effects of catechins found in green tea on cartilage extracellular matrix components using in vitro model systems. Bovine nasal and metacarpophalangeal cartilage as well as human nondiseased, osteoarthritic and rheumatoid cartilage were cultured with and without reagents known to accelerate cartilage matrix breakdown. Individual catechins were added to the cultures and the amount of released proteoglycan and type II collagen was measured by metachromatic assay and inhibition ELISA, respectively. Possible nonspecific or toxic effects of the catechins were assessed by lactate output and proteoglycan synthesis. Catechins, particularly those containing a gallate ester, were effective at micromolar concentrations at inhibiting proteoglycan and type II collagen breakdown. No toxic effects of the catechins were evident. **Conclusion:** We conclude that some green tea catechins are chondroprotective and that consumption of green tea may be prophylactic for arthritis and may benefit the arthritis patient by reducing inflammation and slowing cartilage breakdown. Further studies will be required to determine whether these compounds access the joint space in sufficient concentration and in a form capable of providing efficacy in vivo.