Animal Health Benefits of HIDROX™

Executive Summary

- Multiple lines of converging evidence link polyphenols, particularly hydroxytyrosol and HIDROX™, to improved clinical outcomes in animals and humans.
- Animal and human studies of hydroxytyrosol and HIDROX™ have demonstrated their significant therapeutic effects on bone and joint health, the cardiovascular system, and in reducing inflammation. These findings have all been reported in peer-reviewed, internationally-recognised academic journals.
- Hydroxytyrosol is well absorbed following oral administration, and rapidly reaches high levels in the blood.
- HIDROX™ and hydroxytyrosol have strong safety profiles and are not associated with major adverse events.

HIDROX™

HIDROX™ is CreAgri’s trademarked name for hydroxytyrosol, which is produced using a unique, patent protected process. Hydroxytyrosol is a natural, potent, and protective polyphenol derived from olive juice and olive oil. However, olive juice has over 300 times the level of antioxidant polyphenols compared to olive oil.

Hydroxytyrosol is scientifically recognized for its powerful antibacterial, anti-inflammatory, antioxidant, and cardioprotective health benefits. Independent laboratory analyses have demonstrated that hydroxytyrosol is one of the most potent natural antioxidants yet discovered with the highest level of free radical protection activity ever reported for any natural antioxidant compound. Hydroxytyrosol’s therapeutics effects have been demonstrated in a large number of published scientific articles in internationally-recognized journals.

Dr Roberto Crea is the Chairman and Chief Executive Officer of CreAgri. Dr. Crea has over 30 years of experience in the biotechnology field as a scientist, investor, and entrepreneur. He is one of the scientific co-founders of Genentech, one of the leading global biotechnology companies. Dr Crea is also the founder of Creative Bio Molecules, Inc (1982), Creagen, Inc (1992), CreAgri (1998), Bioren (2002) and ProtElix (2005). Creagen, Inc was merged into Neurex in 1994, which was then sold to Elan Pharmaceuticals for over $700 million. Pfizer successfully acquired Bioren in 2005. Dr. Crea is the author of more than 25 international patents and has co-authored more than 50 scientific articles.

Anti-Inflammatory Effects of HIDROX™

A key study of the effects of olive juice, which has naturally high levels of hydroxytyrosol, has shown that it has potent anti-inflammatory effects in mice. Administration of olive juice to mice reduced levels of tumour necrosis factor-α (TNF-α) by 95%; TNF-α is a pivotal cytokine involved in inflammation (Bitler et al. 2005). Importantly, the authors of this study further demonstrated that olive juice works synergistically with glucosamine to reduce TNF-α inflammation biomarker in animals. This finding suggests that lower
levels of glucosamine, when given alongside olive juice, could be used to achieve similar or superior anti-inflammatory effects in animals. Furthermore, olive juice exerted no toxic effects in this study.

Hydroxytyrosol has been shown to significantly reduce inflammation in animal paws and to also reduce levels of pain associated with inflammation. Oral administration of hydroxytyrosol to rats with experimentally-induced paw inflammation induced statistically significant reductions in the degree of paw swelling and pain induced by paw inflammation (Gong et al. 2009). Hydroxytyrosol also reduced levels of TNF-α and interleukin 1β (IL-1β; another important proinflammatory cytokine). These findings demonstrate that hydroxytyrosol exerts powerful anti-inflammatory and analgesic effects associated with animal limb inflammation.

One study assessed the anti-inflammatory effects of olive polyphenols, of which hydroxytyrosol and HİDROX are the most potent antioxidants, in animals with acute and chronic inflammation. Rats were fed on diets of either sunflower oil, palm oil, fish oil, or an olive polyphenol diet for 8 weeks. After the study period, markers of inflammation were the lowest in animals given olive polyphenols (Martinez-Dominguez et al. 2001). In animals with arthritis, olive polyphenols reduced inflammation, and was significantly more effective than fish oil. Furthermore animals given olive polyphenols showed substantial increases in body weight, demonstrating the additional beneficial effects of polyphenols in preventing disease-associated weight loss.

In keeping with animal studies of hydroxytyrosol, human studies have also demonstrated its powerful anti-inflammatory effects. A placebo-controlled clinical study of HİDROX™ in patients suffering from rheumatoid arthritis revealed that the supplement significantly reduced levels of C-reactive protein after eight weeks (Bitler et al., 2007). C-reactive protein is an important biochemical marker of inflammation and it has been previously associated with rheumatoid arthritis and cardiovascular disease and mortality.

The same study of HİDROX™ in rheumatoid arthritis patients also demonstrated that the supplement significantly reduced levels of homocysteine after eight weeks. Homocysteine is also an important biochemical marker of inflammation and a number of large clinical studies have established homocysteine as an independent risk factor for venous thromboembolism, stroke, coronary heart disease, and death (Milani et al., 2008).

**Beneficial Effects of HİDROX™ in Promoting Bone and Joint Health**

Olive polyphenols have also been shown to significantly improve bone health in animals. One study assessed the effects of olive polyphenols in animals with osteoporosis. A high olive polyphenol diet prevented bone loss in animals, which was suggested to be due to the antioxidant and anti-inflammatory effects of olive polyphenols, including hydroxytyrosol (Puel et al., 2007). An additional study further supports these earlier findings by showing that olive juice and hydroxytyrosol also prevented bone loss in rats with osteoporosis (Puel et al., 2008).

An eight-week clinical study of HİDROX in osteoarthritis patients demonstrated that the supplement induced significant improvements in quality of life as measured by a health assessment questionnaire disability index (HAQ-DI). The HAQ-DI evaluated nine categories of functional activity; 69% of
An animal health benefits

osteoa rthritis patients receiving HIDROX reported a greater than 20 % improvement in their HAQ-DI scores (Bitler et al., 2007).

Effects of Hydroxytyrosol on Vitamin C Levels

Hydroxytyrosol has been shown to increase levels of vitamin C. Diabetic patients administered 12.5-25 mg hydroxytyrosol per day had raised plasma levels of vitamin C compared to baseline recordings. The authors of this study suggested that hydroxytyrosol may exert antioxidant protective effects on vitamin C (Leger et al., 2005). Vitamin C has been linked to multiple beneficial effects including immune health, however, its water soluble nature results in the inability to store and maintain consistent levels. By raising levels of vitamin C, hydroxytyrosol and HIDROX™ could exert additional therapeutic effects.

Additional Beneficial Effects of HIDROX™

The additional therapeutic effects of hydroxytyrosol and HIDROX™ are wide ranging. A large number of experimental studies of hydroxytyrosol have shown that the agent has multiple cardiovascular benefits. Hydroxytyrosol reduces blood pressure, provides an important safeguard against potentially lethal blood clots, improves blood cholesterol and prevents the formation of plaques within arteries.

HIDROX and hydroxytyrosol have also been shown to have prominent antibacterial effects against at least 14 different strains of bacteria including E. coli, Salmonella enterica, and Staphylococcus aureus, demonstrating the agent’s strong potential as a natural food safety and preservative product. Evidence also suggests that hydroxytyrosol exerts important effects against microbial infections.

Strong Safety Profile of HIDROX™

The safety of HIDROX™ has been formally acknowledged by the United States Food and Drug Administration (FDA); HIDROX™ has been granted GRAS certification. GRAS (Generally Recognized As Safe) is a designation granted by the FDA and states that a chemical or substance added to food is considered safe by experts. GRAS certifications are granted to substances that are generally recognized, among experts qualified to evaluate product safety, as having been adequately shown through scientific procedures to be safe under the conditions of their intended use.

A large number of animal and human studies strongly suggest that daily consumption of polyphenol compounds, including hydroxytyrosol and HIDROX™, is free from major adverse events. Extensive animal toxicology studies of HIDROX™ have revealed its extremely strong safety profile; HIDROX™ administered in single or multiple dosages of up to 2000 mg/kg/day resulted in no adverse clinical, haematological, biochemical, or reproductive effects (Christian et al., 2004). Furthermore, HIDROX™ has been successfully used in a number of human studies, with no major adverse events reported.
Research on the Beneficial Effects of HIDROX™, Hydroxytyrosol, and Polyphenols


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Ravishankar S, et al. (2010). Research on antimicrobial effects of HIDROX™ on contaminated raw and cooked meats and on lettuce. CreAgri-funded research and development in collaboration with the University of Arizona.


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Biography

Dr. Matthew Killeen - CreAgri’s Scientific Affairs Advisor. Dr Killeen received his undergraduate degree in pharmacology with highest honors and was awarded a Ph.D. in cardiovascular electrophysiology from the University of Cambridge. At Cambridge he studied the mechanisms underlying sudden cardiac death and identified a number of effective pharmacological treatment strategies. Following his Ph.D., Dr. Killeen was awarded research fellowships at Harvard Medical School and the Massachusetts General Hospital. Dr. Killeen has authored 19 peer-reviewed publications in leading international journals. He is a member of the Cardiac Safety Research Consortium, a collaborative initiative between the FDA and Duke University. Dr. Killeen developed the concept for and co-chaired an FDA Think Tank on pediatric drug safety. Dr. Killeen has also previously worked for Eli Lilly and he is the author of the forthcoming book, “Cardiac Drug Safety: A Bench to Bedside Approach,” which will be published in 2011.