CapsiAtra®

glanbia nutritionals

Capsinoids as Natural Energy Regulators for Enhanced Athletic Endurance & Weight Management

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INTRODUCTION

Each year the sports nutrition industry is flooded with new weight management and endurance products. In 2014, consumers spent over $6 billion[1], however recent scandals questioning the validity and safety of a number of high profile ingredients has left consumers in search of products that contain safe ingredients they can trust and are backed by science. One such ingredient is Glanbia Nutritionals' CapsiAtra®, a dihydrocapsiate compound naturally found in CH-19 Sweet peppers. CapsiAtra® has extensive safety and toxicity data gathered from over 50 published studies on capsiates reflecting its benefits on exercise, weight management, endurance and metabolism. In humans, cardiovascular safety parameters and hematology/urology studies have been conducted. Animal studies include acute and chronic (long-term) toxicity studies, multi-generation studies, and genotoxicity and pharmacokinetics studies.

REE: RESTING ENERGY EXPENDITURE

The resting energy expenditure (REE) is the number of calories burned in order to maintain homeostasis while at rest. Similar to the basal metabolic rate (BMR), it fluctuates to accommodate the level of activity it is accustomed to, meaning people who are more active tend to have a higher metabolic rate. The REE is the main determinant of daily energy expenditure, representing 60–70% of total energy output in sedentary adults, with exercise comprising the remainder. Since REE declines with age, at a rate of as much as 2% per decade after the age of 20 years, it is necessary to either decrease calorie intake or increase energy expenditure through physical exercise in order to avoid weight gain over time. These changes are due in part to declining thyroid function, loss of lean muscle mass and reduced metabolic activity in lean tissue. Though there is considerable variation between individuals and studies, the general rule is that older people burn fewer calories at rest than their younger counterparts.[2] It has been estimated that after adjusting for differences in fat and lean tissue mass, REE is lower (by an average 644 kJ/day) in healthy older adults between 50 and 77 years old than in young adults aged 18–35.[3]

Age is a factor in energy regulation, but it is not the only facet. Heavier individuals are more susceptible to greater weight gain because an increase in body mass index (BMI) brings about further attenuation of the REE. There are also some genetic factors that can come into play such as leptin hormone deficiency.[4] While reducing calories is a logical solution to weight gain caused by positive energy balance, studies have shown that unless the subjects are enrolled in exercise programs, calorie restriction can actually result in a measurable decrease in physical activity.

WHAT MAKES CAPSIATRA® AN INNOVATIVE WEIGHT MANAGEMENT & SPORTS NUTRITION INGREDIENT

> Dihydrocapsiate is a compound found in CH-19 Sweet peppers
  - Non-burning and non-irritating to the stomach

> Increases REE
  - The amount of calories burned by the body under normal resting conditions
  - Reduces age-related REE slowdown

> Increases fat oxidation
  - The ability of the body to burn calories off of stored fat within the body
  - Significant reduction in abdominal fat seen in human studies

> Optimizes energy expenditure through fat oxidation and decreased utilization of carbohydrates
  - Reduction of anaerobic respiration in favor of aerobic respiration by sparing muscle glycogen stores
  - Sparing glycogen in the muscle while reducing lactic acid levels

> Safety Profile
  - GRAS with letter of no objection from FDA
  - No known adverse side effects
  - No impact on blood pressure or heart rate

> NDI notification letter

> EU novel food approved

> Shelf-life of 24 months

> Manufactured in Japan

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This mechanism is a result of adaptive evolution. It is well understood now that reducing caloric intake, as with a low calorie diet, causes a physiological response that tells the body to slow the metabolic rate. It is a function of evolution to enable survival in times of famine. This is a case of a battle between modern living and thousands of years of complex evolutionary adaptations.

THERMOGENISIS: NATURE'S WARMING SOLUTION

Clinicians and researchers have been searching for therapeutic agents that can counteract this mechanism by up- regulating thermogenesis (production of heat from energy stored in fat cells) and increasing REE. The treatments that have come to the forefront often carry negative side effects, such as with amphetamines. These work by stimulating the central nervous system (CNS) to release catecholamines which decrease appetite and elevate the metabolic rate.[5] However the potential for dependency on these makes their use discouraged. Given the limitations of drug therapies in this context, many patients try botanical medicines and plant-derived substances promoted for increasing thermogenesis and fat oxidation. Popular options include: Green Tea (and extracts made from it), Bitter Orange, Guarana, Hoodia, Psyllium, Kelp, and Forskolin. The science supporting these products is variable; some are supported by good efficacy and safety studies, others are not. The most promising, well-researched, and safest botanically-derived metabolic up-regulators are compounds found in chili peppers (Capsicum genus). Capsaicin is the compound that gives chili peppers their pungent "hot" taste sensation. It is the most commonly known constituent of chili peppers and its thermogenic effects are well documented.

Capsaicin enhances catecholamine secretion and energy expenditure.[6] Early studies proved that long-term intake could suppress body fat accumulation in animals[7], clearly a highly desirable effect which sparked a great deal of research. In humans, researchers showed that daily intake of capsaicin (or peppers containing it) increased fat oxidation and elevated resting energy expenditure.[8] Newer evidence suggests that capsaicin may suppress appetite as well, increasing the sense of satiety particularly during prolonged periods of negative energy balance.[9]

CHILI EXTRACTS: A HOT TOPIC

The intense pungency of capsaicin is off-putting from a sensory perspective. More seriously, its tendency to be absorbed systemically means it can contribute to increases in heart rate and blood pressure. In certain populations this could be lethal, especially given that many individuals seeking weight management options may already be predisposed to cardiovascular issues. These factors make capsaicin a non-viable nutraceutical option. An alternative is required.

Japanese investigators have been at the forefront of research on bioactive compounds in chili peppers. Among the most important recent discoveries is the identification and characterization of the capsinoids. These substances, produced by certain strains of chili peppers, are structurally similar to capsaicin but have several distinct properties that make them a much better option in the context of sports nutrition, weight management and energy regulation. Capsinoids exert similar thermogenic and lipolytic effects as capsaicin but without noxious sensations of pungency or "hotness." To put this in perspective, capsinoids are approximately 1,000 times less hot than capsaicin. Further, capsinoids are hydrolyzed into fatty acids and vanillyl alcohol as they pass through the gastrointestinal tract.

The Effect of Capsaicin and Capsinoids on Blood Pressure and Heart Rate

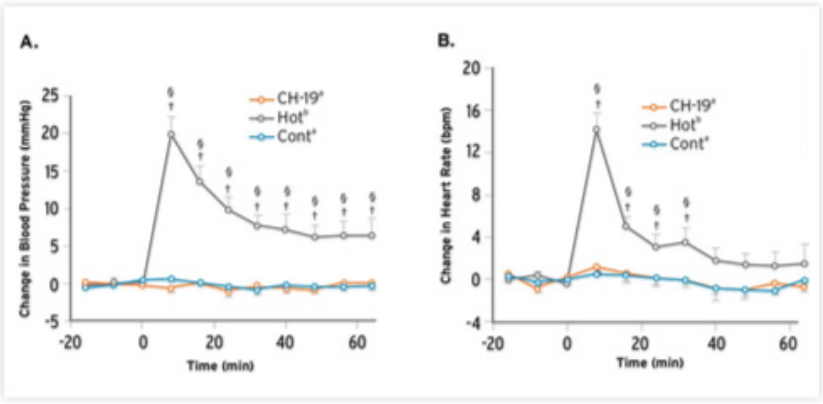

Figure 1

Source: Hachiya S, et al. Biosci Biotechnol Biochem. 2007; 71(3): 671-676

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These end products are then converted into inactive conjugates, removing the possibility of systemic side effects. A study comparing a pepper rich in capsinoids with one rich in capsaicin and an alternative pepper source which lacked both compounds, showed that the capsinoids had no effect on heart rate or blood pressure, unlike capsaicin which significantly raised both (Fig 1).[10]

So far researchers have discovered three distinct capsinoids: capsiate, dihydrocapsiate and nordihydrocapsiate (Fig. 2). CapsiAtra® is dihydrocapsiate. Where capsaicin has an amide bond in its side chain that stays intact during digestion, capsinoid compounds have ester bonds that are cleaved in the small intestine, thus eliminating possible systemic side effects. Their heightened safety profile, ability to increase basal metabolism and fat oxidation make them an ideal nutraceutical option for sports nutrition, weight management and energy regulation. Dihydrocapsiate, a member of the capsinoid family, is a non-pungent compound that is highly concentrated in a sweet pepper named "CH-19 Sweet".

The Molecular Structure of the Capsinoids and Capsaicin.
Note CapsiAtra® is a Dihydrocapsiate

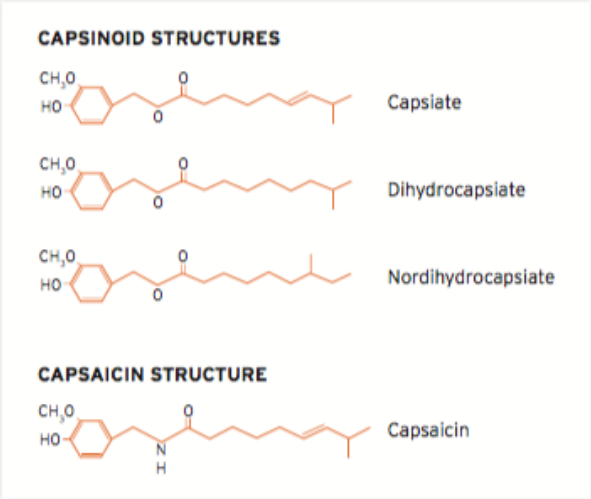

Figure 2

CAPSINOIDS: THE COOLEST COMPOUNDS

The thermogenic and lipolytic effects of capsinoids, like capsaicin itself, are mediated by the Transient Receptor Potential Vanilloid 1 (TRPV1) receptors in the mouth and throughout the gastrointestinal tract. TRPV1 receptors in the gut are linked with the sympathetic nervous system (SNS). When activated, they increase SNS activity (Fig. 3). TRPV1 receptors present on the tongue and in the oral cavity are responsible for, among other things, detection of thermal heat. When capsaicin binds to oral TRPV1 sites, one feels the sensation of heat and pungency. Capsinoids also stimulate TRPV1 receptors, but their effect is primarily on receptors in the throat and gut, not the mouth. Owing to the structural differences from capsaicin, the capsinoids are unable to reach the TRPV1 receptors on the tongue, which are located slightly below the mucosal surface. As a result, capsinoids do not produce the oral sensation of heat or the pungent taste associated with chili peppers, but they do produce the capsaicin-like SNS response once they bind to TRPV1 receptors in the throat and gut.[11]

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The Mechanism of Action by which Capsinoids Accelerate Energy Expenditure

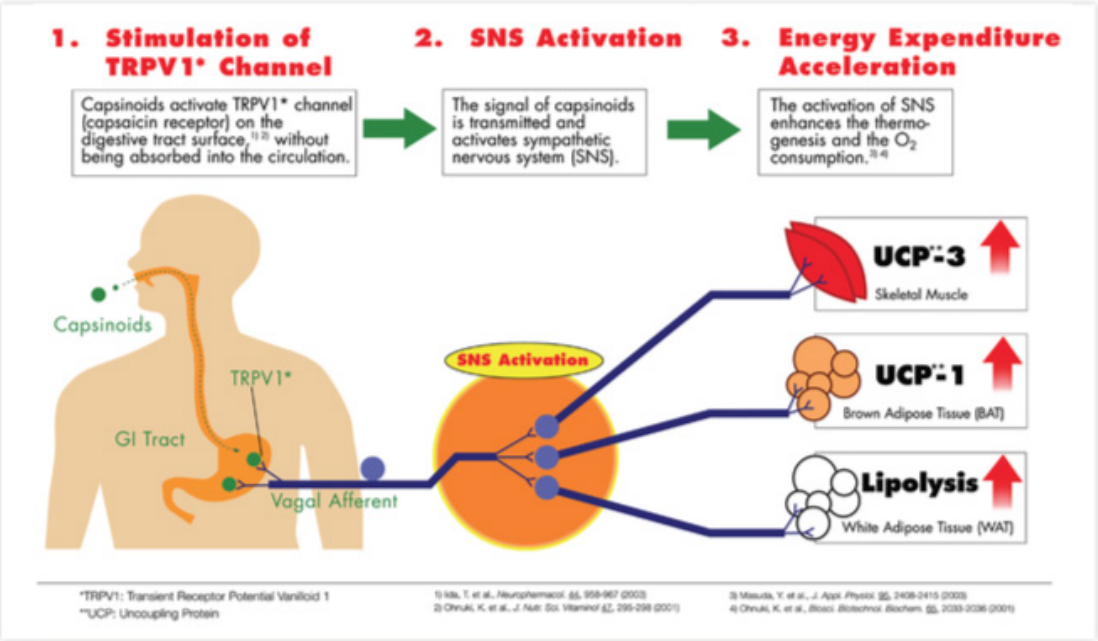

Figure 3

The capsinoids have multiple biological functionalities (Fig 4). The sports nutrition properties are directly linked to their use in energy manipulation. The capsinoids have three principal mechanisms of action. First, they up-regulate UCP-3 (Mitcohondrial Uncoupling Protein-3) in muscle cells. This causes ATP production to be dissociated with the respiration occurring in the mitochondria. This energy is then released as heat: an effect that is mirrored in caloric restriction as a means to economize energy. Second, they up-regulate UCP-1 (Uncoupling Protein-1, aka Thermogenin). This protein is only expressed in brown adipose tissue and is used to generate non- shivering thermogenesis; a process that evolved to protect against hypothermia. The up-regulation of UCP-1 can positively affect fat utilization and improve insulin sensitivity of tissues. Third, the capsinoids stimulate lipolysis via hydrolysis of triglycerides into glycerol plus three fatty acids. The release of these free fatty acids into the circulation is key to the energy regulating properties of the compound. Allowing these to become readily available as energy sources during exercise means that oxidation of muscle glycogen can be delayed, resulting in significant improvements in endurance.

PHYSIOLOGICAL EFFECTS OF CAPSINOIDS

> Increased oxygen consumption
> Transiently elevated body temperature
> Up-regulation of activity of upcoming proteins
> Increased energy expenditure
> Reduced fat accumulation

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ENERGY METABOLISM: GLYCOGEN SPARING AND LIPID UTILIZATION

The body can capitalize on this shift in energy regulation, bringing about a more efficient system that may lead to improved or prolonged physical performance in sports. Nutrients are the source of fuel but the time of use and way in which they are used can give rise to different efficiencies, depending on what type of activity is being demanded of the body. The mobilization of the adipocytes brought about by the lypolytic activity of the capsinoids not only means greater propensity for weight loss but also brings about a ready source of energy for the body: an energy source that is not muscle-bound glycogen. This is positive for energy conservation, especially in endurance athletes.

The body gets its energy from ATP (adenosine triphosphate). This cannot be stored in large amounts in the body and so it must be continuously converted from a nutrient source through respiration. There are two different sources of obtaining this energy-fueling ATP: breakdown of glycogen from the muscle cells or fat from adipocytes. The breakdown of these nutrients can be done with or without the presence of oxygen: aerobically or anaerobically. Aerobic metabolism is used to fuel shorter bursts of exercise, such as a 100 meter sprint. Initially, ATP stored in the muscle is used, which lasts about 2-3 seconds. Then ATP bound to creatine phosphate (ATP-CP) is used to resynthesize ATP until the CP runs out, which will be approximately another 6-8 seconds. Once the ATP and CP have been used the body turns to glycolysis for energy.

Anaerobic glycolysis obtains ATP from carbohydrates (either free or from the muscle stores). Lactic acid is produced as a by-product, which builds up, creating the lactic acid threshold. At this point muscle pain and fatigue make it difficult to maintain exercise at that intensity and aerobic metabolism must kick in. Since this relies on the circulatory system for the delivery of sufficient oxygen to continue fuelling, it is generally used for more endurance-style exercise over longer time periods. The body naturally transitions between these forms of energy metabolism depending upon available oxygen and demand on muscle.

In sports nutrition there is a huge interest in products that will help redirect energy metabolism to avoid the wasting of muscle glycogen stores. This is referred to as glycogen-sparing. Certain compounds found in nature can assist in offering the body an alternative source of energy so that utilization of the muscle glycogen stores can be preserved for a longer time, thereby delaying the accumulation of lactic acid and its associated fatigue. During exercise the need for energy increases several fold over the requirement at rest: both fat and carbohydrate will be oxidized for this purpose. However, once a steady, aerobic state is reached and the metabolic demand has been established, there can be a shift in the use of the two energy sources.[13] The availability of substrate as well as exercise intensity and duration will affect this shift. Supplementation with free fatty acids has been shown to decrease the net glycogen use by approximately 50% in the initial 15 minutes of exercise at 80% of the $VO2_{max}$ with a simultaneous increase in fat oxidation of 15%.[14,15] This results in an advantageous shift in mitochondrial respiration which favors overall energy efficiency. The same effect can be achieved using CapsiAtra® dihydrocapsiate to oxidize fatty acids, increasing their presence in the circulation.

CAPSIATES: SPARING GLYCOGEN AND BOOSTING ENDURANCE

The release of free fatty acids by the action of capsiates via the activation of the uncoupling processes is central to its energy manipulation abilities. A study performed on mouse skeletal muscle showed that single oral dosing with capsiate at either 10 or 100 mg/kg body weight showed that both doses brought about beneficial shifts in the energy metabolism away from glycogen oxidation.[16] The higher dose in this case also increased the overall force-generating capacity of the muscle, demonstrating other capsinoids such as CapsiAtra®'s potential use as a muscle and endurance enhancing supplement. Elsewhere, in a study of mice consuming capsiate or control, it was seen that both 10mg and 100mg doses of capsiate significantly decreased the amount of ATP production coming from glycolysis. In addition, creatine kinase reaction and oxidative ATP contributions were significantly larger in the capsiate doses compared to control (Fig 5). The authors highlighted the potential for the use of capsiate as a candidate for enhancing both muscle performance and oxidative phosphorylation during exercise.

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Elsewhere, mice who were given oral capsiate at 10mg/ kg bodyweight and forced to swim were able to maintain the swimming effort for significantly longer before exhaustion set in compared to controls (Fig 6).[17] This translated as a ten minute, or 25% increase in swim time. After 30 minutes swimming the residual glycogen in the gastrocnemius muscle (located in the calf of the leg) was higher, as was the serum free fatty acid concentration. Further to these, the lactic acid concentration was significantly lower; meaning the mice were able to avoid reaching the lactic acid threshold for a longer period of time.

Similarly, mice given 10 mg/kg bodyweight capsiate were engaged in a treadmill running regime which saw them forced to run for 60 minutes.[17] The capsiate was administered 60 minutes prior to the running test. Compared to the control, mice given capsiate demonstrated enhanced fat oxidation and decreased utilization of carbohydrates (Fig 7). They experienced a reduction in anaerobic respiration in favor of aerobic respiration by sparing muscle glycogen stores. This was accompanied by a reduction in lactic acid accumulation.

Capsinoids Alter the Method of ATP Production

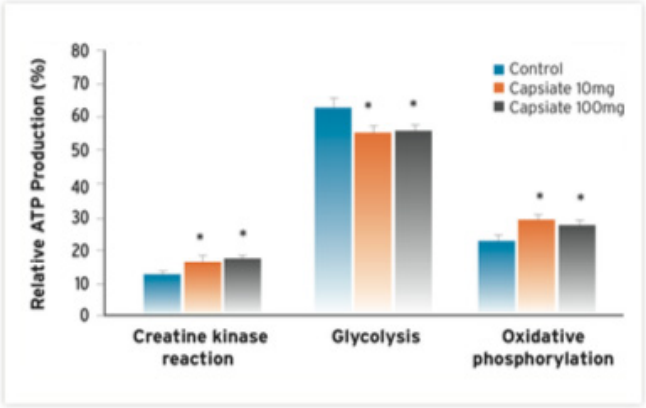

Figure 5 *Source: Yashiro et al. (2014) Am J Physiol Endocrinol Metab 306(10): E1110-9*

Improvement of Swimming Endurance Among Mice Fed with CapsiAtra®

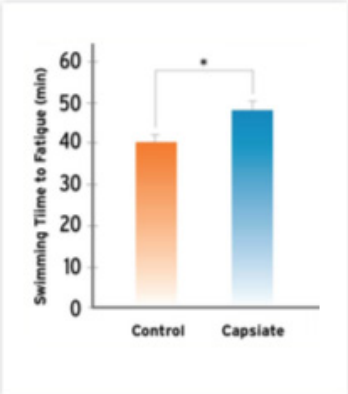

Figure 6
Source: Haramizu et al. (2006) Biosci Biotechnol Biochem 70(4): 774-781

Enhanced Fat Oxidation Among Mice Fed CapsiAtra®

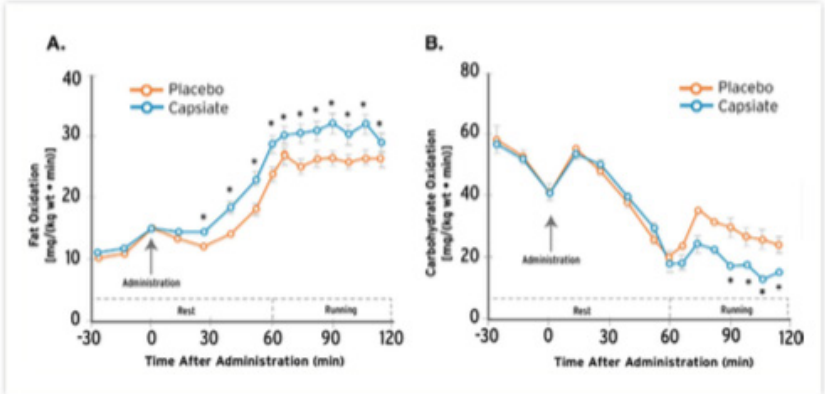

Figure 7 *Source: Haramizu et al. (2006) Biosci Biotechnol Biochem 70(4): 774-781*

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Similar metabolic changes have been reported in multiple human studies.[10,18-20] While many of these have focused on the weight management element of the capsiates, the core mechanism of action is consistently the redirection of glycogen oxidation toward lipid oxidation. A double blind, randomized, placebo-controlled study described 78 men who consumed either 3 or 9 mg of dihydrocapsiate per day for 24 days.[19] Among this population significant changes in energy regulation were seen, especially manifested in REE (Fig 8).

Metabolic Rate Increases in Response to CapsiAtra®

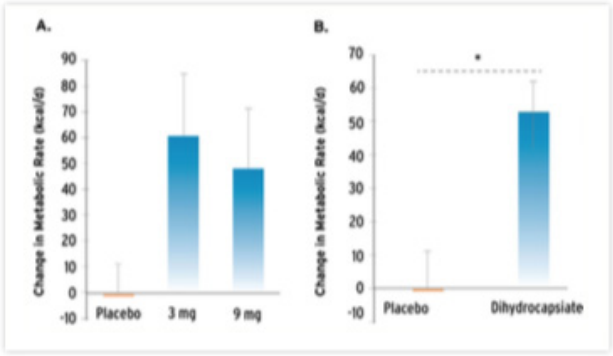

Figure 8 Source: Galgani et al, Am J Clin Nutr. 2010 Nov;92(5):1089-93

As mentioned previously, the weight management properties of capsiate center around its ability to elevate resting energy expenditure. This, in turn is intrinsically linked to the shift in energy utilization from glycogen to fat stores. These events directly enhance physical endurance and have significant applications for the sports supplement market.

CAPSIATRA®: POSITIVE RESULTS

In all CapsiAtra®'s studies, there have been no incidents of allergy or sensitivity to capsinoids. Extensive toxicity and safety data gathered from over 50 published studies on the capsiates formed the basis of the product's FDA GRAS and NDI status. Since capsinoids are broken down as they pass through the GI tract and not absorbed into the blood, there is little chance of systemic reactions. That said, people with known sensitivities to chili peppers should be monitored closely especially during the first weeks of capsinoid ingestion.

CapsiAtra® is dispersed in oil and spray-dried onto an isolmaltulose carrier. This system offers excellent stability, protection from moisture and improves physical functionality. The recommended daily dose is 1-3 mg capsiate (43.5-130 mg CapsiAtra®). It can be provided at varying concentrations depending on the customers' requirements. The principal applications include tablets, capsules, softgels and ready-to-mix beverages. An exciting new addition to Glanbia Nutritionals portfolio includes an agglomerated version of CapsiAtra® which is water-soluble. This new feature means CapsiAtra® can be incorporated into liquid processing stages such as soft- pressed bars and topical coatings.

POSSIBLE CAPSIATRA® MARKETING CLAIMS:

> 1000 x less pungent than capsaicin
> Utilizes fat for energy
> Helps increase basal metabolic rate

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WHY GLANBIA NUTRITIONALS?

Glanbia Nutritionals is a global leader in ingredient solutions, providing precision premixes, amino acids, vitamins, minerals, specialty ingredients and colors for the food, beverage and supplement industries. Built on our reputation for outstanding quality and service, we deliver formulation and ingredient expertise that help our customers optimize their products and propel them to greater success.

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