Akkermat™

The Power of Nature and Innovation for Weight Management and Metabolic Health

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Step into the future of weight loss and metabolic well-being with Akkermat™ – an extraordinary dietary supplement thoughtfully crafted with the essence of nature's finest elements. At its core, Akkermat™ synergizes the potent attributes of chili pepper extract, rich in capsaicinoids, and fenugreek extract, celebrated for its dietary fiber galactomannans.

Capsaicinoids, the natural compounds found in chili peppers (*Capsicum* species), impart that characteristic spicy zest to these peppers. Among them, capsaicin takes center stage, influencing an array of physiological processes, from pain modulation to insulin sensitivity, glucose metabolism, and even blood pressure regulation.[34] Known for its potential to ignite thermogenesis, increase energy expenditure, curb appetite, and enhance lipid oxidation, capsaicin is celebrated for its role in boosting metabolism and supporting weight loss.[37,38]

On the other hand, fenugreek galactomannans, hailing from fenugreek seeds, emerge as soluble dietary fibers characterized by their unique structure. These fibers effortlessly dissolve in water, lending themselves to dietary fiber supplements, culinary thickening agents, and food texture enhancers. Beyond these culinary applications, galactomannans may contribute to better blood sugar control, reduced cholesterol levels, and weight management, while offering the prebiotic potential to nurture the growth of beneficial gut bacteria responsible for the production of beneficial short-chain fatty acids (SCFs).[39-41]

This remarkable and convenient fusion of chili pepper extract and fenugreek extract forms the heart of Akkermat™'s potential and its symphony of effects to support metabolic health and weight loss.

What is Akkermat™?

Akkermat™ is a fusion of cutting-edge science and natural ingredients, meticulously crafted to support weight loss and metabolic health goals. Akkermat™ combines the potential of chili pepper extract standardized to 2% capsaicinoids (including capsaicin, dihidrocapsaicin, and nordihidrocapsaicin) encapsulated into a fenugreek extract matrix, rich in galactomannan, utilizing Fenumat technology to create a **time-released effect and enhanced bioavailability** in a form of beadlets.[1]

The synergy between chili pepper extract and fenugreek extract is remarkable. While capsaicinoids are known for their metabolism-boosting properties and appetite-suppressing effects when used alone, they can sometimes lead to discomfort due to their intense spiciness, making them less tolerable for some individuals. Fenugreek extract, on the other hand, provides a balancing act. It not only serves as a dietary fiber but also creates a sustained-release matrix for capsaicinoids, allowing for a more gradual and controlled release. This controlled release of capsaicinoids thanks to the fusion with fenugreek galactomannans makes Akkermat™ a more tolerable option for individuals who might otherwise experience discomfort or gastrointestinal distress[2] when taking chili pepper extract and capsaicinoids alone. In addition, glucomannan fiber is not digested by human digestive enzymes and is available for fermentation by gut microbiota.

Mechanism of action

The mechanism of action of chili pepper is attributed to its bioactive compounds including capsaicinoids such as capsaicin, which acts as a metabolic activator influencing several pathways, genes, and proteins involved in interconnected processes that impact energy metabolism including **thermogenesis, energy expenditure, appetite regulation, and lipid oxidation**.[3-7]

Capsaicin acts as an exogenous agonist of the TRPV1: Capsaicin exerts its pharmacological effects primarily through the Transient Receptor Potential Channel Vanilloid type-1 (TRPV1) that responds to various stimuli, including capsaicin. Capsaicin binds intracellularly to the TRPV1 and alters its properties, leading to the opening of the channel pore and permitting Ca2+ influx. TRPV1 is expressed in metabolically active tissues such as adipose tissue, skeletal muscle, liver, and pancreatic beta-cells.

Capsaicin has been shown to **increase thermogenesis**, which is the process of heat production in the body. This occurs through the activation of thermogenic fat cells, known as brown adipose tissue (BAT). Activation of BAT involves the upregulation of genes and proteins responsible for thermogenesis. Capsaicin, through TRPV1 activation, can influence processes like the browning of fat cells and the activation of metabolic regulators such as AMPK, PPARα, UCP1, and GLP-1, as well as inhibition of the AKT/mTOR pathway, major regulators of hepatic lipogenesis.[5-10]

Capsaicin can influence the expression of genes involved in metabolism. For instance, it may upregulate the expression and levels of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) which is a key regulator of mitochondrial biogenesis and energy metabolism.[10]

Moreover, capsaicin activates adrenergic receptors, particularly the beta-3 adrenergic receptor, which triggers the release of norepinephrine and increases UCP1 expression.[11,12] UCP1 is a protein found in brown fat cells that uncouples oxidative phosphorylation, leading to heat generation instead of ATP production.

Capsaicin has been found to increase the secretion of GLP-1 (glucagon-like peptide-1), which is an incretin hormone that stimulates insulin secretion and improves insulin sensitivity and glucose metabolism.[13-15] It can also decrease the secretion of **ghrelin**,[13,14] a hormone that stimulates appetite.

Capsaicin can **increase energy expenditure** by stimulating the sympathetic nervous system. This leads to an increase in heart rate and metabolic rate. Activation of the sympathetic nervous system can result in the release of catecholamines (epinephrine and norepinephrine). Catecholamines bind to beta-adrenergic receptors on the surface of fat cells. This binding initiates a process called lipolysis, which is the breakdown of stored triglycerides (fat) within adipocytes into free fatty acids and glycerol. In addition, neurotransmitters such as substance P and calcitonin gene-related peptide (CGRP), playing roles in pain perception and inflammation, are also released.

Capsaicin **possesses anti-inflammatory properties**, reducing inflammation in adipose tissue and other organs. Capsaicin has been shown to inhibit the nuclear factor-kappa B (NF-κB) and microtubule-associated protein kinase (MAPK) signaling pathways, reducing the expression of pro-inflammatory genes and cytokines, including interleukins.[16]

Capsaicin has **antioxidant properties** that enable it to scavenge free radicals, particularly reactive oxygen species (ROS). Some studies suggest that capsaicin may increase the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase, further enhancing the body's defense against oxidative damage.[17]

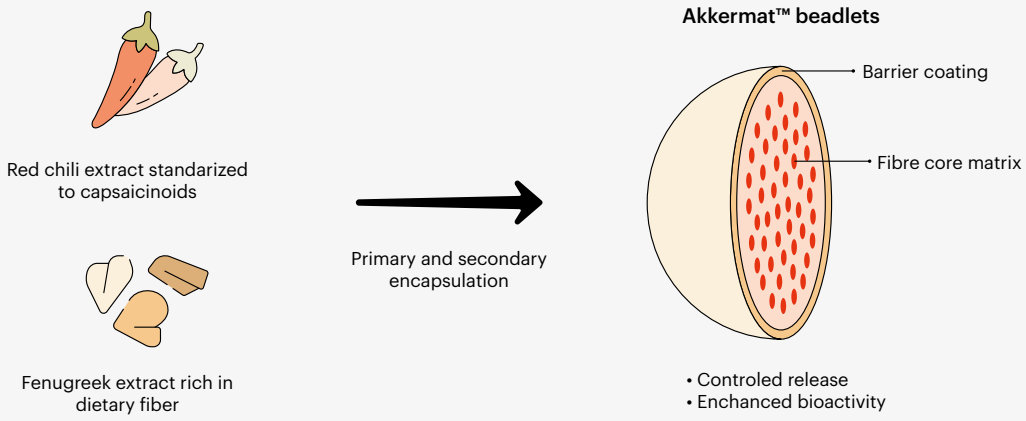


Figure 1. Schematic representation of the Akkermat™ formulation utilizing the Fenumat technology.

Pre-clinical studies, modulation of gut microbiota and increase of *Akkermansia muciniphila* gut bacteria

Interestingly, dietary capsaicin may influence glucose homeostasis, weight, and metabolic health, through modulatory action on the intestinal environment and gut microbiota, influencing its composition.[18] This action can be mediated by both TRPV1-dependent and TRPV1-independent mechanisms.

For instance, the animal study investigating the impact of capsaicin, on the gut barrier and mucus production in a diet-induced obesity mouse model found that capsaicin supplementation induced an increase in the availability of mucin/mucus in the intestines which might contribute to capsaicin's anti-obesity effects. Capsaicin and mucin had similar anti-obesity effects, suggesting that mucus modulation may also be a contributing factor to TRPV1-independent capsaicin's benefits agonism.[19]

Animal studies also indicate that capsaicin can increase the levels of gut bacteria Akkermansia muciniphila known for its health-promoting properties and involvement in weight management.

Such observation was made in a study that investigated the impact of capsaicin on gut microbiota and obesity. The researchers fed mice a high-fat diet with or without capsaicin for 9 weeks and found that capsaicin reduced weight gain and improved glucose tolerance. Through genetic analysis, they discovered that mice receiving capsaicin responded with a decrease in the bacteria belonging to the *Proteobacteria* phylum (including potentially harmful bacterial species) and an increase in *Akkermansia muciniphila*, a beneficial bacterium involved in host metabolism. Additionally, capsaicin was found to upregulate the expression of the *muc2* gene regulating mucin synthesis.[20]

Furthermore, another study in rats found that capsaicin altered the gut microbiota composition by promoting the growth of *Akkermansia* and decreasing potentially harmful bacteria such as *Desulfovibrio*. Capsaicin also promoted the increased levels of certain bile acids, and increased expression of TRPV1 while the reduction of triglycerides, total cholesterol levels, and inflammatory markers was observed.[21] The same research group embarked on investigating the combined effects of capsaicin and dietary fibers on male rats with a high-fat diet and their impact on blood lipids and gut microbiota. The results showed that when capsaicin and dietary fiber were administered together, there was a more significant reduction in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) compared to capsaicin alone. The combination also increased the diversity of gut bacteria and the abundance of beneficial species like *Akkermansia* while decreasing harmful bacterial species like Desulfovibrio.[22]

In addition, researchers from China conducted experiments on mice (wild type and TRPV1knockout) fed a high-fat diet and found that capsaicin intake was associated with increased populations of beneficial bacteria like *Akkermansia*, and Prevotella, while reduced levels of harmful bacteria like *Desulfovibrio*, *Escherichia*, *Helicobacter*, and *Sutterella*. Capsaicin also reduced weight gain, food intake, and levels of triglycerides, cholesterol, glucose, and insulin, and increased the relative abundance of bacteria that produce SCFAs (short-chain fatty acids), leading to higher concentrations of acetate and propionate in the intestines. These results suggest the TRPV1-independent anti-obesity effect of capsaicin.[23]

Similarly, the study that investigated the impact of capsaicin on the intestinal microbiome and physiological state of mice found significant differences between mice treated with capsaicin and those without it. These differences included changes in body weight, leukocyte count, fecal humidity, and the composition of intestinal bacteria, particularly *Faecalibacterium*, *Akkermansia*, *Roseburia*, *Helicobacter*, and *Bacteroides* species. The findings suggested that Akkermansia levels in response to capsaicin were sex-dependent and *Akkermansia's* relative abundance and mice body weight were inversely proportional to each other.[24]

In another study, researchers examined the effects of capsaicin treatment on the serum metabolome and gut microbiome in a mice model for Alzheimer's disease. They found that capsaicin treatment led to an increase in the abundance of beneficial gut bacteria like *Akkermansia* and *Faecalibacterium* while decreasing the levels of some harmful bacteria. The serum metabolomic analysis revealed changes in metabolites related to tryptophan metabolism and lipid metabolism in capsaicin-treated mice compared to control mice.[25]

Capsaicinoids in Energy Metabolism

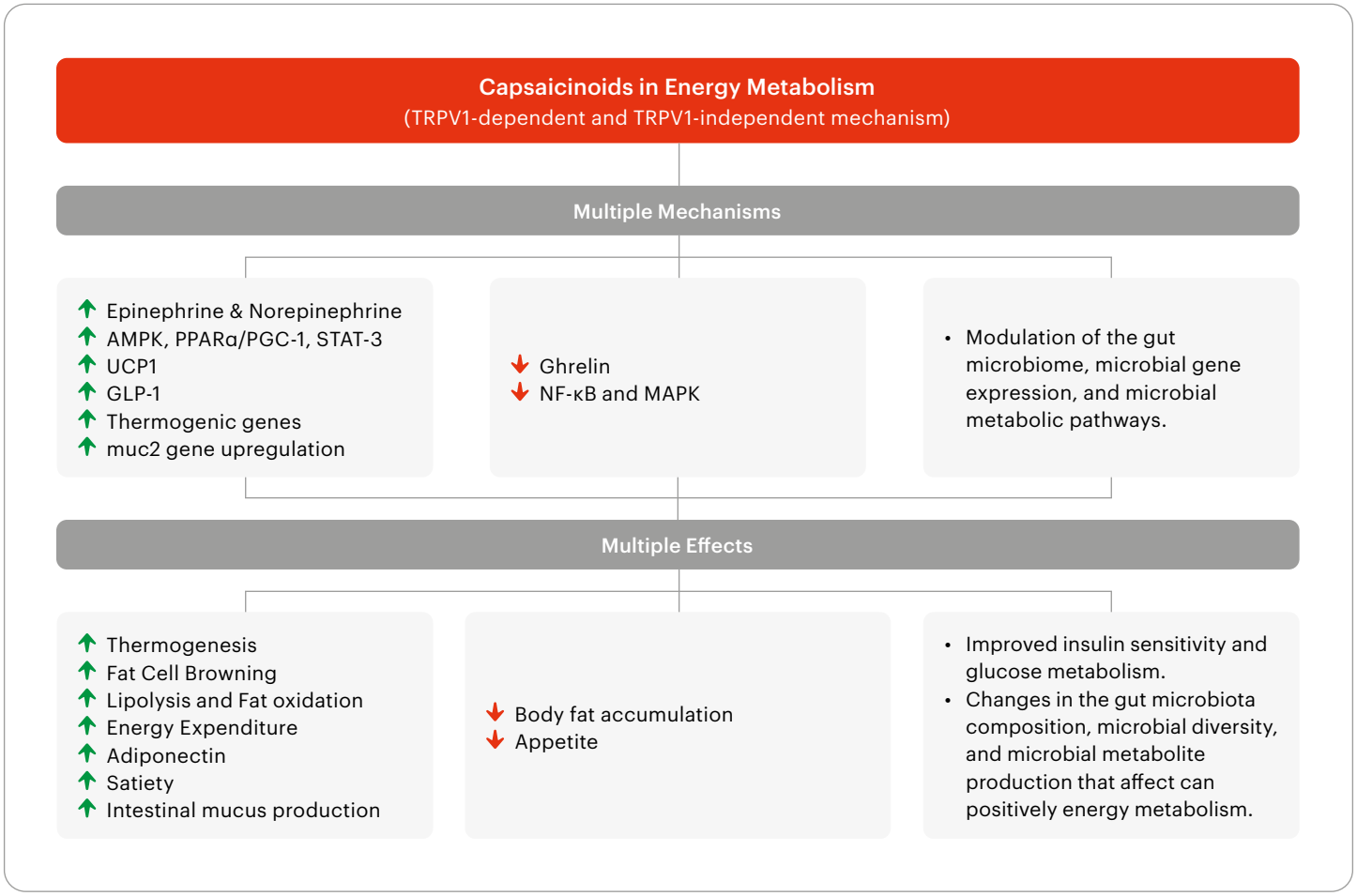
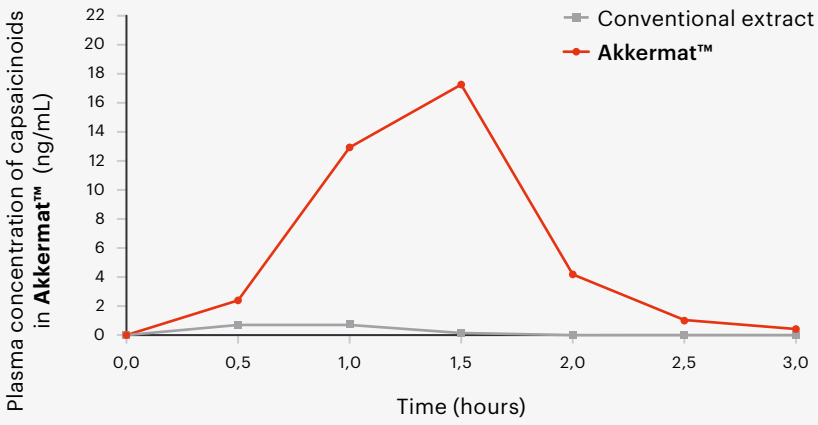


Figure 2. Mechanism of Action of Capsaicinoids in Energy Metabolism. Prepared based on publications of Zheng, Ávila DL, Panchal, and Sanati (4-7). Capsaicinoids including capsaicin bind to and activate TRPV1 receptors, located in various tissues, influencing the expression of genes and secretion of proteins involved in energy metabolism. Abbreviations: AMPK - adenosine monophosphate-activated protein kinase; GLP-1 - Glucagon-like peptide-1; MAPK - microtubule-associated protein kinase; muc2 – gene encoding oligomeric mucus gel-forming protein; NF-κB - the nuclear factor-kappa B; PPARα - Peroxisome proliferator-activated receptor alpha; PGC-1 - PPAR-γ coactivator 1; STAT-3 - signal transducer and activator of transcription-3, TRPV1 - Transient Receptor Potential Channel Vanilloid type-1; UCP1 - uncoupling protein 1.

Bioavailability



Akkermat™ demonstrates safety and significantly higher bioavailability, manifesting a remarkable 19-fold increase in plasma concentration of capsaicinoids when compared to conventional extracts. This enhancement is attributed to the innovative FENUMAT™ technology, which facilitates a prolonged release within the neutral pH environment of the intestine. This unique mechanism also offers protection to the gastric mucosa, mitigating any potential adverse effects associated with direct contact.

Figure 3. Enhanced Bioavailability through FENUMAT™ Technology.

Clinical Insights

Capsaicinoids, the natural compounds found in chili peppers, have been studied for their potential clinical benefits in the management of metabolic syndrome, weight, and appetite control.

The four meta-analysis studies,[26-28] collectively suggest that capsaicinoids, mainly capsaicin, can enhance energy expenditure, promote fat oxidation, and reduce cholesterol and appetite. More specifically, Jang's study focused on *Capsicum annuum* supplementation's impact on factors related to Metabolic Syndrome (MetS). The analysis of 11 studies involving 609 participants indicated that *C. annuum* supplementation significantly **reduced LDL-C levels**.[26] Irandoost's systematic review and meta-analysis centered on the thermogenic effects of capsaicinoids/capsinoids in healthy adults. Thirteen placebo-controlled clinical trials were reviewed, revealing that capsaicinoids/capsinoids supplementation **significantly increased resting metabolic rate (RMR), energy expenditure, and fat oxidation** while decreasing respiratory quotient (RQ) and carbohydrate oxidation.[26] Zsibora's meta-analysis investigated the influence of capsaicin and capsinoids on energy expenditure and respiratory quotient, taking into account participants' BMI (Body Mass Index). The results demonstrated that these compounds significantly **increased energy expenditure and promoted fat oxidation**. Importantly, studies involving participants with a mean BMI exceeding 25 kg/m² showed notable effects, while those with a mean BMI below 25 kg/m² did not exhibit significant changes.[28] In addition, Whiting's systematic search of medical databases using 8 clinical trials for analysis, involving a total of 191 participants, revealed that capsaicinoid ingestion before a meal led to a significant **reduction in ad libitum energy intake** with a minimum dose of 2 mg of capsaicinoids to achieve reductions in energy intake.[29]

Furthermore, in a study with overweight participants who received a capsaicinoid-rich formulation (200 mg formulation equivalent to 4 mg of capsaicinoids) consisting of chili extract encapsulated in a fenugreek extract matrix, for 4 weeks, a significant decrease in body weight (2.1%), waist-to-hip ratio (4%), and body mass index (BMI) (2.2%) was observed compared to the placebo group. Additionally, participants in the capsaicinoids group reported improvements in uncontrolled eating and a reduction in appetite, as indicated by questionnaires.[30]

In the randomized crossover study investigating the effects of capsaicin on appetite profile and energy balance, with fifteen subjects, it was found that capsaicin increased the sensation of fullness and decreased the desire to eat.[31]

In a randomized, double-blind, controlled clinical trial involving adults with low high-density lipoprotein cholesterol (HDL-C), the effects of capsaicin intervention (4 mg daily for 3 months) on serum lipid profiles showed that the capsaicin group experienced a significant increase in fasting serum HDL-C levels. Additionally, levels of triglycerides, C-reactive protein, and phospholipid transfer protein activity decreased in the capsaicin group indicating improved risk factors associated with coronary heart disease (CHD) in individuals with low HDL-C levels.[32]

It is important to note that the effects of capsaicin on metabolism can vary among individuals, and the extent of metabolic activation may depend on factors such as dosage, duration of exposure, individual tolerance, lifestyle, and health status.

Safety

Rest assured, Akkermat™ is designed with safety in mind. Our product undergoes rigorous quality control and is free from harmful additives. Capsaicinoids, when used in the standardized form found in Akkermat™, are safe for most people, but it's contraindicated for children, pregnant or lactating women, and those with gastrointestinal issues or pepper allergies.

Meta-analyses combining data from various sources, including foods and supplements at the capsaicinoid dosages ranging between 2 - 9 mg/day for 4 - 12 weeks, have reported no serious adverse events related to capsaicinoids consumption.[26]

A single-center, open-label, short study involving twelve healthy overweight female subjects, investigated the safety of different doses of capsaicinoids (ranging from 2 mg to 10 mg daily) from *Capsicum* extract compared to a placebo over a week for each dose. The study found that escalating doses of capsaicinoids were well-tolerated and safe for weight management studies. Tolerability assessments and safety blood markers did not show significant changes from baseline, and no serious adverse events were reported during the study duration.[33]

In another study, overweight subjects taking 200 mg daily of a formulation consisting of a chili extract (4 mg capsaicinoids/day) and fenugreek extract for 28 days did not report any adverse events or deviations in hematology and biochemical parameters related to safety.[30]

Moreover, the animal study assessing the safety of capsaicinoids-rich red chili pepper extract combined with fenugreek-derived galactomannan soluble dietary fiber, at acute (300, 2000, 5000 mg/kg body weight for 14 days) and subchronic (250, 500, and 1000 mg/kg body weight) dosage regimen in Wistar rats showed that none of the treated groups, exhibited adverse events related to feeding behavior, urine analysis, or hematology/biochemical parameters when compared to the control group. However, it was noted that the 500 and 1000 mg/kg body weight treated groups experienced a decrease in body weight. As a result, the Low-Observed-Adverse-Effect Level (LOAEL) for this preparation was determined to be 500 mg/kg body weight per day.[34]

Capsaicin can irritate skin, eyes, digestive tract upon ingestion, and respiratory tract upon inhalation. The LD50 in mice is 47.2 mg/kg.[35]

Recommended Use and Dose

Akkermat™ is intended for use as a dietary supplement. For optimal results and based on clinical evidence, the daily dosage of Akkermat™ ranges between 100 mg and 300 mg, equivalent to 2 to 6 mg of capsaicinoids, respectively.

The innovative Fenumat technology with the fenugreek extract rich in galactomannans encapsulating chili pepper extract guarantees a controlled release, ensuring a sustained and lasting effect.

Specifications

Ingredients	Chili pepper extract *(Capsicum annum/frutescens)*, debittered fenugreek extract *(Trigonella foenum-graecum)* rich in soluble dietary fiber, cellulose powder.
Total Capsaicinoids (capsaicin, dihydrocapsaicin, nordihydrocapsaicin)	2%
Additives/Excipients	Sunflower lecithin
Appearance	Free-flowing beadlets
Color	Light yellowish brown
Solvents used	Ethanol, acetone, water
Other	Gluten-free, Vegan, Kosher, Halal, Non-GMO
Storage	Store in tightly sealed containers, at 20-30°C protected from direct sunlight.

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