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REPORT

AMPK

By James Robbins

If one were to travel back in time to the **1800s**, it would have been difficult to imagine that **bacterial diseases** would ever cease being the leading cause of suffering and death.[1]

Even highly educated doctors of the era would point out that no one knew what caused tuberculosis, cholera, diphtheria, and other infectious diseases. Educated skeptics could go further and state that assuming the cause of these plagues was someday discovered—could they ever be cured?

No one could have predicted what happened during the following 100 years. **Bacteria** would be proven to be the cause behind these epidemic killers and **antibiotics** were developed to cure most of them.

The 20th century was characterized by fantastic advances in **life expectancy** as factors behind human mortality shifted from **bacterial infections** to **degenerative disease**.[2]

You're about to discover a novel method to circumvent a major underlying cause of obesity, age-related decline and cessation of life.

As **2015** approaches, we have a **huge advantage** over our ancestors who died of bacterial diseases. We already know many of the underlying causes of **degenerative disease** and are rapidly developing technologies to circumvent them.

In this special issue, we're introducing you to an ***enzyme*** within our cells called **AMPK**. In youth, AMPK is more ***activated***[3] and helps protect against **obesity**[4] and **diabetes**.[5]

As we grow older, cellular **AMPK** activation *decreases,* **weight gain** often follows, and we are more likely to succumb to the destructive factors of **aging**.[6-8]

AMPK is found inside every cell and serves as your body's "**master regulating switch**." It determines **body fat** composition and how **long** you'll live.

Unlike previous generations that wallowed in medical ignorance, documented methods exist right now to activate **AMPK** and in the process, reduce storage of **body fat** and protect against **degenerative disorders** that are today's leading killers.

Scientists view the discovery of **AMPK** as a major advance in how we understand and combat aging. By reactivating cellular **AMPK**, we move tantalizingly closer to gaining meaningful control over deadly aging processes, such as **excessive weight gain**, that predispose us to so many degenerative disorders.

This article will explain the significance of **AMPK** in age-related disease and reveal several proven ways to *enhance* activation of this youth-promoting enzyme.

Why AMPK Levels Decline

Most humans today suffer chronic nutritional overload.[9] When this happens, vital life functions may become disrupted, such as the proper uptake of **glucose**[10] and **fat**[11] from our blood for effective energy regulation.

In response to excess calorie consumption, cellular housekeeping decreases, resulting in the accumulation of **cellular waste**[12] and **damaged proteins**.[13] Abundant food intake impairs beneficial longevity genes while causing pro-inflammatory genes to become dominant.[14]

Just imagine what would happen if you never got out of bed and had all meals delivered to you. In the hospital setting, this lack of mobility increases mortality risk. Your cells are no different.

When cells are chronically over-nourished, the energy-mobilizing ***enzymatic*** activity of AMPK diminishes.[15,16] The outward effects manifest in the form of unwanted weight gain, diabetes, degenerative disease, and premature death.

Few individuals are able to consistently under eat. Fortunately, scientists have identified a cellular enzyme called **AMPK** that, when activated, mimics many of the beneficial effects observed in calorie restrictors, including **loss of surplus body fat**.[17]

WHAT YOU NEED TO KNOW

AMPK Promotes Longevity And Reduces Fat Storage

- The science of bioenergetics is producing paradigm-shifting discoveries, including the role of AMPK in regulating the ways our bodies use and transform energy.
- AMPK is the "switch" that is the link between metabolic disease, inflammation, and longevity. This "switch" tells our cells when to store and generate energy-containing molecules such as fat, and when to "hunker down" and use existing energy stores.
- When switched "on," AMPK triggers the use of stored energy from fats, enhances removal of fats and sugar from the blood, increases production of mitochondria, and reduces inflammation and cellular "junk."
- Calorie restriction and vigorous exercise activate AMPK, shrinking body fat stores (especially in the belly region), lowering blood sugar and lipid levels, and producing other beneficial effects that retard the aging process.
- The drug metformin also activates AMPK, with similar body-wide results.
- A pair of natural botanical extracts have now been found to activate AMPK, reducing belly fat, cholesterol, blood sugar, and insulin levels.
- Instead of combating longevity threats using multiple drugs, supplementation with AMPK-activating botanicals can address these problems at its source.
- Age-induced risk factors can be tackled efficiently by boosting AMPK activity with Gynostemma pentaphyllum and trans-tiliroside from rose hips.

Your Cells' "Master Switch"

A large part of the reason you are alive at this moment is because of the ***enzymatic reactions***[18,19] occurring in the **trillions** of cells[20] in your body.

Cells can be described as little bundles of biochemical reactions. **Enzymes** often make biochemical reactions in the cell possible. Vital life functions our cells perform are dependent on cellular ***enzyme*** activity.

Over the past 30 years, scientists have been investigating the properties of an ***enzyme*** called **AMPK**, which is a " **master switch**"[21] that, in many ways, controls how our cells behave.

Extensive research shows that by increasing **AMPK** activation, we can reduce many of the destructive factors of aging, thus enabling cells to return to their youthful vitality.

In preclinical research, enhanced **AMPK** activity has been associated with a **20-30%** increase in life span,[7,22,106] but that's just the beginning of the health benefits conferred by this critical cellular enzyme.

Increased **AMPK** activation has been shown to help reduce **fat storage** (especially dangerous belly fat), increase **insulin sensitivity** (to lower blood glucose), reduce **cholesterol/triglyceride** production, and suppress **chronic inflammation**.[7,23] All of these factors underlie the lethal diseases of aging.

WHAT IS AMPK?

AMPK is found in every cell in our body.[23,24] It serves as the body's "master regulating switch" that fends off degenerative factors by *revitalizing* aging cells.

AMPK is involved in reducing fat storage,[25] regulating glucose uptake,[26,27] creating new mitochondria,[28] and eliminating cellular garbage that accumulates inside aging cells.[29]

The discovery of how **AMPK** regulates aging processes has been decades in the making. A PubMed search now delivers over **7,500** published articles on various aspects of AMPK. For those who are curious, **AMPK** is the acronym to define the enzyme ***adenosine monophosphate-activated protein kinase***.[30]

An important property of AMPK is that it induces multiple ***longevity factors***, which have been shown to increase stress-resistance and extend life span in many organisms.[31,32]

One such longevity factor boosted by AMPK is the **SIRT1** enzyme.[7] **SIRT1** operates by silencing genes that code for unhealthy responses to stress, including the inflammatory response,[33,34] excess fat storage,[35] and new fat production.[32,36,37] SIRT1 activity is also increased by **calorie restriction**,[38,39] the only fully proven way to increase life span in all animal models tested to date, further indicating the importance of AMPK in activating SIRT1.[40,41]

Resveratrol found in red wine helps activate SIRT1,[42,43] but AMPK activates SIRT1 more directly.[7,44,45]

The Dangers Of Reduced AMPK

In many ways, AMPK acts as a traffic cop, efficiently moving excess fat and sugar into our cells to be burned for energy. When we are young, AMPK keeps our metabolic functions running smoothly. Ideally, we are slim and disease-free. But as we age, AMPK signaling declines, which may quickly lead to an excess buildup of blood glucose and dangerous fat accumulation.[7] This turns into a lethal combination for many aging humans.

With reduced AMPK signaling, a range of damaging conditions begins to take over a previously healthy body, often leading to an early death. These damaging conditions include:

- Increased belly fat,[46,47]
- Chronic inflammation,[7,46,47]
- Elevated blood sugar,[46-49]
- Insulin resistance,[7,46-49]
- High cholesterol and triglycerides,[46,47]
- Decreased numbers and function of mitochondria,[7,46,47]
- Increased accumulations of abnormal or damaged proteins in our cells that lead to neurodegeneration.[7,50]

Conventional medicine diagnoses and treats each of the above conditions as a separate disease requiring separate medications when, in fact, they are all associated with one source: declining **AMPK** activity.

Another deadly impact of reduced AMPK activation is a decreased number of functional mitochondria[28,51] and the accumulation of cellular garbage,[7,52,53] which eventually renders cells nonfunctional.[50,54,55]

As scientists continue to unravel the mystery of **AMPK**, they are discovering that many of the known biochemical longevity factors (such as **SIRT1**, **FoxO**, and **p53**) are activated by normal **AMPK** function.[7] For example, **p53** is a tumor-suppressing gene that inhibits uncontrolled cell propagation. Without AMPK, these longevity genes fail to perform their duties, potentially resulting in premature death.[7,32]

Fortunately, research demonstrates that when AMPK signaling is boosted, these deteriorating processes are reversed,[56] restoring more youthful metabolism, preventing related chronic diseases, and potentially adding years of useful, productive life.

HOW TO BOOST AMPK

As researchers continue to unravel the mysteries of AMPK, they have discovered four ways to boost the body's AMPK activity:

1. **Exercise:** AMPK activity increases with regular vigorous exercise.[72] This beneficial effect of exercise on AMPK, however, may vanish in the elderly.[5]
2. **Calorie Restriction:** When you under eat, you create increased AMPK activity as cells sense a requirement to function more efficiently in the presence of diminished energy (food) intake. However, when normal food intake resumes, AMPK activity declines.[73,74]
3. **Metformin:** One of the drug metformin's most beneficial mechanisms is to activate AMPK.[75] This is one way it lowers elevated glucose.[76] Unfortunately, most physicians only prescribe metformin for type II diabetes, making access to this drug difficult for most people. Some people also experience digestive upset in response to metformin and cannot take it.[77]
4. **Botanical Extracts:** Two natural agents (the Chinese herb ***Gynostemma pentaphyllum***[78] and ***trans* -tiliroside derived from rose hips**[79]) have been shown to activate **AMPK**. Each of these agents triggers different downstream metabolic benefits, and in one study, ***trans*-tiliroside** led to an even **greater** glucose-lowering effect than the AMPK-activating antidiabetic drug **metformin**.[80]

With these four documented methods of boosting **AMPK** signaling, there is no reason for aging humans to suffer the degenerative impact caused by loss of activated AMPK.

Beneficial Effects Of Restoring AMPK

When AMPK is increased, the body kicks into high gear and functions with youthful vitality. Activated AMPK helps remove excess glucose and fats, burning them for energy instead of depositing them in the belly and elsewhere.[57,58] To support all this increased fat burning, cells manufacture new mitochondria in a process known as *mitochondrial biogenesis*.[59] These newly created mitochondria burn fuel more cleanly and efficiently than older, worn-out mitochondria,[60] resulting in a higher energy output for the entire body.[61-63]

AMPK-activated cells are generally cleaner, healthier cells. Old cells with decreased AMPK activity tend to become clogged with cellular debris, which reduces their efficiency and shortens their life span. These junk-laden cells accelerate the aging process and contribute to neurodegenerative diseases like Alzheimer's[7] and Parkinson's,[64] and to the thickening and stiffening

of vital tissues throughout the body.[65,66]

Cells that have been energized by AMPK empty their internal garbage cans of accumulated damaged proteins and then convert these damaged proteins for recycling into healthy new ones.[55,67] The result of AMPK re-activation is enhanced efficient cellular activity. Finally, increased AMPK activation can suppress body-wide inflammatory responses such as those produced by excess belly fat.[62]

Over the last few years, research has shown that it is possible to revitalize AMPK to youthful levels of activity. To date, experiments have shown that increased AMPK activation is associated with:

- Extended life span by as much as **20-30%** in animals,[7,22,104]
- Improved glucose uptake in cells, lowering blood sugar,[57,68,69]
- Inhibiting excess fat synthesis and increased burning of stored fat,[17,70]
- Reduction of blood triglycerides,[71]
- Decreased liver fat accumulation and fat-related chronic inflammation,[62]
- Increased numbers of new, healthy mitochondria.[61-63,68]

Fat-Loss Effects Of New AMPK-Activator

Gynostemma pentaphyllum is a plant distantly related to the cucumber.

In traditional Asian medicine, it's used to promote longevity.[81] Today's scientists have discovered why Asian doctors prescribed *G. pentaphyllum* to address age-related health issues: It promotes **AMPK** activation.[78,82]

G. pentaphyllum not only activates **AMPK**, but it also shuttles excess fats into the mitochondria to be utilized for energy and safe disposal.[82] The result is efficient energy production and a sharp reduction in unnecessary **fat storage**.

Results of *G. pentaphyllum*-induced AMPK activation include increased **fat burning**, as well as an increase in cellular **glucose uptake**.[78,82] Extracts of *G. pentaphyllum* have other beneficial properties as well, including the ability to prolong cellular life in the face of stresses induced by oxidation, fat accumulation, and diabetes.[83,84]

When scientists began exploring the benefits of *G. pentaphyllum* for AMPK activation, they turned to animal studies. What they found was that leaf extracts of *G. pentaphyllum* activate **AMPK**, resulting in reduced body weight gain and fat accumulation.[78] In a preclinical study, obese mice supplemented with *G. pentaphyllum* showed impressive declines in markers associated with obesity and its related diseases.

In another study, this time using **diabetic** rats, three weeks of *G. pentaphyllum* supplementation resulted in improved glucose tolerance by **35%** and reduced new glucose production in the liver by **29%**, with a reduction in liver glycogen, the storage form of sugar.[85]

These results show the enormous beneficial impact of reducing circulating sugar and fats in response to **AMPK** activation by *G. pentaphyllum*.

Human studies have confirmed what many of the researchers had found in the lab: *G. pentaphyllum* boosts **AMPK activity** and provides important longevity benefits.

In a compelling human study, **type II diabetics** who were not using diabetic medications drank a tea made with *G. pentaphyllum*. The results compared to controls were:[86]

- A **5-fold** reduction in **fasting glucose**,
- A **10-fold** reduction in **hemoglobin A1c**, a measure of chronic glucose exposure,
- A near **3-fold** decrease in **insulin resistance**,
- No dangerously low blood sugar episodes, which can often occur with certain oral antidiabetic drugs (especially sulfonylurea class drugs).

In another human study, those taking *G. pentaphyllum* significantly boosted the effects of a sulfonylurea antidiabetic drug, producing an additional fasting glucose reduction of **52.2 mg/dL** compared with just **16.2 mg/dL** for the drug alone.[87]

None of these findings should be surprising since the prescription drug **metformin**, which is an AMPK activator, produces many of these same benefits.[88,89]

AMPK-Boosting Effects Of Trans-Tiliroside

The second **natural** compound found to increase **AMPK activity** is ***trans*- tiliroside**, extracted from plants such as rose hips.

***Trans*- tiliroside** also boosts **AMPK** signaling, but it triggers different downstream metabolic benefits than *G. pentaphyllum.*[79,90,91] Combining these two bioactives (*G. pentaphyllum* and *trans*-tiliroside) provides broader **AMPK** activation effects than each one separately.

Scientists are now finding that *trans*-tiliroside increases the **GLUT4** transporter in cell membranes, which helps pull excess sugar out of the blood and into cells, where it is burned for energy, thereby reducing circulating blood glucose.[91]

In animal studies, *trans*-tiliroside supplementation significantly reduces dangerous *after-meal* **glucose** spikes while also suppressing surges in **insulin**.[92] A laboratory study of insulin-resistant human liver cells found that *trans* -tiliroside boosted cellular glucose consumption in a manner that compared favorably to **metformin**, a widely used antidiabetic drug.[93]

Not surprisingly, in mouse models of diabetes, daily oral administration of *trans*-tiliroside reduced fasting blood sugar by up to nearly **30%** after 15 days of treatment, while diabetic mice treated with metformin had a near **23%** reduction.[80] Supplemented animals also had significant reductions in serum triglycerides and total cholesterol, while experiencing beneficial increases in HDL cholesterol levels.

And in obese-diabetic mice, supplementation with *trans*-tiliroside increased fat burning, lowered plasma insulin, lowered free fatty acids, and lowered triglycerides, while increasing levels of *adiponectin,* a protein hormone that regulates glucose and breaks down fat.[90] Moreover, oral supplementation of *trans*-tiliroside in mice for two weeks with the human equivalent dose of **56 mg/day** significantly reduced plasma **glucose** levels.[94]

Along with reducing the dangers of excess blood glucose, *trans*-tiliroside has been shown to battle obesity, especially by reducing cellular **fat**. In a laboratory experiment, *trans*-tiliroside also demonstrated reduced plasma cholesterol and a lower ratio of LDL to HDL (which means beneficial HDL levels increased in relation to atherogenic LDL).[80]

Another study showed that ***rose hip powder*** prevented obesity in lean mice on a high-fat diet and reversed weight gain and body fat mass increases in obese mice on the same diet.[95] Baseline levels of glucose and insulin were lowered and glucose tolerance was improved.

An additional manifestation of AMPK activation resulted in a reduction in liver fat stores, the result of reduced fat production.[95] Still more impressively, studies have now shown that *trans*-tiliroside can significantly inhibit the accumulation of **visceral fat** and gain in body weight in mice after just two weeks' supplementation, without any change in food intake at the human equivalent dose of **56 mg/day**.[94]

Are AMPK Activators Weight-Loss Agents?

When **AMPK** is activated, cells go into a survival mode, making and storing no new fat, while burning up available fat from storage, pumping glucose in from the blood for additional energy, building new mitochondria for more efficient energy use, and recycling damaged or dysfunctional proteins. These are all beneficial anti-aging mechanisms.

The net effects of **AMPK** activation closely resemble those of **calorie restriction** and vigorous exercise. This is because both calorie restriction and vigorous exercise activate AMPK in response to energy needs that exceed supply. The drug metformin independently activates AMPK, producing similar benefits, which include reduction in dangerous belly fat stores, general weight loss, and reductions in blood sugar and fat levels.[77,96,97]

G. pentaphyllum and ***trans*-tiliroside** have induced profound **weight-loss** effects in controlled studies. The question is how well will they work in real-world settings, where overweight individuals often over-consume so many calories that no drug, hormone, or supplement can induce meaningful fat loss.

The answer to the question of the weight-loss benefits of **AMPK** activators can be analogized to cancer patients who take aggressive steps to boost **immune** function. Restoring optimal immune status alone will not cure most malignancies, but failing to address immune deficits places cancer patients at significantly greater risks of dying.

Likewise, we suspect that ***G. pentaphyllum*** and ***trans*-tiliroside** by themselves are not going to enable significantly overweight individuals to become normal weight. But if one is serious about shedding excess body fat, and they don't take steps to reactivate their cellular **AMPK**, it may be less likely that they will be able to achieve their fat-loss objectives.

In response to aging, vigorous **exercise** may not induce an **AMPK** activating effect[5] and most people are unable to consistently restrict their **caloric intake**.

It's abundantly clear that those seeking to shed excess fat (especially in the belly) should take measures to activate their **AMPK** so that they may assist the body in restoring the youthful enzymatic activity needed to help safely manage body weight.

DEADLY DELAYS…

What History Has Taught Us

In **1796**, Edward Jenner demonstrated that inoculation using fluid from cowpox lesions could safely prevent **smallpox**.[101]

This research was initially rejected, but by **1840**, the British government provided Jenner's smallpox vaccine free of charge.

What few people realize is that **700 years** before Jenner's discovery, the Chinese had developed a crude form of inoculation. Yet no one in Europe paid attention despite widespread smallpox outbreaks that ravaged all social classes.

Even more surprising are the **300 million** people who perished from **smallpox** in the **20th century**[102] because of the delay in implementing universal smallpox vaccination.

When Edward Jenner discovered the smallpox vaccine, no one knew that **viruses** existed. They only observed that those inoculated with his vaccine were immune from smallpox for life.

Gynostemma pentaphyllum was first described in a Chinese medical book in **1406**.[103] Doctors in the following centuries discovered the multiple disease-fighting benefits this herb conveyed, but they had no idea how it worked in the body. Back in those days, no one knew about blood **glucose** and certainly nothing was understood about something as sophisticated as **AMPK**.

All doctors could do in early centuries was observe the beneficial effects that occurred when patients were treated with ***Gynostemma pentaphyllum***.

Today we know that declining **AMPK** activity predisposes humans to **degenerative diseases**, and we know of validated methods to markedly increase **AMPK** signaling. One low-cost approach to activating AMPK is to take **450 mg** of standardized ***Gynostemma pentaphyllum*** extract daily plus **56 mg** of ***trans*-tiliroside** for optimal effects.

Summary

Activating **AMPK** represents a **major advance** in our ability to combat degenerative disease and obesity. AMPK is now being intensively studied in the prevention and treatment of many age-related disorders.[98,99]

When **AMPK** is activated, cells decrease production and storage of new **fat** and burn stored body fat. In addition, AMPK activation results in glucose being pumped out of the blood and into cells for additional energy. Mitochondrial biogenesis occurs, leading to more efficient energy use while cellular debris and dysfunctional proteins are removed.

The net effects of **AMPK** activation closely resemble those of **calorie restriction** and vigorous exercise. This occurs because both calorie restriction and vigorous exercise activate AMPK in response to energy needs that exceed supply. (Exercise may not increase AMPK in elderly individuals.)[5]

Gynostemma pentaphyllum and ***trans*-tiliroside,** two naturally sourced extracts, uniquely increase **AMPK** activation without drugs, severe calorie restriction, or exercise. Studies show that these supplements significantly reduce risky belly fat accumulation, promote weight loss, normalize blood sugar, improve insulin resistance, and lower serum lipid levels.

When looking at the chart on this page, one can see that human life expectancy has more than doubled since the founding years of our country.

What's encouraging is that these averages include people who don't take care of themselves (including tobacco smokers and those who eat an unhealthy diet). This means that individuals who follow healthier lifestyles, which includes taking steps to activate AMPK, may add many more healthy years to their projected life spans.

According to the latest data, a man reaching age 65 today can expect to live on average until age **84.3**. Women have it better and can expect to live to **86.6** if they make it to age 65. One out of every four 65-year-olds will live past age **90**.[100] Life Extension®'s healthy longevity objectives stretch far beyond this.

Activation of the **AMPK enzyme** is a critical component in warding off degenerative disease. As stated in the beginning of this article, vital life functions are dependent on cellular ***enzyme*** activity.

By activating cellular **AMPK**, we provide our body with the opportunity to reverse physical and mental decline associated with aging, buying us time to take advantage of future **longevity breakthroughs** that will markedly extend healthy human life spans.

If you have any questions on the scientific content of this article, please call a **Life Extension®** Wellness Specialist at 1-866-864-3027.

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