
**Teir 1: Supplements**

**NMN:** (B-nicotinamide mononucleotide) is a form of Vitamin B3 that plays crucial role in maintaining and increasing NAD+ in the body. See below for summary of the importance of boosting NAD levels:

https://jgignac.com/nmn-powder

**TMG:** Anti-Inflammatory, liver protectant and methyl donor that supports conversion of NMN to NAD in the body. TMG supports methylation and works especially well to assisting the conversion of NMN to NAD.

https://jgignac.com/tmg

**Trans-Resveratrol Powder:** Anti-inflammatory, activates the Sirtuins genes, a class of signaling proteins that strength the human biology through autophogy, DNA repair and much more. Sirtuins are NAD dependant. Low NAD levels = LOW Sirtuin activity. See below for summary of the role of the Sirtuin genes:

https://jgignac.com/resveratrol-powder

**Fisetin**: Is a powerful natural senolytic, which has the ability to clear senescent cells, activate AMPK, lower inflammation and increase $NAD.^{+}$ In addition to support elevated NAD levels, it is very good and helping the body get rid of zombie cells (senescent cells) that cause inflammation in the body. See below for more on the since of senolytic compounds and senescent cells

https://jgignac.com/lipo-fisetin

**Molecular Hydrogen (H2):** Help to powerfully limit the oxidative damage that can lead to accelerated cellular aging and changes in your cells and organs.

https://jgignac.com/MolecularHydrogen

**Methylene Blue:** Is a strong anti-oxidant neuroprotectant, enhances mitochondrial function and much more. See below for more information potential side-effects. Methylene Blue is not for everyone.

https://jgignac.com/MethyleneBlue

**CaAKG (Alpha-Ketoglutarate):** Support healthy aging, mitochondrial function & metabolic health. See below for more information.

https://jgignac.com/caakg

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# The Critical Role of NAD

Nicotinamide adenine dinucleotide (NAD) plays a crucial role in the metabolic pathways that generate energy within cells. Its main functions in energy metabolism can be summarized as follows:

1. **Redox Reactions**: NAD exists in two forms: NAD+ (oxidized form) and NADH (reduced form). It serves as an electron carrier in various biochemical reactions. When a molecule is oxidized, it loses an electron (and sometimes a proton), and NAD+ accepts this electron, becoming NADH. Conversely, NADH can donate this electron to other molecules, returning to its oxidized form.

2. **Glycolysis**: In the glycolytic pathway, which breaks down glucose into pyruvate, NAD+ is reduced to NADH in the reaction catalyzed by the enzyme glyceraldehyde-3-phosphate dehydrogenase. This NADH can later be used to produce ATP, the cell's main energy currency.

3. **Citric Acid Cycle (Krebs Cycle or TCA Cycle)**: During this cycle, which is central to aerobic metabolism, NAD+ is reduced to NADH in several steps. These NADH molecules produced are then used in the electron transport chain to produce ATP.

4. **Electron Transport Chain (ETC) and Oxidative Phosphorylation**: Located in the inner mitochondrial membrane, the ETC uses NADH (and another molecule, FADH2) to transfer electrons through a series of protein complexes. This electron transfer creates a proton gradient across the inner mitochondrial membrane, which drives ATP synthesis through the ATP synthase enzyme. Oxygen is the final electron acceptor in this chain, combining with electrons and protons to form water.

5. **Beta-Oxidation**: This is the pathway by which fatty acids are broken down to produce energy. NAD+ is again reduced to NADH during this process, and the NADH produced is used in the electron transport chain to generate ATP.

6. **Regeneration of NAD+**: The conversion of NADH back to NAD+ is essential for many metabolic processes (like glycolysis) to continue. In the presence of oxygen, this regeneration mainly happens in the mitochondria via the electron transport chain. In anaerobic conditions (absence of oxygen), cells often use fermentation pathways to regenerate NAD+. In human muscle cells, this leads to the production of lactate.

7. **Other Roles and Signaling**: Beyond energy metabolism, NAD+ and its related molecules play roles in DNA repair, gene expression, and cell signaling. NAD+ is also a substrate for several enzymes that are involved in longevity and cellular health, such as sirtuins.

In summary, NAD is a central molecule in cellular energy metabolism, participating in a multitude of reactions that lead to ATP production, the cell's primary energy currency.

## The role of Sirtuin Genes:

Sirtuins are a family of proteins that have garnered significant attention due to their roles in metabolism, aging, and overall cellular health. In mammals, there are seven sirtuins (SIRT1-SIRT7), and each has distinct cellular locations and functions. They are NAD+-dependent deacetylases, meaning they remove acetyl groups from other proteins in the presence of the cofactor NAD+. Here are some of the key roles and functions of sirtuins:

1. **Cellular Metabolism and Energy Homeostasis**:

   - **SIRT1**: It is involved in the regulation of metabolic pathways in response to nutrient availability. Activated by caloric restriction, SIRT1 can deacetylate key metabolic regulators like PGC-1α and FOXOs, leading to enhanced mitochondrial function and improved oxidative metabolism. SIRT1 also plays a role in regulating circadian rhythms and glucose homeostasis.

   - **SIRT3, SIRT4, and SIRT5**: These sirtuins are primarily found in mitochondria and regulate various aspects of mitochondrial metabolism. SIRT3, for example, has been shown to promote mitochondrial fatty acid oxidation, ATP synthesis, and the antioxidant response.

2. **DNA Repair and Genome Stability**:

   - **SIRT1 and SIRT6**: They play roles in DNA repair pathways, ensuring the integrity of the genome. For instance, SIRT6 promotes DNA double-strand break repair.

3. **Cell Survival and Stress Resistance**:

- **SIRT1 and SIRT3**: Activation of these sirtuins can lead to increased resistance to oxidative stress, thereby promoting cell survival. This is, in part, due to the deacetylation and activation of various antioxidant enzymes and regulators.

4. **Aging and Longevity**:

- Studies, especially in lower organisms like yeast, worms, and flies, have shown that increasing sirtuin activity can extend lifespan. The role of sirtuins in mammalian lifespan is still a topic of research, but it's clear that they play crucial roles in many processes related to aging, including DNA repair, stress resistance, and metabolic regulation.

5. **Inflammation and Cellular Health**:

- **SIRT1 and SIRT6**: Both have anti-inflammatory roles, in part by repressing the activity of NF-κB, a key regulator of inflammatory gene expression.

6. **Regulation of Protein Homeostasis**:

- Sirtuins can also post-translationally modify other proteins, thereby affecting their stability, activity, or localization. This helps in maintaining proper protein function and cellular homeostasis.

7. **Chromatin Remodeling and Gene Expression**:

- **SIRT1, SIRT6, and SIRT7**: Located in the nucleus, these sirtuins can modify histones, leading to alterations in chromatin structure and, consequently, gene expression. For example, SIRT1-mediated deacetylation of histone H4 at lysine 16 promotes gene silencing.

Given the central roles sirtuins play in cellular metabolism, health, and longevity, they have become attractive targets for therapeutic interventions in various diseases, including metabolic disorders, neurodegenerative diseases, and aging-related conditions.

## Fisetin: Why is it important to clear senescent cells?

Senescent cells are cells that have entered a state where they no longer divide but remain metabolically active. This cellular state can be triggered by various stressors, such as DNA damage, telomere shortening, oxidative stress, or oncogenic signals. While cellular senescence is a defense mechanism against potential tumor formation (by preventing damaged cells from proliferating), the accumulation of senescent cells in tissues can have detrimental effects. Here are several reasons why it is important to clear senescent cells:

1. **Chronic Inflammation**: Senescent cells secrete a variety of pro-inflammatory cytokines, growth factors, and proteases, a phenomenon termed the senescence-associated secretory phenotype (SASP). This can induce chronic inflammation in tissues, which is a key contributor to many age-related diseases.

2. **Tissue Dysfunction**: The SASP can also disrupt the function and structure of tissues. For example, the pro-inflammatory environment can inhibit tissue regeneration, alter extracellular matrix composition, and even promote fibrosis.

3. **Promotion of Tumorigenesis**: While cellular senescence is a defense against cancer, the paradox is that the SASP can have pro-tumorigenic effects. The secreted factors can stimulate the growth of nearby precancerous cells or promote an environment conducive to tumor growth.

4. **Impaired Tissue Repair**: Senescent cells can negatively influence stem cell function, thus impeding the repair and regeneration of tissues. This can slow down the body's ability to heal wounds or regenerate tissues.

5. **Contribution to Age-related Pathologies**: Accumulation of senescent cells is observed in various age-related diseases, including osteoarthritis, atherosclerosis, Alzheimer's disease, and others. Clearing senescent cells has been shown in animal models to mitigate these conditions.

6. **Potential for Rejuvenation**: Animal studies have indicated that removing senescent cells can lead to rejuvenation effects. For instance, in mouse models, clearance of senescent cells led to improved healthspan, delayed onset of age-related pathologies, and even extended lifespan.

Given the implications of senescent cell accumulation in aging and age-related diseases, there is growing interest in developing therapeutic strategies to selectively remove or rejuvenate these cells. These strategies, termed senolytics (drugs that can selectively kill senescent cells) and senomorphics (drugs that can modulate the SASP), are being explored for their potential benefits in treating age-related conditions and improving healthspan.

## Benefit of Methylene Blue

Methylene blue, a synthetic compound with a blue hue, has been used historically as a dye, in biological staining, and for medical purposes. More recently, research has explored its potential as a therapeutic agent in a variety of conditions. While not all applications have well-established evidence, some of the potential health benefits and therapeutic uses of methylene blue include:

1. **Methemoglobinemia Treatment**: One of the classic and approved medical uses of methylene blue is for the treatment of methemoglobinemia, a condition where the iron in hemoglobin is oxidized, making it unable to bind and carry oxygen effectively. Methylene blue helps reduce methemoglobin back to hemoglobin.

2. **Potential Neuroprotective Agent**: Some research suggests methylene blue might have neuroprotective effects, possibly benefiting conditions like Alzheimer's disease and Parkinson's disease. The proposed mechanisms include enhancing mitochondrial function and reducing tau protein aggregation.

3. **Cognitive Enhancement**: Preliminary studies have indicated that methylene blue might improve cognitive function and memory. The mechanisms could be linked to its effects on brain energy metabolism and increasing oxygen availability.

4. **Antimicrobial Properties**: Methylene blue has demonstrated antimicrobial effects against certain bacteria, parasites, and viruses. Historically, it has been used as an antimalarial agent.

5. **Cancer Therapy**: There's ongoing research into methylene blue's potential role in cancer treatment, specifically in enhancing the effectiveness of radiation therapy and some types of chemotherapy.

6. **Vasoplegia Syndrome Treatment**: Methylene blue has been used as a treatment for vasoplegia during cardiopulmonary bypass surgery, which is a condition where blood vessels fail to constrict in response to vasoconstrictor agents, leading to dangerously low blood pressure.

7. **Antioxidant Properties**: Methylene blue can act as both an antioxidant and a pro-oxidant, depending on the context. Its antioxidant properties may help protect cells from damage in certain situations.

8. **Potential in Psychiatric Disorders**: Some preliminary studies suggest methylene blue might have potential in treating bipolar disorder and depression, possibly due to its effects on the monoamine oxidase enzyme.

However, while methylene blue has potential therapeutic benefits, it is essential to note that it can also have side effects and interact with other medications. For instance, when combined with certain serotonin reuptake inhibitors (a class of antidepressants), there's a risk of serotonin syndrome, a potentially life-threatening condition.

As always, any consideration of using methylene blue or any other drug for therapeutic purposes should be discussed with a healthcare professional.

## Benefits of CaAKG:

Calcium alpha-ketoglutarate (CaAKG) is a salt form of the molecule alpha-ketoglutarate, which is a key intermediate in the Krebs cycle (also known as the citric acid cycle or TCA cycle). This cycle is a central metabolic pathway involved in cellular energy production. Alpha-ketoglutarate and its salt forms have been studied for various health benefits, though research is ongoing. Some potential health benefits and applications of CaAKG include:

1. **Lifespan and Healthspan Extension**: Preliminary studies, particularly in model organisms like worms, have suggested that alpha-ketoglutarate might promote lifespan extension. Research is still in early stages, and the mechanisms and potential benefits in humans remain to be thoroughly studied.

2. **Bone Health**: There's some evidence to suggest that alpha-ketoglutarate may benefit bone health, possibly by promoting collagen synthesis and reducing bone breakdown.

3. **Muscle Mass and Athletic Performance**: Alpha-ketoglutarate has been studied for its potential role in promoting muscle growth and enhancing athletic performance, though the evidence is mixed. Some believe it might improve exercise endurance and strength by enhancing the Krebs cycle function.

4. **Supporting Kidney Health**: Alpha-ketoglutarate might help in the prevention and treatment of kidney stones by binding with ammonia and other waste products to be excreted in the urine.

5. **Wound Healing**: Some studies suggest that alpha-ketoglutarate could play a role in accelerating wound healing, possibly through collagen synthesis promotion.

6. **Neuroprotective Effects**: Alpha-ketoglutarate may have neuroprotective properties, potentially beneficial in conditions like Alzheimer's disease or other neurodegenerative disorders.

7. **Liver Health**: Alpha-ketoglutarate has been proposed to support liver health and function, possibly by aiding in the detoxification of ammonia and other waste products.

8. **Reduction of Protein Breakdown**: In some clinical settings, like major surgeries, trauma, or sepsis, alpha-ketoglutarate has been studied for its potential to reduce muscle protein breakdown.