Beyond The Spine: Navigating Traumatic Injuries and Promoting Healthy Aging and Longevity In Your Practice

Introduction to Brain-Based Therapies/Neuro-Orthopedic Rehabilitation for Concussions & Traumatic Injuries Like Post-Auto Whiplash

Dr. Erik Reis DC, DACNB, CBIS

Erchonia Clinical Educator
Board Certified Doctor of Chiropractic
Board Certified Chiropractic Functional Neurologist
Certified Brain Injury Specialist
Clinic Director/Founder - The Neural Connection - Edina, MN, USA
Co-Founder, Director of Health and Wellness - Nobody Studios - Los Angeles, CA, USA

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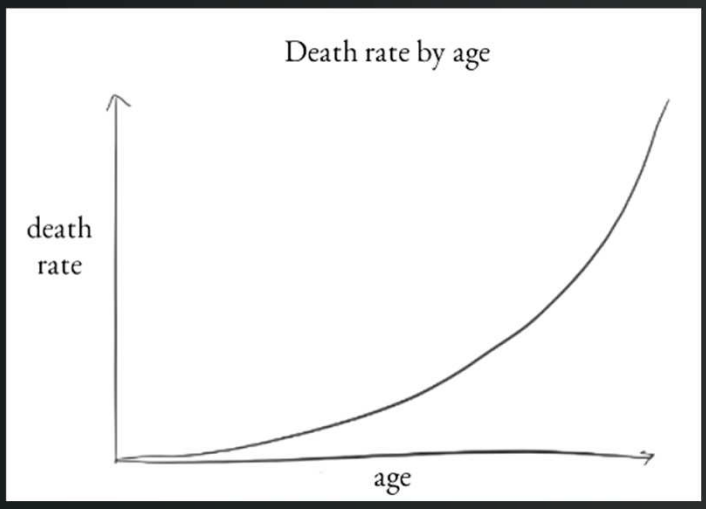
Diet, Lifestyle, and Nutrition for Longevity

2

Our Chance of Death Goes Up With Age



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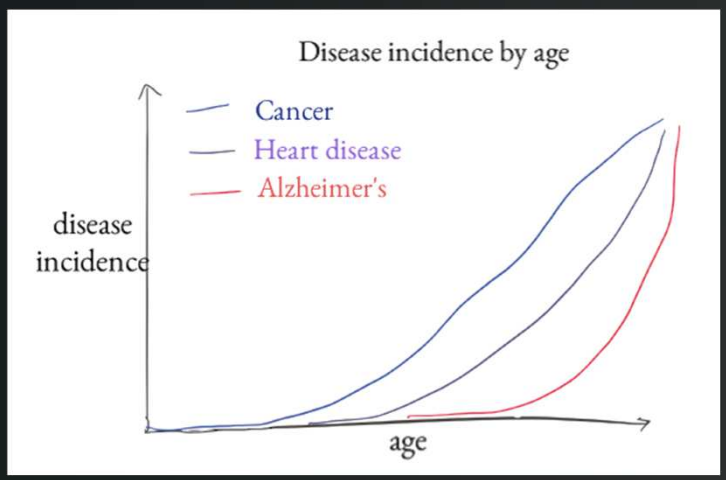
Our Chances for Disease Also Go Up



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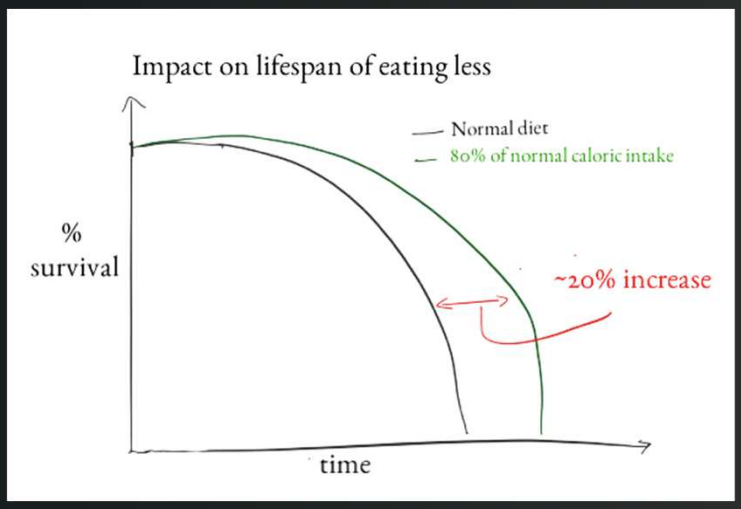
Eating Less Makes Mice Live Longer



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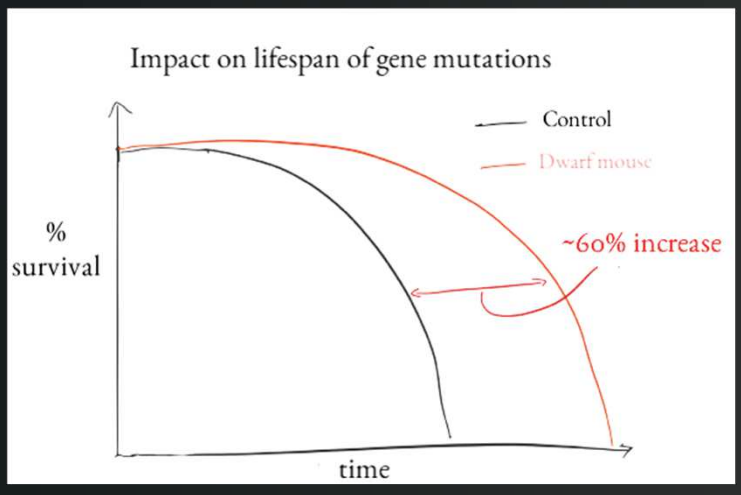
Specific Genes, When Mutated, Make Mice Live Longer Too



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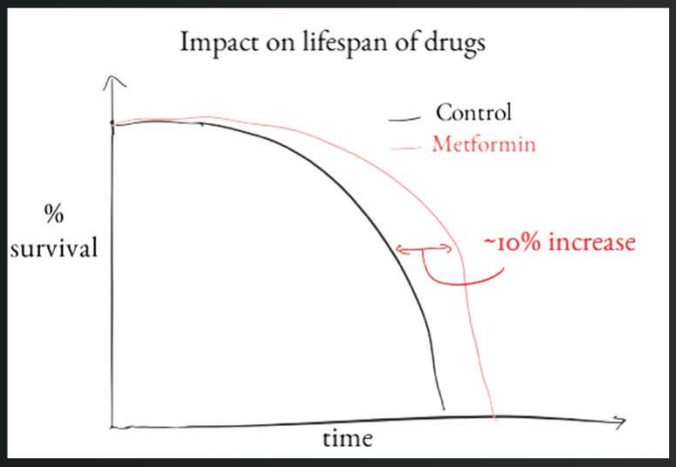
Metformin Has Interesting Effects As Well



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TL:DR - We're Still Figuring It Out

- Genetic and pharmacological intervention studies have identified evolutionarily conserved and functionally interconnected networks of cellular energy homeostasis, nutrient-sensing, and genome damage response signaling pathways as prominent regulators of longevity and health span in various species.
- Mitochondria are the primary sites of ATP production and are key players in several other important cellular processes.
- Mitochondrial dysfunction diminishes tissue and organ functional performance and is a commonly considered feature of the aging process.

Mitochondria in the signaling pathways that control longevity and health span

Mansour Akbari[a], Thomas B.L. Kirkwood[a,b], Vilhelm A. Bohr[a,c,*]

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Mitochondria Seem To Hold The Answer

- Mitochondria are implicated in the lifespan modulation function of these pathways, constituting a highly dynamic and complex system that controls the aging process.
- An important characteristic of these pathways is their extensive crosstalk and apparent malleability to modification by non-invasive pharmacological, dietary, and lifestyle interventions, with promising effects on lifespan and health span in animal models and potentially also in humans.
  - This is why we're so excited about modalities that modify mitochondrial function to promote longevity and haunt the aging process…!

Mitochondria in the signaling pathways that control longevity and health span

Mansour Akbari[a], Thomas B.L. Kirkwood[a,b], Vilhelm A. Bohr[a,c,*]

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Pharmacy May Hold The Answer…

Table 1. Examples of Adaptive Metabolic Cellular Stress Response-Based Pharmacological Strategies to Ameliorate Age-Related Neurological Deficits and Diseases

Agent	Mechanism of Action	Preclinical Findings	References
Ketone (ester)	energy substrate induces BDNF expression	improves cognition and endurance beneficial in seizure, AD, and PD models	Murray et al., 2016; Kashiwaya et al., 2000, 2013; Marosi et al., 2016
Nicotinamide riboside	bolsters bioenergetics and sirtuin activity	extends lifespan and beneficial in AD model	Gong et al., 2013; Zhang et al., 2016a; Hou et al., 2018
2,4-dinitrophenol	mild mitochondrial uncoupling adaptive cellular stress responses	beneficial in TBI, AD, and PD models	Pandya et al., 2007; Geisler et al., 2017; Lee et al., 2017
Diazoxide	K-ATP channel opener	beneficial in stroke, PD, and AD models	Liu et al., 2002, 2010; Yang et al., 2005
2-deoxyglucose	induces adaptive cellular stress responses	neuroprotective in stroke and PD models	Duan and Mattson, 1999; Yu and Mattson, 1999
Rapamycin	mTOR inhibitor and autophagy inducer	beneficial in stroke, AD, and PD models extends lifespan	Buckley et al., 2014; Spilman et al., 2010; Siddiqui et al., 2015
Exendin-4 and liraglutide	GLP-1R agonist and insulin sensitizer induces BDNF expression	beneficial in stroke, AD, and PD models	Li et al., 2009, 2010
Metformin	inhibits liver glucose production, activates AMP, and inhibits mTOR	beneficial in PD and AD models extends lifespan	Martin-Montalvo et al., 2013; Bayliss et al., 2016; Niccoli et al., 2016

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Metabolic Pathways Involved In Inflammaging

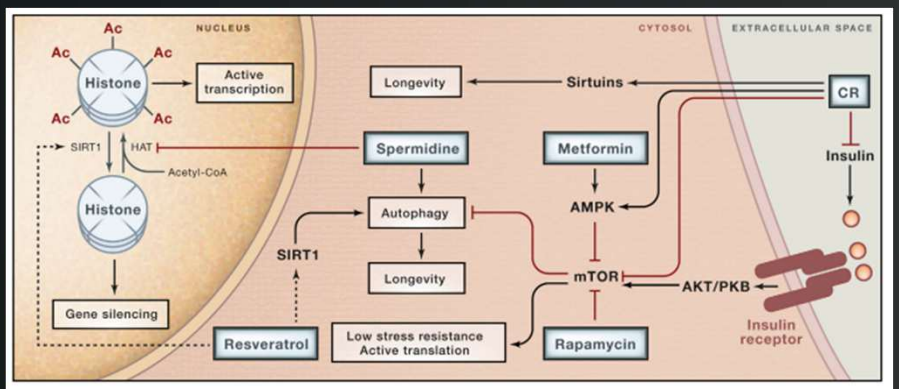

Figure 2. Molecular Targets for Caloric Restriction and Pharmacological Interventions against Premature Aging
Caloric restriction promotes longevity through sirtuin activation as well as through inhibition of the insulin and TOR pathways, which both lead to stress resistance and autophagy activation. Resveratrol, rapamycin, and spermidine exert autophagy-dependent antiaging mechanisms that are exerted both at the cytosolic and nuclear levels. Whether resveratrol directly interacts with the sirtuin family member SIRT1 remains controversial. Metformin promotes AMPK activity and prevents oxidative damage. Ac, acetyl residue; HAT, histone acetyltransferase; AMPK, adenosine monophosphate-activated protein kinase; AKT/PKB, protein kinase B; CR, caloric restriction.

The Search for Antiaging Interventions: From Elixirs to Fasting Regimens

Rafael de Cabo,[1,*] Didac Carmona-Gutierrez,[2] Michel Bernier,[1] Michael N. Hall,[3] and Frank Madeo[2,*]
[1]Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21224, USA
[2]Biozentrum, University of Basel, Basel 4056, Switzerland
[3]Institute of Molecular Biosciences, University of Graz, Graz 8010, Austria
*Correspondence: dacabora@mail.nih.gov (R.d.C.), frank.madeo@uni-graz.at (F.M.)

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Metformin

- Our knowledge of the effect of metformin on human health is increasing.
  - In addition to its ability to improve the control of hyperglycemia, metformin has been shown to reduce the burden of aging via its effects on damaged DNA and the process of apoptosis.
- In vivo and in-vitro studies have shown that metformin has anti-cancer properties, and population studies have suggested that metformin may reduce the risk of cancer or improve cancer prognosis.
  - It is thought that it exerts its anti-cancer effect through the inhibition of the mammalian target of rapamycin (mTOR) signaling pathway.

The journey of metformin from glycaemic control to mTOR inhibition and the suppression of tumour growth

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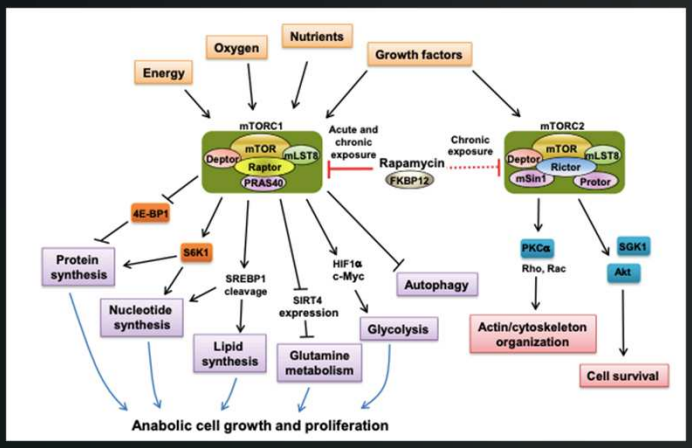
Rapamycin



- The mammalian target of rapamycin (mTOR) signaling pathway is a master regulator of cell growth and metabolism.
- Deregulation of the mTOR pathway has been implicated in a number of human diseases such as cancer, diabetes, obesity, neurological diseases, and genetic disorders.
- Rapamycin, a specific inhibitor of mTOR, has been shown to be useful in the treatment of certain diseases.

Rapamycin: One Drug, Many Effects

Jing Li,[1] Sang Gyun Kim,[1] and John Blenis[1,*]
[1]Department of Cell Biology, Harvard Medical School, 240 Longwood Avenue, Boston, MA 02115, USA
*Correspondence: john_blenis@hms.harvard.edu
http://dx.doi.org/10.1016/j.cmet.2014.01.001

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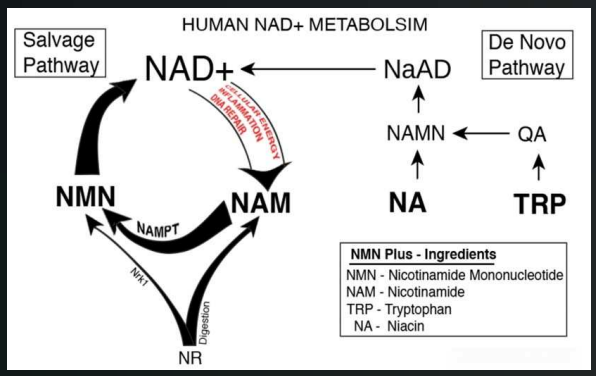
Nicotinamide Mononucleotide (NMN)



- NAD+ is a compound found in every cell in your body and involved in many critical processes, including energy metabolism, DNA repair, and gene expression.
- NAD+ levels decline with age, and this decline is thought to be associated with accelerated physical decline and the onset of age-related diseases like Alzheimer's.
- Studies have shown that supplementing with NAD+ precursors like NR restores NAD+ levels and prevents age-related physical decline.

NAD$^+$ metabolism and its roles in cellular processes during ageing

Anthony J. Covarrubias, Rosalba Perrone, Alessia Grozio & Eric Verdin

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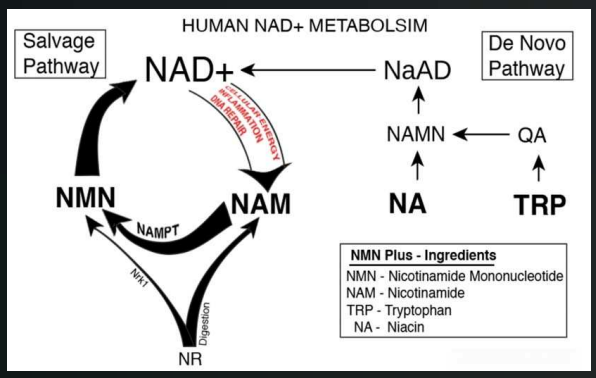
Nicotinamide Mononucleotide (NMN)



- For example, a study in aging subjects demonstrated that supplementing orally with Nicotinamide Mono prevented age-associated genetic changes and improved energy metabolism, physical activity, and insulin sensitivity.
- A 2019 study in 12 men with an average age of 75 showed that supplementing with up to 1 gram of Nicotinamide daily for 21 days increased NAD+ levels in skeletal muscle and reduced levels of inflammatory proteins in the body.

NAD$^+$ metabolism and its roles in cellular processes during ageing

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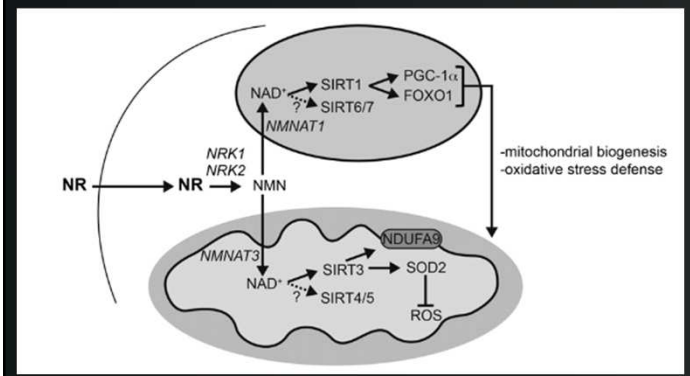
Nicotinamide Riboside (NR)



- Nicotinamide Riboside (NR) is a pyridine nucleoside form of vitamin B3 that is naturally found in milk and is available as a nutraceutical.
- NR is converted by nicotinamide riboside kinases (NRK1,2) to NMN, which is subsequently converted to NAD+ by nicotinamide mono-nucleotide adenylyltransferase (NMNAT).
- Oral supplementation with NR has been shown to increase NAD+ in brown adipose tissue, skeletal muscle and liver, and to improve mitochondrial function in a mouse model of diet-induced obesity.

An open-label, non-randomized study of the pharmacokinetics of the nutritional supplement nicotinamide riboside (NR) and its effects on blood NAD+ levels in healthy volunteers

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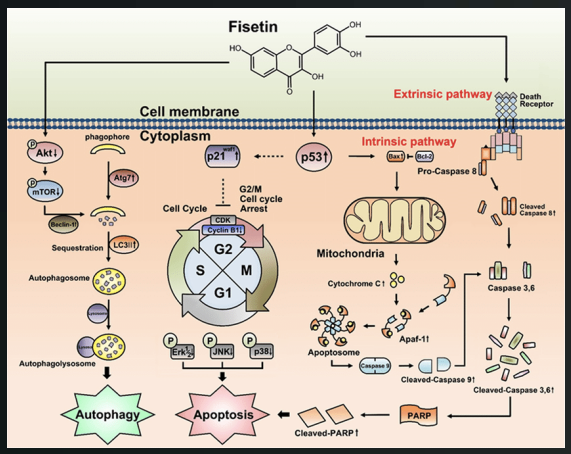
Fisetin



- Fisetin is a flavonoid compound that's considered a senotherapeutic, meaning it can kill senescent cells.
- It acts as an anticancer agent targeting the growth signaling pathways.
  - Rodent studies suggest that it may reduce the number of senescent cells in tissues and extend lifespan.
- Fisetin can also act as a dietary antioxidant for health promotion.

The flavonoid fisetin as an anticancer agent targeting the growth signaling pathways

Thamaraiselvan Rengarajan [1], Nik Soriani Yaacob [2]

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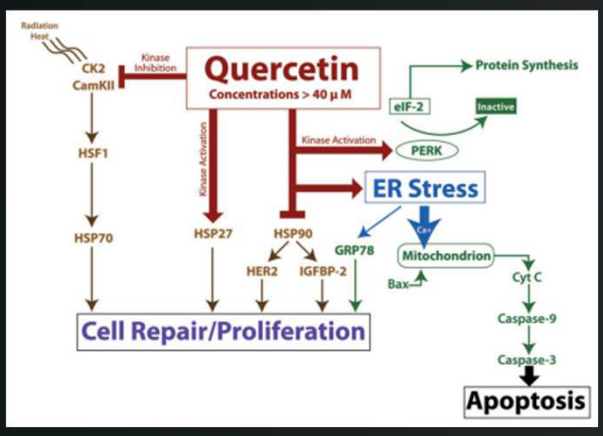
Quercetin



- Quercetin is a plant pigment (flavonoid). It is found in many plants and foods, such as red wine.
- It has antioxidant and anti-inflammatory effects, which might help reduce inflammation, kill cancer cells, control blood sugar, and help prevent heart disease.
- Quercetin has been shown to be effective in cancer prevention and therapy.
- Fisetin and Quercetin have been shown to have promising chemo protective potential.

Review

Fisetin and Quercetin: Promising Flavonoids with Chemopreventive Potential

Dharambir Kashyap [1], Vivek Kumar Garg [2], Hardeep Singh Tuli [3,*], Mukerrem Betul Yerer [4], Katrin Sak [5], Anil Kumar Sharma [3], Manoj Kumar [6], Vaishali Aggarwal [1] and Sardul Singh Sandhu [7]

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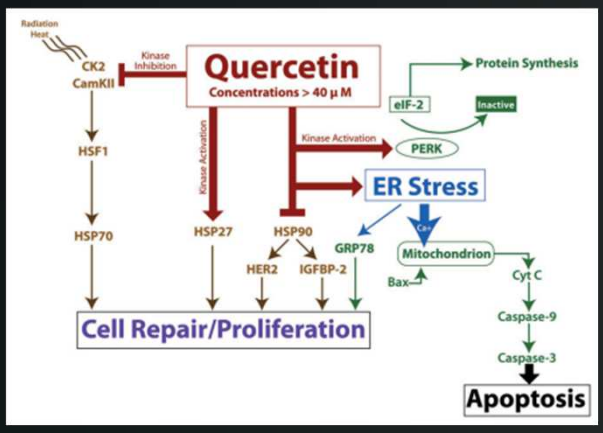
Quercetin



- Promising preliminary investigations demonstrating the effect of Quercetin on the expression of genes related to cell-cycle arrest, apoptosis and xenobiotic metabolism in human CO115 colon-adenocarcinoma cells using DNA microarray.
- Quercetin, Caffeic Acid, and Resveratrol regulate circadian clock genes and aging-related genes in young and old human lung fibroblast cells.

The flavonoid fisetin as an anticancer agent targeting the growth signaling pathways

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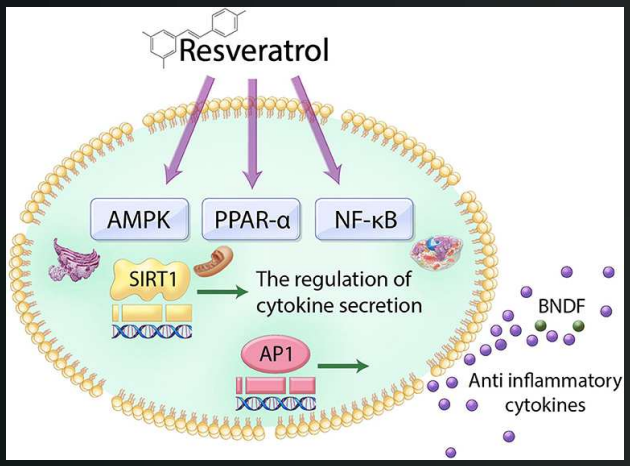
Resveratrol



- Resveratrol is a polyphenol in grapes, berries, peanuts, and red wine that may promote longevity by activating certain genes called sirtuins. It has been shown to increase the lifespan of fruit flies, yeasts, and nematodes.
- It is an Nrf2 activator and has been shown to alleviate aging-related progressive renal injury.
- Resveratrol regulates cellular defense systems against oxidative stress.

A comparative study of anti-aging properties and mechanism: resveratrol and caloric restriction

Juan Li[1], Chun-Xia Zhang[1], Yi-Mei Liu[1], Ke-Li Chen[1] and Gang Chen[1,2]

[1]Key Laboratory of Ministry of Education on Traditional Chinese Medicine Resource and Compound Prescription, Hubei University of Chinese Medicine, Wuhan 430065, Hubei, China

[2]Hubei College of Chinese Medicine, Jingzhou 434020, Hubei, China

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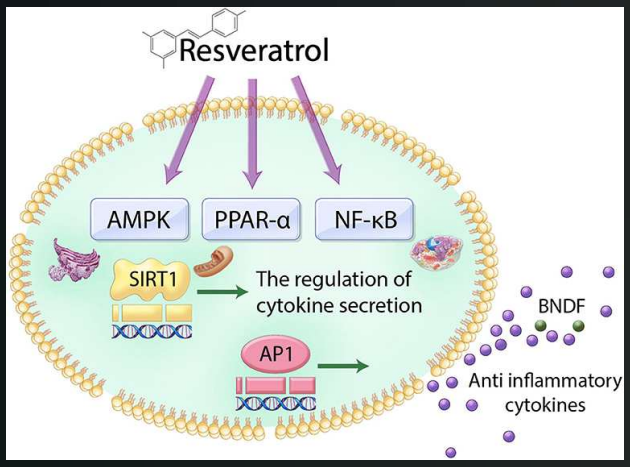
Resveratrol



- Resveratrol plays a role in the regulation of cellular defense systems against oxidative stress.
- Resveratrol and Pterostilbene show positive effects on aging and longevity.
- It also improves oxidative stress and prevents the progression of periodontitis via the activation of the Sirt1/AMPK and the Nrf2/antioxidant defense pathways in a periodontitis model.

A comparative study of anti-aging properties and mechanism: resveratrol and caloric restriction

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[2]Hubei College of Chinese Medicine, Jingzhou 434020, Hubei, China

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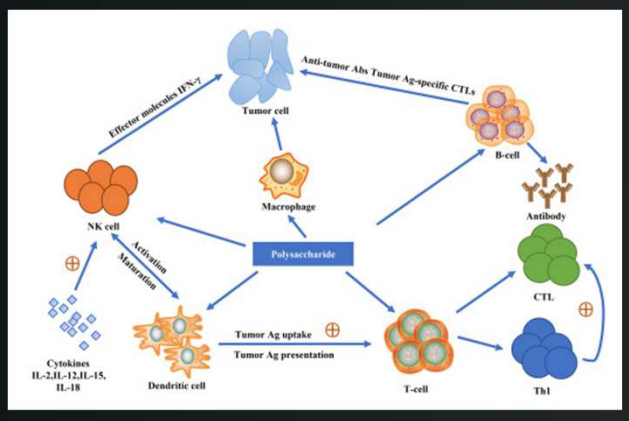
Astragalus



- *Astragalus membranaceus* is a stress-reducing herb used in traditional Chinese medicine.
  - It may help combat aging by reducing oxidative stress, promoting immune function, and preventing cellular damage.
- Astragalus polysaccharide exerts anti-Parkinson via activating the PI3K/AKT/mTOR pathway to increase cellular autophagy levels in vitro.
- It can also protect against gastrointestinal cancers.

Anti-Aging Implications of *Astragalus Membranaceus* (Huangqi): A Well-Known Chinese Tonic

Ping Liu[1], Haiping Zhao[1,#], Yumin Luo[1,2,3,*]

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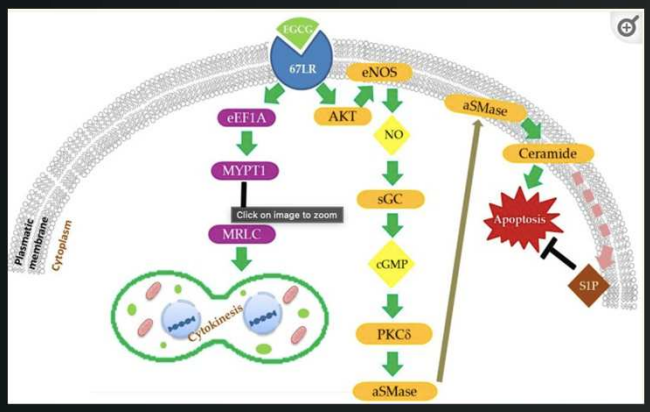
Epigallocatechin Gallate (EGCG)



- Epigallocatechin Gallate (EGCG) is a well-known polyphenol compound concentrated in green tea.
  - It offers impressive health benefits, with research supporting its use to reduce the risk of certain cancers, as well as other health conditions like heart disease.
- Among EGCG's diverse array of potential health-promoting properties is its ability to promote longevity and protect against age-related disease development.

Molecular Targets of Epigallocatechin—Gallate (EGCG): A Special Focus on Signal Transduction and Cancer

Aide Negri,[1,†] Valeria Naponelli,[1,2,*,†] Federica Rizzi,[1,2,3] and Saverio Bettuzzi[1,2,3]

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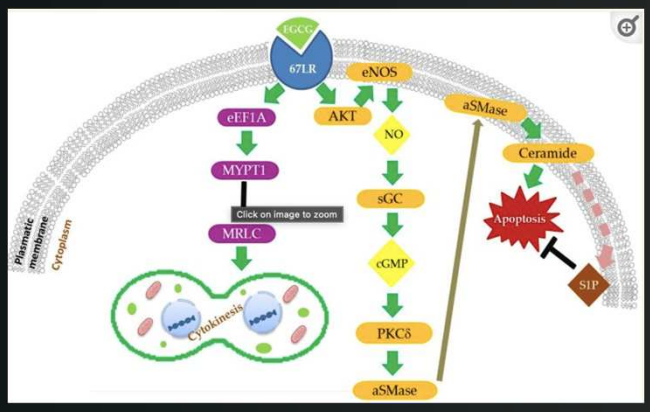
Epigallocatechin Gallate (EGCG)



- EGCG may slow aging by restoring mitochondrial function in cells and acting on pathways involved in aging, including the AMP-activated protein kinase signaling pathway (AMPK).
  - It also induces autophagy, the process by which your body removes damaged cellular material.
- EGCG intake has been associated with a reduced risk of all-cause mortality, diabetes, stroke, and heart-disease-related death.
  - Animal studies have shown that it can protect against skin aging and wrinkles caused by ultraviolet (UV) light.

Molecular Targets of Epigallocatechin—Gallate (EGCG): A Special Focus on Signal Transduction and Cancer

Aide Negri,[1,†] Valeria Naponelli,[1,2,*,†] Federica Rizzi,[1,2,3] and Saverio Bettuzzi[1,2,3]

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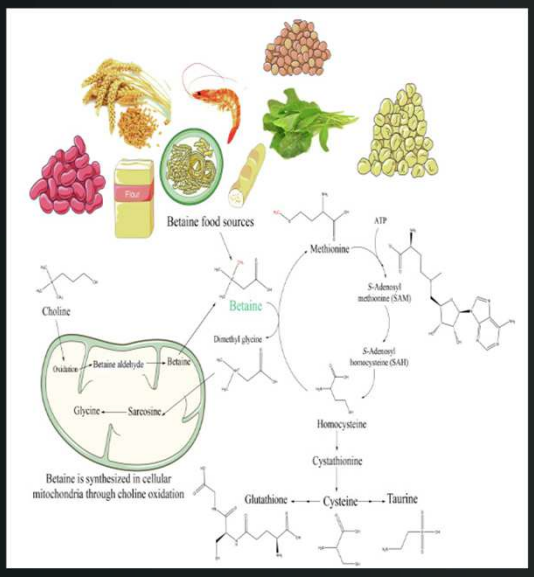
Trimethylglycine (TMG)



- TMG has outstanding effects on controlling homocysteine levels in the blood.
  - Homocysteine significantly increases around the middle stage of life, and it's linked to the development of heart disease and stroke.
- In a breast cancer study, having more TMG in patients' diets was linked to fewer deaths from cancer.
  - In another study of more than 2800 lung cancer patients, high betaine intake was found to be protective against lung cancer.

Association between malnutrition and hyperhomocysteine in Alzheimer's disease patients and diet intervention of betaine

Jianying Sun [1], Shiling Wen [1], Jing Zhou [1], Shuling Ding [1]

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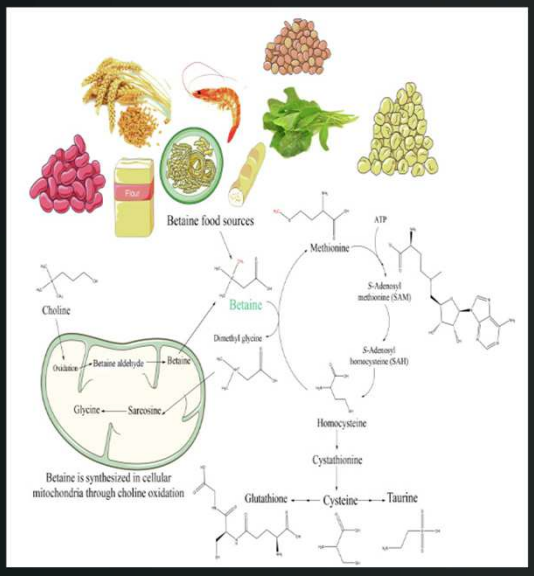
Trimethylglycine (TMG)



- A study including 193 senior citizens showed that an increase in TMG was linked to improvements in response time, memory, and brain function.
  - People whose TMG levels went up the most also saw the most improvement in their memories.
- Additionally, TMG is also being explored as treatment for other neurological disorders such as Alzheimer's disease.

Association between malnutrition and hyperhomocysteine in Alzheimer's disease patients and diet intervention of betaine

Jianying Sun [1], Shiling Wen [1], Jing Zhou [1], Shuling Ding [1]

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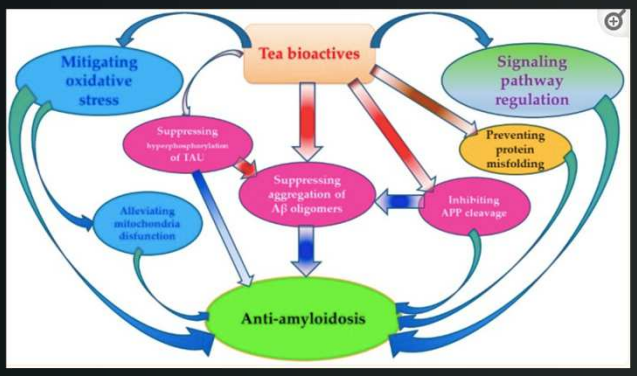
L-Theanine



- L-Theanine is an amino acid concentrated in certain teas, including green tea.
  - It may help protect against mental decline and has been shown to extend the lifespan of roundworms by around 5%.
- L-Theanine attenuates liver aging by inhibiting advanced glycation end products in d-galactose-induced rats and reversing an imbalance of oxidative stress and inflammation.
- There is a potential for a neuroprotective effect against Lipopolysaccharide (LPS) induced inflammation and acute liver injury.

Association of Tea Consumption with Risk of Alzheimer's Disease and Anti-Beta-Amyloid Effects of Tea

Curt Anthony Polito,[1] Zhuo-Yu Cai,[1] Yun-Long Shi,[1] Xu-Min Li,[1] Rui Yang,[1] Meng Shi,[1] Qing-Sheng Li,[1] Shi-Cheng Ma,[2] Li-Ping Xiang,[3] Kai-Rong Wang,[4] Jian-Hui Ye,[1] Jian-Liang Lu,[1] Xin-Qiang Zheng,[1] and Yue-Rong Liang[1,*]

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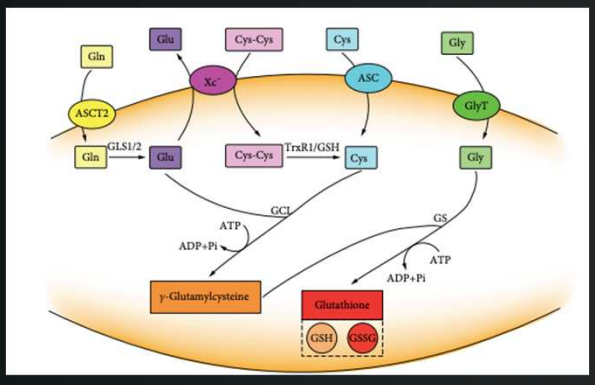
Glutathione



- Glutathione is the principal intracellular antioxidant buffer against oxidative stress and mainly exists in the forms of reduced glutathione (GSH) and oxidized glutathione (GSSG).
- The processes of glutathione synthesis, transport, utilization, and metabolism are tightly controlled to maintain intracellular glutathione homeostasis and redox balance.
- As for cancer cells, they exhibit a greater ROS level than normal cells in order to meet the enhanced metabolism and vicious proliferation.
- Growing numbers of studies have implicated that altering the glutathione antioxidant system is associated with multiple forms of programmed cell death in cancer cells.

Review Article

Unraveling the Potential Role of Glutathione in Multiple Forms of Cell Death in Cancer Therapy

Huanhuan Lv,[1,2,3,4,5] Chenxiao Zhen,[1,2,3] Junyu Liu,[1,2,3] Pengfei Yang,[1,2,4,5] Lijiang Hu,[1] and Peng Shang[1,2,4,5]

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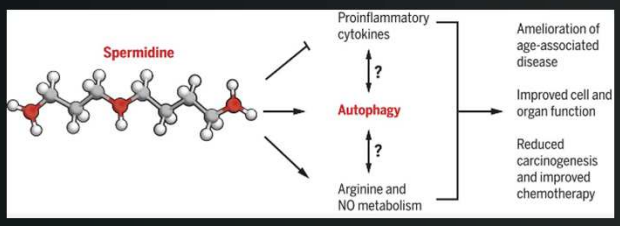
Spermidine



- Spermidine has anti-inflammatory and anti-antioxidant properties, and can also enhance respiration and metabolic function.
  - Increased dietary spermidine intake is thought to reduce the risk of diseases like cancer, metabolic disease, heart disease and neurodegeneration.
- It can also improve memory and slow cognitive decline, as autophagy clears Alzheimer's-causing amyloid-beta plaques in the brain and can thereby be used to prevent memory loss in older people suffering from mild dementia.

Spermidine in health and disease

FRANK MADEO, TOBIAS EISENBERG, FEDERICO PIETROCOLA, AND GUIDO KROEMER Authors Info & Affiliations

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Caloric Restriction & Longevity

- Calorie restriction (CR) is a nutritional intervention of reduced energy intake of about 25–30% without lack of essential nutrients, with a well-established role in extending health span and lifespan in rodent and primate models.
  - Moderate CR in humans enhances multiple metabolic and hormonal factors that are implicated in the pathogenesis of age-associated metabolic alterations, cancer, and others, which are leading causes of morbidity, disability, and mortality.
- Furthermore, moderate CR can prevent and reverse the harmful effects of the accumulation of excessive body fat and obesity, Type II Diabetes, dyslipidemia, and hypertension, all factors included in metabolic syndrome (MS)

Review

Effects of Calorie Restriction on Health Span and Insulin Resistance: Classic Calorie Restriction Diet vs. Ketosis-Inducing Diet

Ana Napoleão [1,2], Lívia Fernandes [2], Cátia Miranda [2] and Ana Paula Marum [1,2,3,*]

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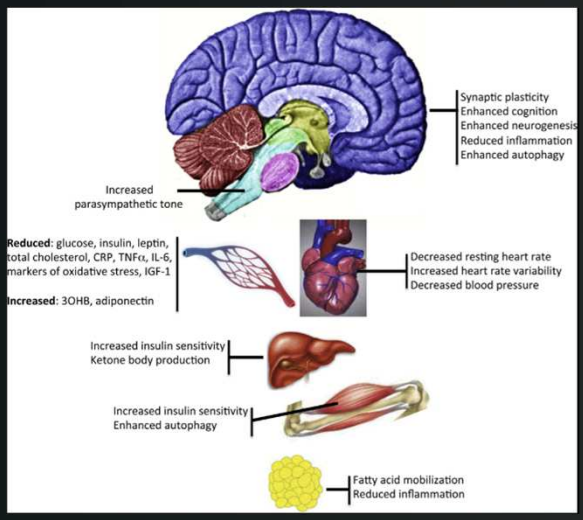
Intermittent Fasting (IF) & Longevity



- Intermittent fasting (IF) encompasses eating patterns in which individuals go extended time periods (e.g., 16 - 48h) with little or no energy intake, with intervening periods of normal food intake, on a recurring basis.
  - Fasting allows the brain and body to take out the day's trash, repair cells, and dampen inflammation.
- It can also have profound effects on improving insulin sensitivity, decreasing glucose levels, and improving fatty acid profiles.

Impact of intermittent fasting on health and disease processes

Mark P Mattson [1], Valter D Longo [2], Michelle Harvie [3]

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Intermittent Fasting (IF) & Longevity

- In laboratory rats and mice Intermittent Fasting (IF) and Periodic Fasting (PF) have profound beneficial effects on many different indices of health and, importantly, can counteract disease processes and improve functional outcomes in experimental models of a wide range of age-related disorders, including diabetes, cardiovascular disease, cancers and neurological disorders such as Alzheimer's disease, Parkinson's disease and stroke.
- Studies of IF (e.g., 60% energy restriction on 2 days per week or every other day), PF (e.g., a 5day diet providing 750-1100kcal), and time-restricted feeding (TRF; limiting the daily period of food intake to 8h or less) in normal and overweight human subjects have demonstrated efficacy for weight loss and improvements in multiple health indicators including insulin resistance and reductions in risk factors for cardiovascular disease.

Impact of intermittent fasting on health and disease processes

Mark P Mattson [1], Valter D Longo [2], Michelle Harvie [3]

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Intermittent Fasting (IF) & Longevity

- The cellular and molecular mechanisms by which Intermittent Fasting improves health and counteracts disease processes involve the activation of adaptive cellular stress response signaling pathways that enhance mitochondrial health, DNA repair and autophagy.
  - Periodic Fasting also promotes stem cell-based regeneration as well as long-lasting metabolic effects.
- Randomized controlled clinical trials of IF versus PF and isoenergetic continuous energy restriction in human subjects will be required to establish the efficacy of IF in improving general health, and preventing and managing major diseases of aging.

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Fasting And Neural Autophagy

- Disruption of autophagy—a key homeostatic process in which cytosolic components are degraded and recycled through lysosomes—can cause neurodegeneration in tissue culture and in vivo.
- Upregulation of this pathway may be neuroprotective, and much effort is being invested in developing drugs that cross the blood-brain barrier and increase neuronal autophagy.
- One well-recognized way of inducing autophagy is by food restriction, which upregulates autophagy in many organs, including the liver.
- This study found that short-term fasting leads to a dramatic upregulation in neuronal autophagy via changes in mTOR activity, specifically in mice who fasted for 24-48 hours.

Short-term fasting induces profound neuronal autophagy

Mehrdad Alirezaei,[1,*] Christopher C. Kemball,[1,*] Claudia T. Flynn,[1] Malcolm R. Wood,[2] J. Lindsay Whitton[1,*] and William B. Kiosses[2]

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Exercise & Longevity

- Aging is a natural and complex physiological process influenced by many factors, some of which are modifiable.
  - As the number of older individuals continues to increase, it is important to develop interventions that can be easily implemented and contribute to "successful aging".
- In addition to a healthy diet and psychosocial well-being, the benefits of regular exercise on mortality, and the prevention and control of chronic disease affecting both life expectancy and quality of life are well established.

Exercise and longevity

Vincent Gremeaux [1], Mathieu Gayda, Romuald Lepers, Philippe Sosner, Martin Juneau, Anil Nigam

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Exercise & Neuroprotection

- Regular exercise is associated with pronounced health benefits. The molecular processes involved in physiological adaptations to exercise are best understood in skeletal muscle.
- Enhanced mitochondrial functions in muscles are central to exercise-induced adaptations.
  - However, regular exercise also benefits the brain and is a major protective factor against neurodegenerative diseases, such as the most common age-related form of dementia, Alzheimer's disease, or the most common neurodegenerative motor disorder, Parkinson's disease.
- While there is evidence that exercise induces signaling from skeletal muscle to the brain, the mechanistic understanding of the crosstalk along the muscle–brain axis is incompletely understood. Mitochondria in both organs, however, seem to be central players.

The Muscle-Brain Axis and Neurodegenerative Diseases: The Key Role of Mitochondria in Exercise-Induced Neuroprotection

Johannes Burtscher,[1,2,*] Grégoire P. Millet,[1,2] Nicolas Place,[1,2] Bengt Kayser,[1,2] and Nadège Zanou[1,2]

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Sleep & Longevity

- Deep Sleep = Increased velocity of CSF for clearing out damaged structures and waste
- Energy repletion
- Memory consolidation
- Autophagy and cellular regeneration
- Optimization of blood sugar levels
- Immune optimization
- The list goes on…

The aging brain: sleep, the circadian clock and exercise

M. Panagiotou*, S. Michel, J.H. Meijer, T. Deboer

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Anti-Neuro-Inflamm-Aging Practices

- Non-Invasive Low-Level Laser Therapy (Vagal N., Head, Intra-Nasal, Abdomen, etc.)
- Intermittent Fasting (IF) / Time-Restricted Eating
- Physical Exercise (HIIT is optimal for mitochondrial health, but for specific populations, low-grade cardiovascular exercise & light weight training may be more appropriate; **Movement = Life**)
- Sleep Support (Habits & Nutrition/Supplementation)
- Heat/Cold Exposure (Cold/Heat-Shock Proteins)
- Mindfulness/Stress Relieving and Diaphragmatic/Belly Breathing Techniques
- Nutrition/Supplementation
  - Vitamin D3/K2 + Magnesium (Threonate and Glycinate)
  - Mitochondrial Support - NR/NMN (NAD+ precursors), Quercetin, Fisetin, ECGC, Methylated B Complex, Resveratrol, L-Theanine, etc.
  - Anti-Inflammatory - Turmeric/Curcumin, Resveratrol, Omega 3's, Berberine
  - Gut Support - Spore-based probiotic, SCFA's, L-Glutamine

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Why Non-Thermal Low-Level Laser?

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Why Non-Thermal Low-Level Laser (NTLLL)?

- Non-Invasive
- No Downtime
- No Pain
- Short Treatment Time
- Pain Relieving Properties
- Decreases Swelling
- Improves Blood Flow
- Enhances Energy Production
- Optimizes Mitochondrial Function
- Anti-Inflammatory
- Immune-Boosting Properties
- Promotes Stem-Cell Production
- Decreases Stress Hormones
- Neuroprotective
- Downregulates Stress Responses in Brain
- Accelerated Wound Healing
- Upregulates Collagen Production
- Non-Invasive Fat Loss
- Enhanced Cellular Repair

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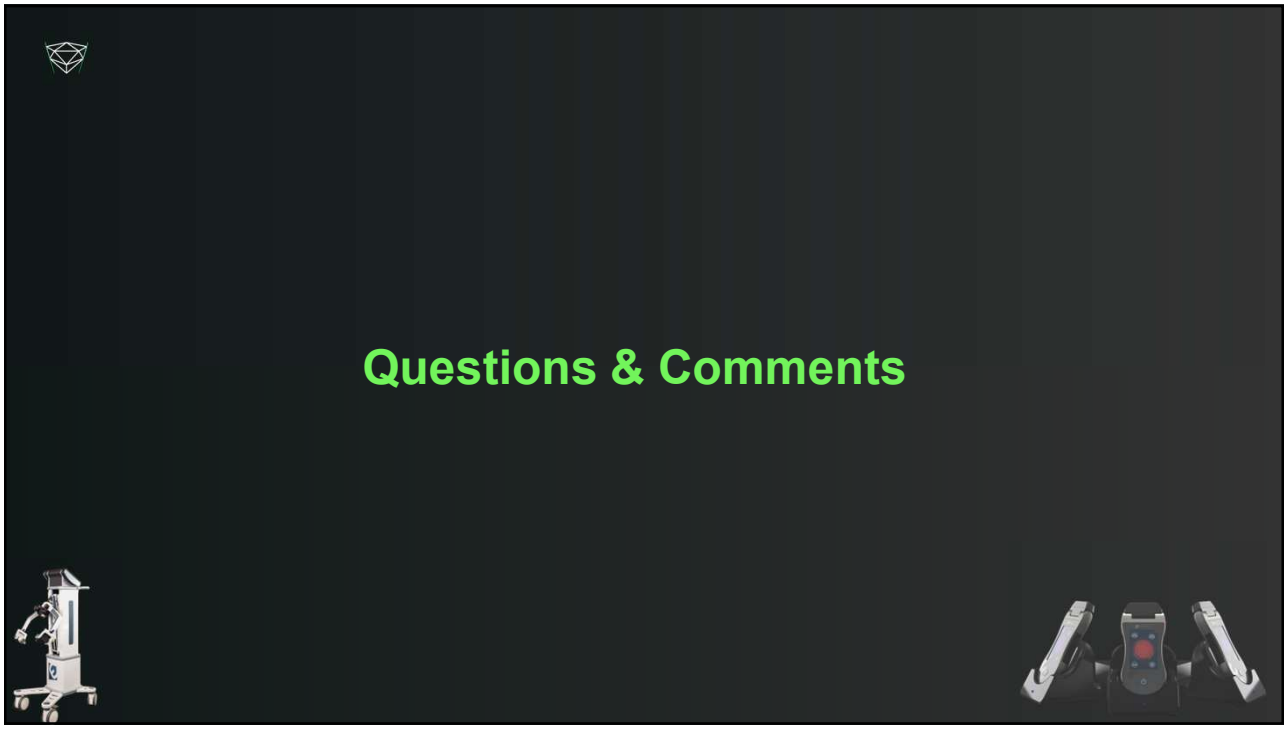

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