Immortal™

Formula 210108-02v1

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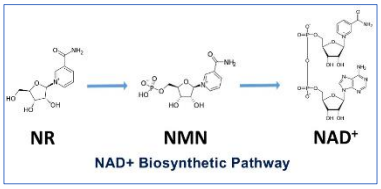
Nicotinamide Mononucleotide (NMN)

Background: *Sirtuins are a family of seven intercellular proteins, fueled by nicotinamide adenine dinucleotide (NAD), which are responsible for metabolism, apoptosis (cell replacement), inflammation and aging. A gradual decline in NAD disrupts sirtuins levels manifest as chromosomal DNA damage and age-related disease. Supplementation with NAD precursors, such as NMN or nicotinamide riboside (NR), increases NAD and correspondingly sirtuin levels. NMN is a direct precursor to NAD while NR must first convert to NMN before it increases NAD levels. Thus, NMN supplementation is more efficacious and bioavailable in a lower dose than NR. Doses of NMN up to 500mg in humans has shown to be safe and without side-effects.*[1-6]



1. Imai S, Guarente L. NAD+ and sirtuins in aging and disease. *Trends Cell Biol*. 2014. 24(8):464-71.
2. Haigis M, Sinclair D. Mammalian sirtuins: biological insights and disease relevance. *Annu Rev Pathol*. 2010. 253-295.
3. Preyat N, Leo O. Sirtuin deacylases: a molecular link between metabolism and immunity. *J Leukoc Biol*. 2013. 93(5):669-80.
4. Yoshino J, Baur J, Imai S. NAD^+ Intermediates: The Biology and Therapeutic Potential of NMN and NR. Cell Metab. 2018. 27(3):513-528.
5. Irie J, Inagaki E, Fujita M *et al*. Effect of oral administration of nicotinamide mononucleotide on clinical parameters and nicotinamide metabolite levels in healthy Japanese men. *Endocr J*. 2020. 67(2):153-160.
6. Airhart S, Shireman L, Risler L *et al*. 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. *PLoS One*. 2017. 12(12):e0186459

Retinal NAD+ deficiency is an early feature of retinal disease and vision loss as it causes photoreceptor death. Supplemental NMN repaired vision (in mice).

Lin J, Kubota S, Ban N *et al*. NAMPT-Mediated NAD(+) Biosynthesis Is Essential for Vision In Mice. *Cell Rep*. 2016. 17(1):69-85.

NMN suppressed age-associated body weight gain, enhanced energy metabolism, promoted physical activity, improved insulin sensitivity and plasma lipid profile, and ameliorated eye function and other pathophysiologies. It prevents age-associated gene expression changes in key metabolic organs and acts as an effective anti-aging intervention in humans

Mills K, Yoshida S, Stein L *et al*. Long-Term Administration of Nicotinamide Mononucleotide Mitigates Age-Associated Physiological Decline in Mice. *Cell Metab*. 2016. 24(6):795-806.

Yoshino J, Mills K, Yoon M *et al*. Nicotinamide mononucleotide, a key NAD(+) intermediate, treats the pathophysiology of diet- and age-induced diabetes in mice. *Cell Metab*. 2011. (4):528-536.

NMN increases NAD availability and may protect skeletal muscle from age-related decline.

Fletcher S, Ratajczak J, Doig C *et al*. Nicotinamide riboside kinases display redundancy in mediating nicotinamide mononucleotide and nicotinamide riboside metabolism in skeletal muscle cells. *Mol Metab*. 2017. 6(8):819-832.

Heart failure is associated with mitochondrial dysfunction regulated by NAD activity. Short-term NMN infusion preserves cardiac mitochondrial homeostasis and prevents heart failure.

Zhang R, Shen Y, Zhou L *et al*. Short-term administration of Nicotinamide Mononucleotide preserves cardiac mitochondrial homeostasis and prevents heart failure. *J Mol Cell Cardiol*. 2017. 112:64-73.

NMN supplementation reverse age-related arterial dysfunction by decreasing oxidative stress.

de Picciotto N, Gano L, Johnson L *et al*. Nicotinamide mononucleotide supplementation reverses vascular dysfunction and oxidative stress with aging in mice. *Aging Cell*. 2016. 15(3):522-30.

NMN improves the quality of aged oocytes (egg cells) increasing ovulation and enhancing meiotic competency and fertilization, maintaining the normal spindle/chromosome structure, restoring mitochondrial function and suppressing apoptosis. NMN supplementation is a feasible approach to protect oocytes from advanced maternal age-

related deterioration, contributing to the improvement of reproductive outcome of aged women and assisted reproductive technology.
Miao Y, Cui Z, Gao Q *et al*. Nicotinamide Mononucleotide Supplementation Reverses the Declining Quality of Maternally Aged Oocytes. *Cell Rep*. 2020. 32(5):107987.

Pterostilbene

Background: *Pterostilbene is a stilbenoid, an methylated analog of resveratrol (methylresveretrol), with similar antioxidant, neuroprotective, cardioprotective, analgesic, anti-atherosclerosis, anti-aging, anti-diabetic, anti-inflammatory and anti-obesity activities. It is 400 times more bioavailable (80% v 20%), more biologically active and has a longer half-life (stays in the system longer) than resveratrol. In addition, combined with piperine, the bioavailability of pterostilbene increases further.*

1. Akinwumi B, Bordun K, Anderson H. Biological Activities of Stilbenoids. *Int J Mol Sci*. 2018. 19(3):792.
2. Kapetanovic I, Muzzio M, Huang Z *et al.* Pharmacokinetics, oral bioavailability, and metabolic profile of resveratrol and its dimethylether analog, pterostilbene, in rats. *Cancer Chemother Pharmacol*. 2011. 68(3):593-601.
3. Johnson J, Nihal M, Siddiqui I et al. Enhancing the bioavailability of resveratrol by combining it with piperine. *Mol Nutr Food Res*. 2011. 5(8):1169-1176.
4. Liu Y, You Y, Lu J *et al.* Recent Advances in Synthesis, Bioactivity, and Pharmacokinetics of Pterostilbene, an Important Analog of Resveratrol. *Molecules*. 2020. 25(21):5166.
5. *Tsai H, Ho C, Chen Y. Biological actions and molecular effects of resveratrol, pterostilbene, and 3'-hydroxypterostilbene. J Food Drug Anal. 2017. (1):134-147.*
6. Chan E, Wong C, Tan Y *et al*. Resveratrol and pterostilbene: A comparative overview of their chemistry, biosynthesis, plant sources and pharmacological properties. *Journal of Applied Pharmaceutical Science*. 2019. 9(7):124-129.

Pterostilbene is a more potent modulator of cognition, cellular stress, inflammation and other pathologies associated with Alzheimer's Disease than resveratrol.
Chang J, Rimando A, Pallas M *et al*. Low-dose pterostilbene, but not resveratrol, is a potent neuromodulator in aging and Alzheimer's disease. *Neurobiol Aging*. 2012. 33(9):2062-71.

Pterostilbene inhibits enzymes and proteins implicated in aging and the development, or worsening, of many degenerative diseases, such as cataracts, diabetes, atherosclerosis, chronic kidney disease, and Alzheimer's disease.
McCormack D, McFadden D. A review of pterostilbene antioxidant activity and disease modification. *Oxid Med Cell Longev*. 2013. 2013:575482.

Pterostilbene inhibits glaucoma and other diabetic related pathologies, protecting pancreatic beta cells from apoptosis (death).
Dodda D, Rama Rao A, Veeresham C. In vitro and in vivo evaluation of pterostilbene for the management of diabetic complications. *J Ayurveda Integr Med*. 2020. 11(4):369-375.
Bhakkiyalakshmi E, Shalini D, Sekar T *et al*. Therapeutic potential of pterostilbene against pancreatic beta-cell apoptosis mediated through Nrf2. *Br J Pharmacol*. 2014. 171(7):1747-57.

Pterostilbene was more effective than resveratrol in ameliorating the deleterious effects an neurodegenerative aging (e.g. cognition, Amyloid plaque reduction et al) in an model of Alzheimer's Disease.
Arbo B, André-Miral C, Nasre-Nasser R *et al*. Resveratrol Derivatives as Potential Treatments for Alzheimer's and Parkinson's Disease. *Front Aging Neurosci*. 2020.12:103.

Dyslipidemia (high cholesterol/blood lipids) causes obesity, hypertension, type 2 diabetes, atherosclerosis and coronary heart disease. Pterostilbene decreases "bad" (LDL, VLDL) while increasing "good" (HDL) cholesterol and reduces blood triglycerides.
Satheesh M, Pari L "Effect of pterostilbene on lipids and lipid profiles in streptozotocin-nicotinamide induced type 2 diabetes mellitus." *Journal of Applied Biomedicine*. 2008. 6:31-37.

Pterostilbene was effective in reversing cognitive behavioral deficits, as well as dopamine release, and working memory was correlated with pterostilbene levels in the hippocampus.
Joseph J, Fisher D, Cheng V *et al.* Cellular and behavioral effects of stilbene resveratrol analogues: implications for reducing the deleterious effects of aging. *J Agric Food Chem*. 2008. 56(22):10544-51.

Epigallocatechin gallate (EGCG: Green Tea Extract): *146-238mg EGCG significantly improved attention and psychomotor speeds in response to stimuli; 300mg EGCG significantly increased alpha, beta, theta cerebral activity, and increased self-rated calmness and reduced self-rated stress. Concomitant administration of piperine increases the oral bioavailability of ECGC by 130%.*

1. Dietz C, Dekker M, Piqueras-Fiszman B *et al*. An intervention study on the effect of matcha tea, in drink and snack bar formats, on mood and cognitive performance. *Food Res Int*. 2017. 99(Pt 1):72-83.
2. Scholey A, Downey L, Ciorciari J *et al*. Acute neurocognitive effects of epigallocatechin gallate (EGCG). *Appetite*. 2012. 58(2):767-70.
3. Lambert J, Hong J, Kim D. Piperine enhances the bioavailability of the tea polyphenol (-)-epigallocatechin-3-gallate in mice. *J Nutr*. 2004. 134(8):1948-52.

EGCG from green tea stimulates hair growth.

Kwon O, Han J, Yoo H *et al*. Human hair growth enhancement in vitro by green tea epigallocatechin-3-gallate (EGCG). *Phytomedicine*. 2007. 14(7-8):551-5.

EGCG supplementation delay gastric emptying in healthy women and increased satiety.

Fernandes R, Araújo V, Giglio B *et* al. Acute Epigallocatechin 3 Gallate (EGCG) Supplementation Delays Gastric Emptying in Healthy Women: A Randomized, Double-Blind, Placebo-Controlled Crossover Study. *Nutrients*. 2018. 10(8):1122.

EGCG decreases beta-amyloid in cerebral plaques, enhanced memory and may be beneficial in the prevention of development or progression of Alzheimer's Disease.

Lee J, Lee Y, Ban J *et al.* Green tea (-)-epigallocatechin-3-gallate inhibits beta-amyloid-induced cognitive dysfunction through modification of secretase activity via inhibition of ERK and NF-kappaB pathways in mice. *J Nutr*. 2009. 139(10):1987-93.

EGCG supplementation favorably influences inner retinal function in eyes with early to moderately advanced glaucomatous damage.

Falsini B, Marangoni D, Salgarello T *et al*. Effect of epigallocatechin-gallate on inner retinal function in ocular hypertension and glaucoma: a short-term study by pattern electroretinogram. *Graefes Arch Clin Exp Ophthalmol*. 2009. 247(9):1223-33.

EGCG increases fat oxidation in men and may contribute to the anti-obesity effects of green tea.

Boschmann M, Thielecke F. The effects of epigallocatechin-3-gallate on thermogenesis and fat oxidation in obese men: a pilot study. J Am Coll Nutr. 2007. 26(4):389S-395S

Thielecke F, Rahn G, Böhnke J et al. Epigallocatechin-3-gallate and postprandial fat oxidation in overweight/obese male volunteers: a pilot study. Eur J Clin Nutr. 2010. 64(7):704-13.

EGCG modulates cellular and molecular mechanisms of various symptoms and may prevent metabolic syndrome.

Legeay S, Rodier M, Fillon L *et al*. Epigallocatechin Gallate: A Review of Its Beneficial Properties to Prevent Metabolic Syndrome. *Nutrients*. 2015. 7(7):5443-68.

EGCG improves vascular endothelial function, increased arterial blood flow and may help reverse some of the pathophysiologies associated with cardiovascular disease.

Widlansky M, Hamburg N, Anter E *et al*. Acute EGCG supplementation reverses endothelial dysfunction in patients with coronary artery disease. *J Am Coll Nutr*. 2007. 26(2):95-102.

Piperine: Piperine interrupts first-pass metabolism for many substance increasing bioavailability. *10-20mg/day increases the bioavailability/absorption rates of vitamins (B1, B2, B3, B6, B9, B12, C), minerals (iodine, calcium, iron, zinc, copper, selenium, magnesium, potassium, manganese), amino acids (lysine, isoleucine, leucine, threonine, valine, tryptophan, phenylalanine, methionine), herbal compounds (curcumin, ginsenosides, quercetin, coenzyme Q10, resveratrol, EGCG, pine extract), and drugs (ibuprofen, diclofenac, rifampicin, ampicillin, tetracycline, pyrazinamide, fexofenadine). For example, it has been shown to increase curcumin levels by 2000%.*

Ahmad, N, Fazal H, Abbasi B *et al*: Khan, M.A. (2012) Biological Role of Piper nigrum L. (Black Pepper): A Review. Asian Pac J Trop Biomed, 2010, 5:1945-1953.

Ajazuddin, Alexander A, Qureshi A *et al*: Role of herbal bioactives as a potential bioavailability enhancer for Active Pharmaceutical Ingredients. *Fitoterapia*. 2014 Sep;97C:1-14.

Alodeani E, Arshad M, Izhari M: Drug likeness and physicochemical properties evaluation of the alkaloids found in black pepper: piperine, piperidine, piperettine and piperanine. *Eur J Pharm Med Res*, 2015, 2(6), 296-301.

Badmaev V, Majeed M, Norkus E: Piperine, an alkaloid derived from black pepper increases serum response of beta-carotene during 14-days of oral beta-carotene supplementation. Nutri Res. 1999, 19(3): 381–388.

Badmaev V, Majeed M, Prakash L: Piperine derived from black pepper increases the plasma levels of coenzyme Q10 following oral supplementation. *J Nutri Biochem* 2000; 11(2):109–113.
Bhardwaj K, Glaeser H, Becquemont L *et al*: Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. *J Pharm Exp Ther*. 2002, 302(2):645-650.
Chopra B, Dhingra A, Kapoor R *et al*: Piperine and Its Various Physicochemical and Biological Aspects: A Review. *Open Chem J*, 2016, 3, 75-96.
Dudhatra G, Mody S, Awale M *et al*: A Comprehensive Review on Pharmacotherapeutics of Herbal Bioenhancers. *Sci World J*. 2012, Sept: 637953.
Gopal V, Prakash G, Velvizhi T: Bio-Enhancer: A Pharmacognostic Perspective. *Eur J Mol Biol Biochem*. 2016;3(1):33-38.
Jhanwar J, Gupta S: Biopotentiation using Herbs: Novel Technique for Poor Bioavailable Drugs. *Int J PharmT Res* 2014. 6(2): 443-454.
Johnson J, Nihal M, Siddiqui I *et al*: Enhancing the bioavailability of resveratrol by combining it with piperine. *Mol Nutri Food Res*. 2011, 55(8): 1169–1176.
Kang M, Cho J, Shim B *et al*: Bioavailability enhancing activities of natural compounds from medicinal plants. *J Med Plant Res*. 2009, 3(13): 1204–1211.
Kesarwani K, Gupta R, Mukerjee A: Bioavailability enhancers of herbal origin: an overview. *Asian Pac J Trop Biomed*. 2013 Apr; 3(4):253-66.
influence on brush border membrane fluidity, ultrastructure and enzyme kinetics. *Phytomedicine*. 2002 Apr;9(3):224-31.
Khajuria A, Zutshi U, Bedi K: Permeability characteristics of piperine on oral absorption--an active alkaloid from peppers and a bioavailability enhancer. *Indian J Exp Biol*. 1998 Jan;36(1):46-50.
Kulkarni A, Dias R: Natural products as bioavailability enhancers. *Int J Inv Pharm Sci Res* 2017. 5(12):24-33.
Lambert J, Hong J, Kim D *et al*: Piperine enhances the bioavailability of the tea polyphenol (-)-epigallocatechin-3-gallate in mice. *J Nutrition*. 2004. 134(8); 1948-52.
Majeed M, Badmaev V, Rajendran R, Inventors; Sabinsa Corporation, assignee. Use of piperine to increase the bioavailability of nutritional compounds. US patent 5,536,506, Jul. 16, 1996.
Majeed M, Badmaev V, Rajendran R, Inventors; Sabinsa Corporation, assignee. Use of piperine as a bioavailability enhancer. US patent 5,744,161. April 28, 1998.
Muneer C, Pandey V: Effect of Piperine on Oral Bioavailability of Diltiazem HCl in Rabbits. *Int J Pharm App*. 2012, 3(4):406-413.
Panahi Y, Badeli R, Karami G *et al*: Investigation of the Efficacy of Adjunctive Therapy with Bioavailability-Boosted Curcuminoids in Major Depressive Disorder. *Phytother Res*. 2015, 29(1):17-21.
Panahi Y, Ghanei M, Hajhashemi A *et al*: Effects of Curcuminoids-Piperine Combination on Systemic Oxidative Stress, Clinical Symptoms and Quality of Life in Subjects with Chronic Pulmonary Complications Due to Sulfur Mustard: A Randomized Controlled Trial. *J Diet Suppl*. 2016;13(1):93-105.
Parmar V, Jain S, Bisht K *et al*: Phytochemistry of genus piper. *Phytochemistry* 1997. 46:597-673.
Rahimnia A, Panahi Y, Alishiri G *et al*: Impact of Supplementation with Curcuminoids on Systemic Inflammation in Patients with Knee Osteoarthritis: Findings from a Randomized Double-Blind Placebo-Controlled Trial. *Drug Res (Stuttg)*. 2014 Jul 22. [Epub ahead of print]
Randhawa G, Kullar J, Rajkumar: Bioenhancers from mother nature and their applicability in modern medicine. *Int J Appl Basic Med Res*. 2011 Jan;1(1):5-10.
regulation of CYP1A1 gene expression in the rat hepatoma 5L cell line. *Biochem Biophys Res Commun* 1996. 218(2):562-9.
Shoba G, Joy D, Joseph T *et al*: Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Medica*, 1998. 64(4): 353–356.
Singh A, Duggal S: Piperine- Review of Advances in Pharmacology. *Int J Pharm Sci Nanotechnol*. 2009. 2:615–20.
Singh V, Singh P, Mishra A et al: Piperine: delightful surprise to the biological world, made by plant "pepper" and a great bioavailability enhancer for our drugs and supplements. *World J Pharm Res* 2014: 3(6): 2084-2098.
Srinivasan K: Black pepper and its pungent principle-piperine: A review of diverse physiological effects. *Critical Reviews in Food Science and Nutrition.* 2007. 47(8):735–48.
Srinivasan K. (2013) *Biological Activities of Pepper Alkaloids*. In: Ramawat K., Mérillon JM. (eds) Natural Products. Springer, Berlin, Heidelberg.
Tatiraju D, Bagade V, Karambelkar P et al: Natural Bioenhancers: An overview. *J Pharm Phyto* 2013; 2 (3): 55-60.
Wadhwa S, Singhal S, Rawat S: Bioavailability Enhancement by Piperine: A Review. *Asian J Biomed Pharma Sci*. 2014, 04(36): 1-8.
Wightman E, Reay J, Haskell C *et al*: Effects of resveratrol alone or in combination with piperine on cerebral blood flow parameters and cognitive performance in human subjects: a randomised, double-blind, placebo-controlled, cross-over investigation. *Br J Nutr*. 2014 Jul;112(2):203-13.
Zaveri M, Patel A, Khandhar A *et al*: Chemistry and Pharmacology of Piper Longum L. *Int J Pharm Sci Rev Res*. 2010, Dec; 5(1):67-76.