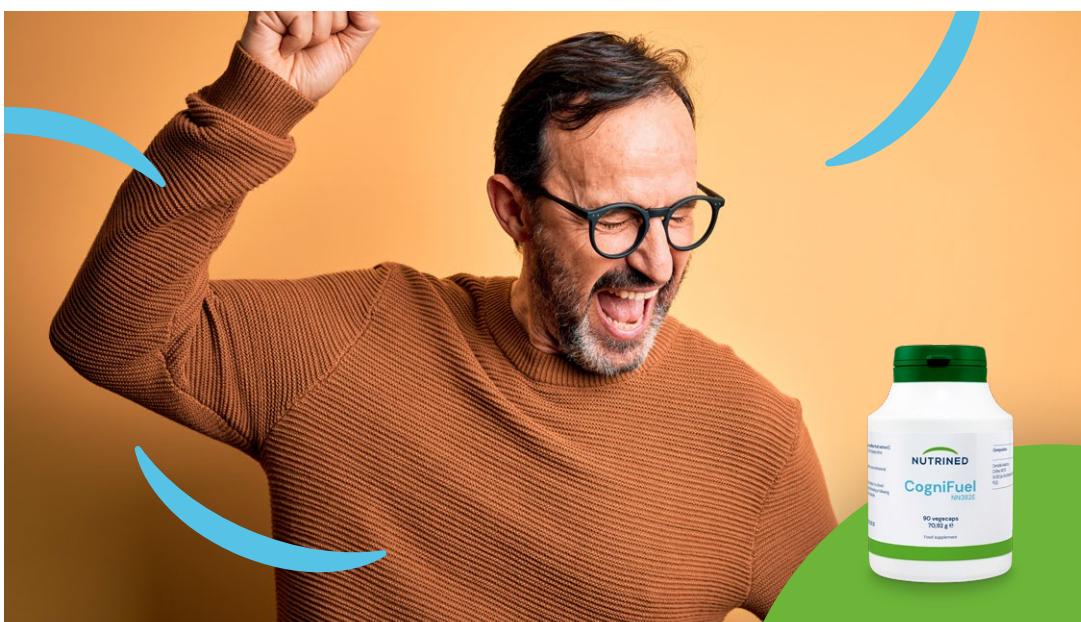
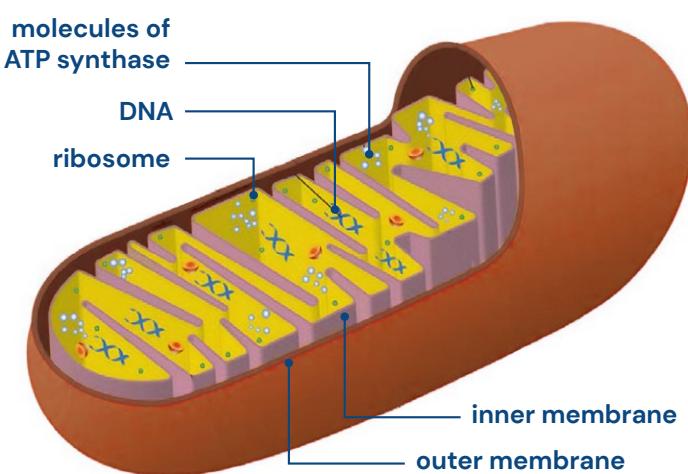


new

Mitochondrial dysfunction drives age-related diseases



Mitochondria
are the power
generators of
our cells



Carbohydrates & Fatty Acids + Oxygen → ATP

Nutrients are converted into ATP in the presence of Oxygen. ATP is the “currency” to power the cell’s metabolic activities.



Neurons need ATP

- Neuronal Activity
- Neuronal survival
- Neurotransmission
- Ca++ homeostasis

Neurodegenerative diseases are correlated with mitochondrial dysfunction:

- reduced function of the electron transport chain with leakage of free radicals
- disrupted mitochondrial biogenesis

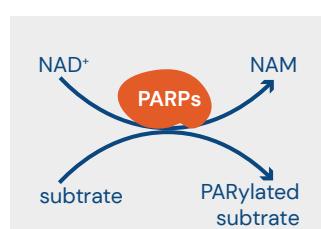
CogniFuel, The answer to brain aging

| | |
|--|--|
| indication | Prevention and treatment of various neurological disorders and neurodegenerative diseases Cognitive disorders Mitochondrial dysfunction and optimisation |
| dosage | 3 x 1 caps per day |
| packaging | 90 vegecaps per container |
| composition (amount per 3 vegecaps) | Centella Asiatica 1000 mg Coffea (Whole Coffee Fruit Extract) 200 mg Vit B3 (as Nicotinamide riboside) 200 mg PQQ 20 mg |

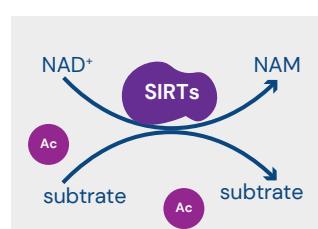


component 1: NAD+

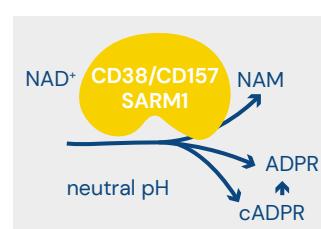
NAD+ is a **vital redox co-factor**, a key substrate for different enzymes.



Genomic integrity
Healthy aging

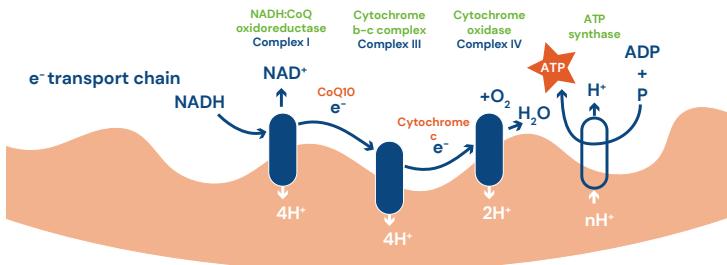


Metabolism, neuroplasticity,
healthspan/lifespan



Mitochondria transfer,
immunity, social behavior

NADH provides **electrons** to the electron transport chain. The efficiency to generate ATP depends on the ratio NAD+/NADH.



NAD⁺ depletion is observed during normal aging and in neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Amyotrophic lateral sclerosis (ALS).

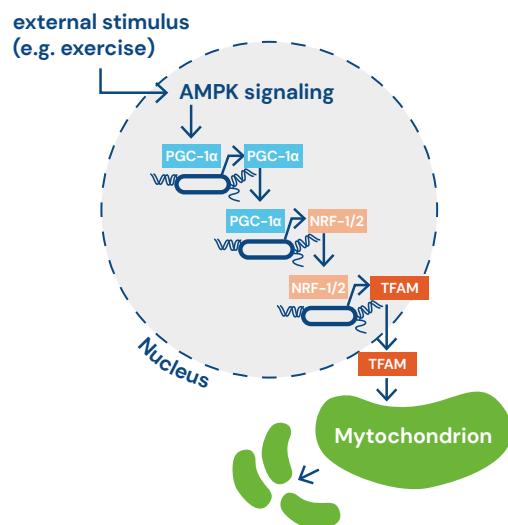
NAD⁺ restoration with NAD⁺ precursor Nicotinamide Riboside as a therapeutic strategy.

component 2: PQQ

PQQ (Pyrroloquinoline Quinone Disodium Salt) is a powerful **redox-agent** and participates to the **electron transport chain**.

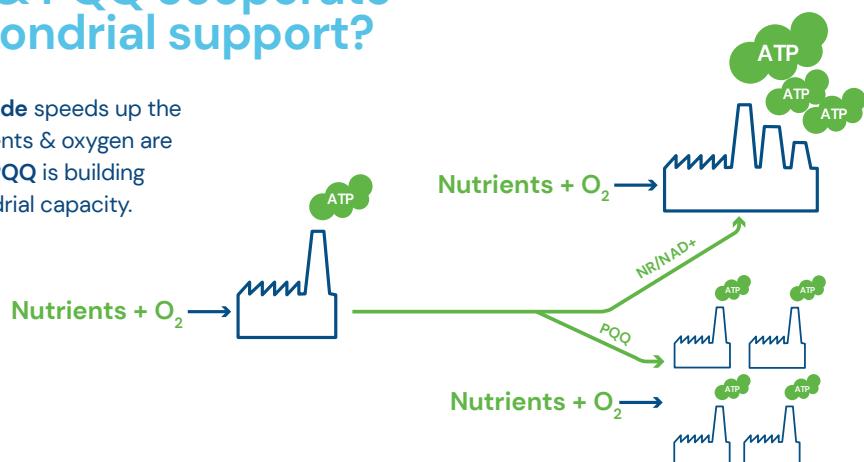
PQQ promotes the **generation of new mitochondria**, the biogenesis, via increased expression of PGC-1α.

Endurance training is the most effective external trigger to induce mitochondrial biogenesis.



How do Nicotinamide Riboside & PQQ cooperate in mitochondrial support?

Nicotinamide Riboside speeds up the process where nutrients & oxygen are converted into ATP. **PQQ** is building additional mitochondrial capacity.



References

Nicotinamide Riboside

Trammell, S. A. et al. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. *Nat. Commun.* 7, 12948 (2016).

Zhu XH, Lu M, Lee BY, Ugurbil K, and Chen W (2015). In vivo NAD assay reveals the intracellular NAD contents and redox state in healthy human brain and their age dependences. *Proc. Natl. Acad. Sci. USA* 112, 2876–2881

Camacho-Pereira J, Tarrag MG, Chini CCS, Nin V, Escande C, Warner GM, Puranik AS, Schoon RA, Reid JM, Galina A, et al. (2016). CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism. *Cell Metab.* 23, 1127–1139.

Fang EF, Scheibye-Knudsen M, Chua KF, Mattson MP, Croteau DL, and Bohr VA (2016b). Nuclear DNA damage signalling to mitochondria in ageing. *Nat. Rev. Mol. Cell Biol.* 17, 308–321.

Fang EF, Kassahun H, Croteau DL, Scheibye-Knudsen M, Marosi K, Lu H, Shamanna RA, Kalyanasundaram S, Bollineni RC, Wilson MA, et al. (2016a). NAD(+) replenishment improves lifespan and healthspan in ataxia telangiectasia models via mitophagy and DNA repair. *Cell Metab.* 24, 566–581. [PMC free article] [PubMed] [Google Scholar]

Mouchiroud L, Houtkooper RH, Moullan N, Katsyuba E, Ryu D, Cant C, Mottis A, Jo YS, Viswanathan M, Schoonjans K, et al. (2013). The NAD(+)/sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling. *Cell* 154, 430–441.

Vaur P, Brugg B, Mericskay M, Li Z, Schmidt M.S., Vivien D, Orset C, Jacotot E, Brenner C, Duplus E. Nicotinamide riboside, a form of vitamin B3, protects against excitotoxicity-induced axonal degeneration. *FASEB J.* 2017;31:5440–5452. doi: 10.1096/fj.201700221RR

Schöndorf, David C., et al. "The NAD⁺ precursor nicotinamide riboside rescues mitochondrial defects and neuronal loss in iPSC and fly models of Parkinson's disease." *Cell reports* 23.10 (2018): 2976–2988.

Martens, Christopher R., et al. "Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD⁺ in healthy middle-aged and older adults." *Nature communications* 9.1 (2018): 1–11.

Dollerup, Ole L., et al. "A randomized placebo-controlled clinical trial of nicotinamide riboside in obese men: safety, insulin-sensitivity, and lipid-mobilizing effects." *The American journal of clinical nutrition* 108.2 (2018): 343–353.

Cant C, Houtkooper R.H., Pirinen E, Youn D.Y., Oosterveer M.H., Cen Y, Fernandez-Marcos P.J., Yamamoto H, Andreux P.A., Cettour-Rose P, et al. The NAD(+) precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. *Cell Metab.* 2012;2012. 15:838–847. doi: 10.1016/j.cmet.2012.04.022

Lautrup, Sofie, et al. "NAD⁺ in brain aging and neurodegenerative disorders." *Cell metabolism* 30.4 (2019): 630–655.

Mitochondrial dysfunction in aging & neurodegenerative diseases

Fang EF, Scheibye-Knudsen M, Chua KF, Mattson MP, Croteau DL, and Bohr VA (2016b). Nuclear DNA damage signalling to mitochondria in ageing. *Nat. Rev. Mol. Cell Biol.* 17, 308–321.

Mattson MP, Gleichmann M, and Cheng A (2008). Mitochondria in neuro-plasticity and neurological disorders. *Neuron* 60, 748–766.

Canter, Rebecca G., Jay Penney, and Li-Huei Tsai. "The road to restoring neural circuits for the treatment of Alzheimer's disease." *Nature* 539.7628 (2016): 187–196.

Mattson, Mark P., and Thiruma V. Arumugam. "Hallmarks of brain aging: adaptive and pathological modification by metabolic states." *Cell metabolism* 27.6 (2018): 1176–1199.

Dong, Yue, and Gregory J. Brewer. "Global metabolic shifts in age and Alzheimer's disease mouse brains pivot at NAD+/NADH redox sites." *Journal of Alzheimer's disease* 71.1 (2019): 119–140.

Hou, Yujun, et al. "NAD+ supplementation normalizes key Alzheimer's features and DNA damage responses in a new AD mouse model with introduced DNA repair deficiency." *Proceedings of the National Academy of Sciences* 115.8 (2018): E1876–E1885.

Carri, Maria Teresa, Nadia D'Ambrosi, and Mauro Cozzolino. "Pathways to mitochondrial dysfunction in ALS pathogenesis." *Biochemical and biophysical research communications* 483.4 (2017): 1187–1193.

Holloszy JO (April 2011). "Regulation of Mitochondrial Biogenesis and GLUT4 Expression by Exercise". *Comprehensive Physiology*. 1 (2): 921–40. doi:10.1002/cphy.c100052. ISBN 9780470650714. PMID 23737207.

Bertholet AM, Delerue T, Millet AM, Moulis MF, David C, Daloyau M, et al. (June 2016). "Mitochondrial fusion/fission dynamics in neurodegeneration and neuronal plasticity". *Neurobiology of Disease*. 90: 3–19. doi:10.1016/j.nbd.2015.10.011. PMID 26494254.

Jornayvaz FR, Shulman GI (2010). "Regulation of mitochondrial biogenesis". *Essays in Biochemistry*. 47: 69–84. doi:10.1042/bse0470069. PMC 3883043. PMID 20533901.

Johri A, Chandra A, Flint Beal M (September 2013). "PGC-1 α , mitochondrial dysfunction, and Huntington's disease". *Free Radical Biology & Medicine*. 62: 37–46. doi:10.1016/j.freeradbiomed.2013.04.016. PMC 3722269. PMID 23602910.

PQQ

Chowanadisai, Winyoo, et al. "Pyrroloquinoline quinone (PQQ) stimulates mitochondrial biogenesis." (2007): A1104–A1104.

Adv Exp Med Biol. 2016;876:319–25. Effect of the Antioxidant Supplement Pyrroloquinoline Quinone Disodium Salt (BioPQQ™) on Cognitive Functions.

Ad Exp Med Biol. 2016;923:215–22. Effects of Antioxidant Supplements (BioPQQ™) on Cerebral Blood Flow and Oxygen Metabolism in the Prefrontal Cortex.

J Nutr Biochem. 2013 Dec;24(12):2076–84. Dietary pyrroloquinoline quinone (PQQ) alters indicators of inflammation and mitochondrial-related metabolism in human subjects.

Medical Consultation and New Remedies, 2011. 48(5):1. Koikeda T et al. Pyrroloquinoline quinone disodium salt improves higher brain function.

Food Style, 2009;13(7):50–3. Nakano M, et al. Effect of pyrroloquinoline quinone (PQQ) on mental status of middle-aged and elderly persons.

Centella Asiatica

Dhanasekaran M, Holcomb LA, Hitt AR, Tharakan B, Porter JW, Young KA, Manyam BV: Centella asiatica extract selectively decreases amyloid beta levels in hippocampus of Alzheimer's disease animal model. *Phytother Res.* 2009, 23: 14-19. 10.1002/ptr.2405.

da Rocha MD, Viegas FP, Campos HC, Nicastro PC, Fossaluzza PC, Fraga CA, Barreiro EJ, Viegas C: The role of natural products in the discovery of new drug candidates for the treatment of neurodegenerative disorders II: Alzheimer's disease. *CNS Neurol Disord Drug Targets.* 2011, 10: 251-270.

Veerendra Kumar MH, Gupta YK: Effect of Centella asiatica on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats. *Clin Exp Pharmacol Physiol.* 2003, 30: 336-342. 10.1046/j.1440-1681.2003.03842.x.

Xu Y, Cao Z, Khan I, Luo Y: Gotu Kola (Centella asiatica) extract enhances phosphorylation of cyclic AMP response element binding protein in neuroblastoma cells expressing amyloid beta peptide. *J Alzheimers Dis.* 2008, 13: 341-349

Coffee Whole Fruit extract

Reyes-Izquierdo T, Nemzer B, Shu C et al. (2013) Modulatory effect of coffee fruit extract on plasma levels of brainderived neurotrophic factor in healthy subjects. *Br J Nutr* 110, 420-425

Mullen, W., et al. "The antioxidant and chlorogenic acid profiles of whole coffee fruits are influenced by the extraction procedures." *Journal of agricultural and food chemistry* 59.8 (2011): 3754-3762.

Heimbach, J. T., et al. "Safety studies on products from whole coffee fruit." *Food and chemical toxicology* 48.8-9 (2010): 2517-2525.