

Optimising NAD+ Restoration

Consumption control, methyl-donor economy and
mitochondrial utilisation in mechanistic medicine

Author

Valentine Wibowo, Clinical Researcher

Medical review

dr. I Wayan Cahyadi Surya Distira Putra, MPH

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ABSTRACT

Restoration is not delivery alone

NAD⁺ restoration is often reduced to delivery: select a precursor or infuse the dinucleotide, then assume that the administered material becomes durable intracellular function. That model is incomplete. A restored vascular or circulating exposure must cross extracellular metabolism, tissue distribution and compartmental transport; it must coexist with enzymatic consumption; and its redox value depends on the metabolic machinery that oxidises substrates and transfers reducing equivalents.

This monograph constructs a biochemical architecture for optimising NAD⁺ restoration without turning a fixed supplement stack into a universal prescription. It examines conditional modules: control of active consumption, continuity of precursor supply, methyl-donor economy during nicotinamide disposal, mitochondrial utilisation through the tricarboxylic-acid cycle and electron-transport chain, and the magnesium-dependent branch from ATP and NAD⁺ toward NADP(H). CD38, PARPs, sirtuins, NNMT, SLC25A51, NAD kinase, coenzyme Q and lipoate-dependent dehydrogenase complexes are treated according to their exact causal roles. Apigenin, TMG, NR, NMN, magnesium, PQQ, ubiquinol and R-alpha-lipoic acid are not presented as interchangeable or automatically required companions.

The hierarchy is causal. Molecular identity and reaction chemistry come first; cellular mechanism, attainable exposure, in-vivo pharmacology and integrated physiology follow. Human intervention studies are used only as a terminal test of translation under the route, dose, population and endpoint actually examined. The result is a falsifiable framework for deciding which bottleneck may matter in an individual and what observation would weaken that decision.

KEY FINDINGS**01 · Delivery is not utilisation**

Direct vascular exposure changes the entry route, but does not establish intact intracellular delivery, mitochondrial access or ATP production.

02 · Drain can dominate supply

CD38, PARPs, sirtuins and other NAD-consuming enzymes can make restoration transient when the underlying demand remains active.

03 · Companions are conditional

Apigenin, NR, NMN, TMG, coenzyme Q, PQQ and lipoate each address a different causal proposition; no generic stack follows from NAD biochemistry.

04 · Methylation is a flux question

NNMT links nicotinamide disposal to SAM, SAH and homocysteine, but this reaction does not prove universal methyl depletion.

05 · Mitochondria need a complete chain

The NAD⁺/NADH pair, SLC25A51, dehydrogenases, coenzyme Q, oxygen and phosphorylation capacity form a coupled system.

06 · Magnesium is a biochemical bridge, not an absorption claim

MgATP chemistry and magnesium-dependent NAD kinase connect NAD⁺ to NADP(H), but do not prove that magnesium increases cellular uptake or the clinical effect of an infusion.

07 · Response must falsify the model

A companion earns its place only when its predicted biochemical or functional consequence is defined and reassessed.

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SECTION 01

Scope and epistemological position

This publication is a mechanistic monograph, not a treatment menu. Its subject is the biochemical problem that follows an attempt to increase NAD⁺ availability: what determines whether an acute or sustained input persists, reaches the relevant compartment and participates in useful redox flux? The question is narrower and harder than whether NAD⁺ is biologically important. NAD⁺ is indispensable; that fact does not identify the limiting step in a particular person.

The evidence hierarchy begins with identity and chemistry. A molecule must be chemically resolved before an effect can be attributed to it. Reaction stoichiometry and enzyme specificity establish what can occur. Cellular mechanism locates the reaction. Pharmacology asks whether the relevant concentration reaches that location for sufficient time. Integrated physiology asks how competing pathways alter the net state. Human observations arrive last and test only the complete proposition actually implemented. A negative terminal observation can refute translation under specified conditions without erasing a demonstrated chemical reaction; a positive observation cannot manufacture a missing mechanism.

The word optimisation therefore does not mean adding the largest number of compounds. It means locating the most plausible constraint, selecting the smallest intervention capable of interrogating it, and preserving attribution. Automatic combinations reduce scientific visibility because a change cannot be assigned to a component and an adverse trajectory cannot be mechanistically isolated.

SECTION 02

Delivery, distribution and intracellular attribution

Intravenous administration bypasses gastrointestinal absorption and produces direct vascular exposure. It does not bypass plasma distribution, endothelial interfaces, ectoenzymes, renal handling or tissue transport. In the human infusion metabolomic study, NAD⁺ delivered at approximately 3 micromoles per minute was removed rapidly from plasma for at least the first two hours, while later metabolite and urinary patterns were compatible with glycohydrolase and pyrophosphatase activity [2]. The causal conclusion is extracellular processing of the administered substrate, not immediate saturation of every intracellular pool.

Compartmentation is decisive. Cytosolic, nuclear and mitochondrial NAD pools exchange information but are not a single homogeneous reservoir. SLC25A51 is required for mitochondrial NAD transport in human cells; its loss depletes mitochondrial NAD⁺ and NADH, impairs complex-I-dependent respiration and reduces tricarboxylic-acid-cycle flux [1]. This establishes that mitochondrial access is a regulated transport problem. It also demonstrates why a rise in a circulating NAD-related marker cannot be assumed to equal restored mitochondrial redox capacity.

Oral NR and NMN create different pathway inputs. They require chemical identity, digestion, absorption, extracellular conversion, transporter and kinase context. Sustained precursor exposure can be useful for continuity, but it is not a weaker copy of an infusion. Acute delivery and continuous pathway input answer different pharmacological questions.

SECTION 03

The active-drain architecture

NAD⁺ is not only recycled between oxidised and reduced states; it is irreversibly consumed. PARPs cleave NAD⁺ during ADP-ribosylation, sirtuins consume it during deacetylation, CD38 hydrolyses NAD-related substrates, and SARM1 can produce catastrophic axonal depletion after injury. Restoration can therefore fail because supply is inadequate, because distribution is constrained, because utilisation is impaired, or because consumption remains excessive.

CD38 is a particularly important drain because its NADase activity links immune state, senescence and extracellular NAD-related metabolism. Aging models show accumulation of CD38-positive immune cells in adipose tissue and liver; senescence-associated inflammatory signals induce that accumulation, and manipulation of CD38 changes tissue NAD and NMN levels [3,4]. This is a deep causal chain: enzyme identity, substrate consumption, cellular source and tissue consequence are each represented.

The chain must still be bounded. CD38 is not a universal explanation for low energy, brain fog or biological aging. PARP demand, sleep disruption, alcohol exposure, inflammatory disease, infection, metabolic overload, poor substrate availability, medication and recovery imbalance may create different or convergent drains. A rational program asks which drain is plausible and measurable rather than labelling every patient CD38-high.

SECTION 04

CD38 modulation and the exact place of apigenin

Apigenin is a flavone with multiple molecular actions. Purified-enzyme and cellular work shows inhibition of CD38 NADase activity, elevation of intracellular NAD⁺ and altered protein acetylation at micromolar experimental concentrations [5]. The biochemical proposition is therefore real: apigenin can inhibit CD38 under defined assay conditions. The mechanistic proposition is also coherent in cells where sufficient free apigenin reaches CD38 and where CD38 materially contributes to NAD consumption.

This does not make an oral milligram dose self-validating. Oral formulation, absorption, conjugation, first-pass metabolism, free concentration, tissue distribution and duration determine whether the experimental inhibitory range is approached in the relevant compartment. The 50–100 mg range sometimes used in supplement protocols cannot inherit the effect observed with recombinant enzyme, cultured cells or intraperitoneal dosing merely because the molecule has the same name.

Apigenin is also not a selective CD38 probe in the organism. It influences inflammatory signalling, calcium flux and other enzyme systems. Recent work in human monocytes and macrophages found suppression of NLRP3 activation that persisted independently of CD38 [6]. This counterevidence does not negate CD38 inhibition; it prevents every downstream effect from being assigned to CD38. The defensible position is conditional: apigenin is a mechanistically coherent candidate for a CD38-directed module, provided formulation and exposure are explicit and the predicted response is not confused with proof of selective target engagement.

SECTION 05

Precursor continuity: NR and NMN are pathway inputs

Nicotinamide riboside and nicotinamide mononucleotide can supply the salvage network, but their routes are enzyme-dependent. NR requires phosphorylation by NR kinases toward NMN. NMN may undergo extracellular dephosphorylation to NR before uptake in some systems, while tissue-specific transport can contribute in others. Both are converted toward NAD⁺ by NMNAT enzymes. The rate-limiting bridge is therefore not the printed position of the precursor in a pathway diagram; it is the identity, exposure and enzymatic capacity of the tissue.

Human studies show that oral NR can raise blood NAD-related metabolites, including NAAD, and can alter tissue metabolomes in selected settings. These observations establish biochemical engagement. They do not prove that an individual symptom is NAD-limited or that every tissue receives the same restoration. Continuity is most coherent when an acute intervention is followed by a sustained pathway input whose engagement and functional consequence can be separated from other changes.

A continuity companion should therefore be chosen against a specific bottleneck: insufficient substrate exposure, adherence failure, intolerance, defective conversion, active drain or tissue distribution. If none is identified, adding a precursor may increase measurable metabolites without correcting the limiting physiology.

SECTION 06

Nicotinamide disposal and methyl-donor economy

NAD-consuming reactions release nicotinamide. Nicotinamide can be salvaged by NAMPT or methylated by nicotinamide N-methyltransferase. NNMT transfers a methyl group from S-adenosylmethionine to nicotinamide, producing N1-methylnicotinamide and S-adenosylhomocysteine. The reaction links NAD turnover to the methionine cycle and can alter both precursor availability and the SAM-to-SAH methylation environment [7]. Increased methylated nicotinamide excretion during IV NAD⁺ exposure demonstrates that this disposal route can carry flux in humans [2].

TMG, or betaine, can support remethylation of homocysteine to methionine through betaine-homocysteine methyltransferase, predominantly in liver and kidney. This is a defined reaction. It creates a rational conditional role when homocysteine is elevated or rising, methyl-donor supply is marginal, B-vitamin status is inadequate, cumulative nicotinamide disposal is high or hepatic handling changes the balance.

The existence of the reaction does not prove that every NAD-directed intervention causes methyl depletion. Nor does it prove that TMG should be administered automatically before every infusion. Betaine can lower homocysteine, but dose-dependent lipid effects have also been observed [8,9]. Folate, B12, B6, choline, protein and methionine context, liver function and baseline lipids must remain visible. TMG is therefore a targeted flux intervention, not a ritual companion.

SECTION 07

From NADH to electron transfer: coenzyme Q

NAD⁺ acquires reducing equivalents during substrate oxidation and becomes NADH. At mitochondrial complex I, NADH donates electrons that enter the respiratory chain. Coenzyme Q, or ubiquinone, is a lipid-soluble redox carrier that receives electrons from complex I and complex II and transfers them toward complex III. The presence of NAD⁺ alone therefore cannot guarantee electron transport: dehydrogenase activity, membrane potential, respiratory complexes, coenzyme Q availability, oxygen and ATP synthase must operate as a coupled system.

Coenzyme Q has an incontrovertible biochemical role as an electron carrier. The separate proposition that oral ubiquinol supplementation improves NAD-directed function requires additional pharmacology: baseline status, formulation, intestinal absorption, lipoprotein transport, tissue uptake and endogenous synthesis. A biochemical requirement for coenzyme Q is not equivalent to a universal deficiency of coenzyme Q.

The appropriate inference is conditional. Ubiquinol may be relevant where the electron-carrier pool is plausibly constrained, where medication or disease alters synthesis, or where a measured functional trajectory supports the hypothesis. It should not be described as substrate hardware that every recipient of NAD⁺ must take.

SECTION 08

Lipoate-dependent dehydrogenases and R-alpha-lipoic acid

Lipoate is covalently attached to enzyme complexes that perform oxidative decarboxylation. The pyruvate-dehydrogenase and alpha-ketoglutarate-dehydrogenase complexes connect glycolytic carbon and tricarboxylic-acid-cycle flux to acetyl-CoA, succinyl-CoA and NADH generation. Lipoamide is reduced during catalysis and reoxidised by lipoamide dehydrogenase with reduction of NAD⁺ to NADH. This is a direct biochemical intersection between lipoate chemistry and the NAD redox pair.

Supplemental R-alpha-lipoic acid is related to that chemistry but is not identical to an enzyme-bound lipoyl cofactor. Uptake, activation, mitochondrial handling and incorporation distinguish an administered molecule from the prosthetic group already assembled on a dehydrogenase complex. R-alpha-lipoic acid also has redox and signalling effects outside cofactor replacement.

Its inclusion is therefore mechanistically coherent only when the proposed constraint is explicit: impaired pyruvate oxidation, oxidative context, deficient lipoate handling or another defined metabolic bridge. A general statement that R-alpha-lipoic acid is required for NAD⁺ assimilation collapses several causal levels and should not be used.

SECTION 09

PQQ and mitochondrial biogenesis

Pyrroloquinoline quinone can influence redox signalling and mitochondrial biogenesis in cellular systems. Experimental work links PQQ exposure to CREB phosphorylation, increased PGC-1 α expression, nuclear respiratory factors and mitochondrial transcriptional machinery [12]. This identifies a signalling route through which mitochondrial content or resilience may change.

PQQ is not a human mitochondrial electron-transport cofactor analogous to NAD or coenzyme Q. Its biological classification, exposure and target spectrum must remain exact. Increasing a biogenesis signal is also not equivalent to producing functional mitochondria: mitochondrial DNA integrity, protein import, membrane assembly, mitophagy, substrate delivery and respiratory demand determine whether additional organelle content is useful.

PQQ may therefore serve as a hypothesis-driven signalling module, not as mandatory machinery for an NAD infusion. The predicted consequence should be specified—such as a change in a validated functional or metabolic trajectory—and failure to observe it should weaken the reason for continuation.

SECTION 10

Magnesium, MgATP and the NADP(H) branch

Magnesium is not an absorption enhancer for intravenous NAD⁺. Intravenous administration already bypasses gastrointestinal absorption, and movement from vascular exposure into cells and organelles remains governed by extracellular processing, membrane transport and compartmental biology. Magnesium occupies a different causal position. In cells, ATP-dependent reactions commonly use magnesium-complexed ATP, and human NAD kinase catalyses transfer of phosphate from ATP to NAD⁺, producing NADP⁺ and ADP. The reviewed human enzyme requires a divalent metal cation; NAD kinase isolated from human neutrophils was strictly dependent on Mg²⁺ under the reported assay conditions [20,21].

This reaction creates a direct biochemical bridge from the NAD⁺ pool to NADP(H). NADPH supplies reducing power to glutathione reductase, thioredoxin systems, reductive biosynthesis and multiple antioxidant reactions. The bridge is exact: NAD kinase, ATP and a compatible divalent cation are required for NADP⁺ synthesis. The broader inference must remain conditional. The existence of magnesium-dependent chemistry does not show that magnesium is limiting in a given person, that an intravenous magnesium dose corrects the relevant intracellular compartment, or that post-infusion magnesium increases the clinical effect of administered NAD⁺.

The tolerability proposition is separate again. A small retrospective human study reported nausea, abdominal cramping, diarrhoea, vomiting, increased heart rate and chest pressure during NAD⁺ infusion, with infusion time constrained by symptoms [22]. It contained no magnesium comparison and therefore cannot establish magnesium prophylaxis. Magnesium administered before NAD⁺ may be used as a physiology-guided clinical hypothesis around neuromuscular, smooth-muscle and electrolyte context; it must be identified as such, with exposure, contraindications and the predicted tolerability consequence stated. Magnesium after NAD⁺ is likewise a mechanistic support proposition centred on MgATP and NAD kinase—not proof of improved NAD⁺ absorption, retention or clinical efficacy.

SECTION 11

Redox sequencing and glutathione

Glutathione is the principal low-molecular-weight thiol buffer in many cellular compartments. Its reduced and oxidised forms participate in peroxide detoxification and maintenance of protein thiol state. NADPH, rather than NADH, supplies reducing power to glutathione reductase. NAD⁺, NADH, NADP⁺, NADPH and glutathione are therefore connected but non-interchangeable redox systems.

A protocol that separates glutathione administration from NAD⁺ infusion days may have operational or tolerability reasons, but biochemistry alone does not impose a universal calendar. The phrase redox sequencing must identify which reaction, transient oxidative load or measurement is expected to differ when the compounds are separated. Without that bridge, timing is a clinic convention rather than a mechanistic law.

The strongest scientific position is to preserve the distinction. Glutathione support may be relevant when oxidative burden, synthesis capacity, cysteine availability or glutathione redox state is plausibly limiting. It should not automatically be presented as neutralising a predictable oxidative surge caused by every NAD⁺ infusion.

SECTION 12

Integrated physiology: the terrain determines the bottleneck

The same administered exposure can meet different biochemical terrains. Inflammation may increase CD38. DNA damage may increase PARP demand. Poor sleep and circadian disruption can alter NAMPT-linked oscillation. Alcohol metabolism changes hepatic redox state. Insulin resistance changes substrate flux. Micronutrient deficiency can constrain dehydrogenases, methylation or antioxidant systems. Deconditioning can reduce mitochondrial demand even when molecular machinery is present.

This is why fasting, Zone-2 exercise, resistance training, thermal stress, sleep regularity and nutrition cannot be bolted onto a universal NAD stack. Each changes physiology through multiple routes. They may improve insulin sensitivity, mitochondrial demand, vascular function, autophagic signalling or circadian organisation; they may also be inappropriate in undernutrition, acute illness, autonomic instability or excessive training load. The intervention follows the constraint.

A precision architecture separates deficit, delivery, distribution, drain and demonstrated response. It then adds an utilisation layer: can the relevant compartment convert NAD availability into redox flux without another limiting substrate, transporter, enzyme, electron carrier or oxygen-delivery problem? This question prevents a larger dose from becoming the automatic answer to a systems failure.

SECTION 13

Mechanistic decision matrix

A consumption module is considered when inflammation, senescence-related signalling, DNA-damage demand or another NADase pathway plausibly dominates restoration. Its readout must distinguish target biology from nonspecific symptom change. A continuity module is considered when sustained precursor input can test a supply limitation. A methylation module is considered when NNMT flux, homocysteine, nutrient status or hepatic context makes methyl-donor economy relevant. A mitochondrial-utilisation module is considered when the bridge from substrate oxidation to electron transfer is plausibly limiting. A magnesium module is considered only when magnesium status, MgATP-dependent function, electrolyte context or a defined tolerability hypothesis makes that bridge plausible; NAD biochemistry alone does not diagnose magnesium limitation.

Each module has a prohibition. CD38 biology does not authorise an unverified apigenin dose. The NNMT reaction does not authorise automatic TMG. The role of coenzyme Q does not diagnose CoQ deficiency. Lipoate chemistry does not prove that oral R-alpha-lipoic acid enters enzyme complexes. PGC-1alpha signalling does not establish useful mitochondrial biogenesis. These prohibitions are not sceptical decoration; they preserve the exact causal depth of each fact.

Combination is justified only after component hypotheses are explicit. Where several bottlenecks plausibly coexist, the sequence should maximise information: correct a proximal deficiency, stabilise major drains, introduce one discriminating module where possible, and observe the predicted trajectory. A stack that cannot be decomposed cannot teach the system which part worked.

SECTION 14

Longitudinal falsification

A mechanistic program becomes clinical science when it states in advance what would count against its own hypothesis. If CD38-directed modulation is proposed, the plan must define the accessible proxy or functional consequence expected to change and recognise that apigenin has non-CD38 actions. If methyl-donor support is proposed, homocysteine, B-vitamin context and lipids should move in a coherent direction. If mitochondrial utilisation is proposed, function should improve without evidence of worsening substrate intolerance, overtraining or redox instability. If magnesium is proposed for infusion tolerance, symptom timing, infusion rate, magnesium exposure and the predefined failure criterion must be recorded; improved tolerance cannot be relabelled as proof of greater intracellular NAD⁺ delivery.

The relevant outcome is not necessarily a population average, nor is it a testimonial. It is a dated within-person trajectory with stable definitions, a plausible time course, adherence and exposure recorded, competing changes identified, and an explicit rule for stopping or revising. Biomarker movement without functional coherence may indicate engagement rather than success. Functional improvement without the predicted biochemical movement may mean that the original mechanism was wrong.

Terminal human studies remain useful: they can estimate the frequency and magnitude of translation for a defined intervention and identify harms not predicted by a narrow mechanism. They remain terminal because they cannot resolve chemical identity, repair inadequate exposure

or explain causality by themselves. The complete hierarchy, not any single layer, determines the strength of the conclusion.

SECTION 15

Scientific conclusion

Optimising NAD⁺ restoration is not equivalent to maximising NAD⁺ delivery. It is the disciplined coordination of supply, compartmental access, active consumption, methyl-donor economy, mitochondrial redox machinery and measured response. The causal chain is strongest where the exact molecule, reaction, target, compartment and attainable exposure are all resolved.

CD38 provides a credible consumption target; apigenin provides a real but pharmacologically incomplete candidate modulator. NNMT establishes a biochemical connection between nicotinamide disposal and methyl balance; TMG provides a conditional remethylation tool, not a compulsory companion. Magnesium participates in MgATP chemistry and the NAD kinase reaction that establishes the NADP(H) branch, but this does not make magnesium a universal NAD⁺ companion or prove improved absorption. Coenzyme Q and lipoate occupy indispensable positions in energy metabolism; supplementation depends on whether their respective steps are actually constrained. PQQ can modulate mitochondrial signalling but is not core NAD machinery. NR and NMN can provide sustained pathway input but cannot be assumed to correct every tissue or symptom.

The practical doctrine is therefore minimal and demanding: identify the limiting bridge, use the smallest coherent module, preserve attribution, and allow longitudinal observation to falsify the model. That is how a protocol aid becomes mechanistic medicine without becoming a supplement brochure.

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AUTHORSHIP AND DECLARATIONS

Valentine Wibowo performed the conceptualisation, evidence synthesis, scientific interpretation and drafting. dr. I Wayan Cahyadi Surya Distira Putra, MPH completed medical review and approved the manuscript.

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