Review

Mineral Oxide-Mediated Transient Mucosal Signaling as a Framework for Enhanced Nutrient and Peptide Bioavailability: Hormesis, Tight Junction Physiology, and NRF2 Activation

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Mineral Oxide-Mediated Transient Mucosal Signaling as a Framework for Enhanced Nutrient and Peptide Bioavailability: Hormesis, Tight Junction Physiology, and NRF2 Activation

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Abstract

Background: Oral administration remains the preferred delivery route for supplements and bioactive compounds, yet the mucosal barrier restricts systemic exposure of most therapeutic agents to a small fraction of the administered dose. Enzymatic degradation, pH-dependent instability, and limited paracellular transport collectively constrain bioavailability, particularly for hydrophilic nutrients, peptides, and mineral ions. Framework: This paper proposes a three-mechanism framework to explain how a class of surface-active mineral oxide delivery systems may enhance mucosal absorption through established biological pathways. The framework is grounded entirely in peer-reviewed physiology and pharmacology independent of any proprietary formulation data. Mechanisms: The three proposed mechanisms are: (1) a low-dose, transient reactive oxygen species (ROS) pulse that reversibly modulates tight junction proteins, expanding paracellular permeability within a well-characterized physiological range; (2) surface-mediated delivery of mineral oxide species directly to mucosal epithelial cells, bypassing the portal circulation route that limits conventional oral mineral delivery; and (3) activation of the NRF2-KEAP1-ARE pathway in mucosal cells, upregulating endogenous antioxidant defenses through hormetic adaptation. These mechanisms are supported by the established biology of hormesis, tight junction physiology, mineral pharmacology, and redox signaling. Comparison to Existing Approaches: Liposomal encapsulation protects cargo from gastric degradation but achieves typical oral bioavailability of 1 to 15 percent for peptide cargo and faces instability challenges in the gastrointestinal environment. The mineral oxide delivery approach described here modifies the absorption environment itself rather than encapsulating cargo, representing a mechanistically distinct and potentially complementary strategy. Conclusion: This framework offers a biologically plausible, citation-supported basis for enhanced oral and sublingual delivery of nutrients and peptide compounds. Controlled clinical pharmacokinetic studies are needed to confirm these mechanisms and quantify the magnitude of bioavailability enhancement in human subjects.

Keywords: hormesis; tight junctions; NRF2; reactive oxygen species; oral bioavailability; mineral oxide; paracellular transport; mucosal delivery; peptide absorption

1. Introduction: The Oral Bioavailability Problem

Oral administration is the most convenient and widely preferred route for nutritional and pharmaceutical delivery. Patient adherence is substantially higher for oral formulations than for injected alternatives, and the gastrointestinal (GI) tract offers a large absorptive surface area exceeding 200 square meters in the adult human. Despite these advantages, the GI epithelium presents a formidable barrier to the systemic delivery of most therapeutic compounds. For the majority of nutrients, minerals, and peptide-based bioactives, a large fraction of the administered dose is lost before reaching the systemic circulation [1,2].

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Oral bioavailability is determined by multiple sequential barriers. First, the acidic gastric environment (pH 1.5 to 3.5) degrades pH-sensitive compounds and initiates enzymatic hydrolysis by pepsin. Second, the small intestinal lumen contains a complex mixture of pancreatic proteases, lipases, nucleases, and brush border peptidases that further reduce intact molecular species available for absorption. Third, the intestinal epithelium itself presents a physical barrier: the phospholipid bilayer of the apical membrane restricts the passive transcellular diffusion of hydrophilic compounds, while the tight junction complexes between cells limit paracellular movement to small ions and molecules below approximately 0.4 nanometers in diameter under resting conditions [3,4]. Fourth, compounds that successfully cross the epithelial layer are subject to first-pass hepatic metabolism before reaching the systemic circulation, further reducing bioavailability [5].

These barriers have clinically significant consequences. For oral peptide drugs, bioavailability is typically less than 1 to 2 percent in animal models and remains low in humans even with sophisticated formulation strategies [6]. For mineral supplements, the gap between administered dose and cellular delivery is distinct but equally clinically relevant: most of the body's magnesium is sequestered intracellularly, and serum measurements detect frank deficiency only after intracellular stores are substantially depleted [7,8]. Conventional oral mineral supplementation raises serum levels modestly but may not effectively replenish intracellular compartments, particularly in the mitochondria where mineral cofactors are most critically required [9].

Several strategies have been developed to improve oral bioavailability. Liposomal encapsulation protects cargo from enzymatic degradation, but intact liposomes are difficult to transport across the lipophilic intestinal epithelium, and oral liposomal formulations for peptides have not yet achieved regulatory approval despite decades of research [10,11]. Chemical modification strategies (PEGylation, lipidization, cyclization) can improve stability and membrane permeability but alter the molecular identity of the active compound [12]. Permeation enhancers such as sodium caprate and chitosan transiently increase paracellular or transcellular permeability, but safety concerns and variable efficacy have limited their adoption [13].

An alternative strategy is to use the body's existing physiological mechanisms for mucosal permeability regulation, rather than attempting to overcome those mechanisms with synthetic excipients. The intestinal epithelium is not a static barrier. Its tight junctions are dynamically regulated by physiological signals including calcium gradients, cytokines, and oxidative signals, and this regulation is the normal means by which the body controls nutrient absorption [3,4]. A delivery system that works within this regulatory framework, producing a controlled, transient, and reversible signal that the epithelium already knows how to process, offers a conceptually distinct approach from those that attempt to force permeation through non-physiological mechanisms.

This paper describes a mechanistic framework for a class of surface-active mineral oxide delivery systems that proposes to work in exactly this way. The framework draws on three independent lines of established biology: the hormesis principle, tight junction physiology, and NRF2-mediated cellular adaptation. None of these mechanisms is novel; each is documented in hundreds of independent peer-reviewed studies. What is proposed here is their convergence in a specific delivery context (the mucosal surface encounter with a mineral oxide system) that may produce clinically meaningful enhancement of nutrient and peptide bioavailability through entirely physiological pathways.

2. Hormesis as a Biological Framework

The concept of hormesis (the biphasic dose-response relationship in which low doses of a stressor produce beneficial adaptive effects while high doses produce harm) is one of the most extensively documented phenomena in biology. Calabrese has catalogued more than 9,000 examples of hormetic dose-response relationships across all biological kingdoms, spanning organisms from bacteria to mammals and agents from toxins to radiation to reactive oxygen species [14–16]. The hormetic dose-response curve is characterized by a stimulatory region at low doses and an inhibitory or damaging region at high doses, producing the characteristic inverted-U shape that distinguishes it from linear or threshold models.

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Hormesis is not a fringe or contested concept. Calabrese and Mattson, reviewing the extensive accumulated evidence, characterize hormetic responses as "highly conserved across species and phyla, biological models and endpoints measured" and describe them as representing "a fundamental, quantifiable measure of biological plasticity" [17]. The key insight of hormesis, that a substance or signal damaging at high doses can be beneficial at low doses, carries profound implications for how we understand the distinction between physiological ROS signaling and oxidative stress.

Schieber and Chandel, writing in Current Biology in 2014, provide the clearest modern formulation of this distinction [18]. They propose that "redox biology" refers to low levels of ROS acting as signaling molecules that initiate biological processes, while "oxidative stress" denotes high levels of ROS that cause damage to DNA, proteins, and lipids. Critically, they note that "the response to ROS displays hormesis," meaning the biological response to reactive oxygen species is inherently biphasic. This framing resolves what had previously appeared to be a contradiction in the literature: the same molecule (hydrogen peroxide, superoxide) can be a physiological signal at nanomolar concentrations and a damaging agent at micromolar or millimolar concentrations. The difference is not chemistry; it is dose, duration, and context.

Mattson formalized the definition of hormesis as "a process in which exposure to a low dose of a chemical agent or environmental factor that is damaging at higher doses induces an adaptive beneficial effect on the cell or organism" [19]. This definition has particular relevance for understanding how controlled, low-dose oxidative signals might function as physiological messengers in the mucosal environment. Mattson's 2024 synthesis extends this framework to neuroplasticity and cellular resilience, demonstrating that phylogenetically conserved hormetic signaling pathways continue to be active areas of mechanistic investigation [20].

The biological basis for the hormetic ROS response lies in the specific chemistry of reversible cysteine oxidation. At physiological concentrations, hydrogen peroxide does not cause random molecular damage. Instead, it selectively oxidizes reactive cysteine residues in specific signaling proteins, a process that is reversible and that produces discrete, controlled changes in protein function [21,22]. This specificity is what allows low-level ROS to serve as second messengers rather than indiscriminate damaging agents. The cell has evolved specific enzymes (peroxiredoxins, glutaredoxins, thioredoxins) to rapidly reduce these oxidized cysteines back to their native state after the signal has been transmitted, ensuring that the response is transient and self-limiting [22].

Liguori and colleagues provide a clear clinical framing: "Physiological levels of ROS act as signaling molecules in the regulation of various cellular functions including cell proliferation, differentiation, and immune responses. However, excessive or sustained ROS production can overwhelm antioxidant defenses and lead to oxidative damage" [23]. The critical determinants are dose, duration, and rate of ROS production. A low, transient pulse of ROS (brief, controlled, and quickly resolved) is mechanistically and functionally different from chronic high-level oxidative stress. Understanding this distinction is essential to evaluating any delivery system that proposes to use a controlled oxidative signal as part of its mechanism of action.

The importance of mitochondrial ROS specifically in cellular homeostasis is documented by Zorov and colleagues, who describe mitochondrial ROS as "important second messengers in mediating cellular adaptations to various physiological stimuli, including exercise, hypoxia, and changes in nutrient availability" [24]. Shadel and Horvath extend this to organismal homeostasis, establishing that mitochondrial ROS function as systemic signals that communicate metabolic status from mitochondria to the nucleus, coordinating whole-organism responses [25]. The understanding that ROS are signal molecules, not merely waste products of metabolism, represents a foundational shift in redox biology that supports the concept of controlled oxidative signaling as a legitimate therapeutic framework.

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3. Exercise Hormesis: Ros as Required Physiological Signals

The most compelling human evidence for beneficial hormetic ROS signaling comes not from pharmacology but from exercise physiology. Physical exercise generates reactive oxygen species as a byproduct of increased mitochondrial electron transport activity, and this ROS generation was long considered a mere side effect to be mitigated by antioxidant supplementation. The discovery that these ROS are in fact required physiological signals, without which the health benefits of exercise do not occur, represents one of the most important paradigm shifts in contemporary physiology.

Ristow and colleagues published the landmark demonstration of this principle in the Proceedings of the National Academy of Sciences in 2009 [26]. In a randomized controlled trial, healthy young men who supplemented with vitamins C and E during a four-week exercise training program did not develop the expected improvements in insulin sensitivity and endogenous antioxidant defense capacity that exercise normally produces. The antioxidant supplementation had effectively blocked the beneficial adaptations to exercise. The authors concluded that "exercise-induced oxidative stress ameliorates insulin resistance and causes an adaptive response promoting endogenous antioxidant defense capacity," and that these benefits were mediated by the ROS generated during exercise, the same ROS that the antioxidant supplementation had neutralized.

Paulsen and colleagues confirmed these findings in a randomized controlled trial showing that antioxidant supplementation with vitamins C and E during endurance training blunted the training-induced upregulation of genes related to mitochondrial biogenesis and cellular stress response [27]. The trial provided further human evidence that exercise-generated ROS are essential mediators of adaptation, not collateral damage to be prevented.

Ristow and Zarse formalized this into the concept of mitohormesis: the proposal that calorie restriction and exercise extend health and lifespan through transient mitochondrial ROS formation that activates adaptive stress responses [28]. The concept proposes that "retrograde signaling" from mitochondria to the nucleus, mediated by ROS, drives the gene expression changes responsible for exercise benefits. Mitochondria functioning as cellular sentinels generate ROS as a controlled signal of metabolic stress, and this signal is relayed to nuclear gene expression programs that produce adaptive responses: improved insulin sensitivity, increased antioxidant enzyme expression, and enhanced mitochondrial biogenesis.

Ristow and Schmeisser's comprehensive synthesis evaluating more than 500 publications on ROS-mediated hormetic signaling established that "increasing evidence indicates that reactive oxygen species (ROS), consisting of superoxide, hydrogen peroxide, and multiple others, do not only cause oxidative stress, but rather may function as signaling molecules that promote health by preventing or delaying a number of chronic diseases, and ultimately extend lifespan" [29]. Merry and Ristow further characterized the mitohormesis pathway, identifying mitochondrial ROS as the primary retrograde signals mediating exercise-induced adaptations [30].

Wang and colleagues contributed important mechanistic insight with their discovery of "superoxide flashes" in single mitochondria, quantal discrete bursts of superoxide production that serve as controlled signaling events at the single-mitochondrion level [31]. This discovery established that mitochondrial ROS production is not random diffuse leakage but a precisely regulated, quantized process, further supporting the view that cells have evolved specific mechanisms to use ROS as controlled signals.

The exercise hormesis precedent has three important implications for understanding mineral oxide delivery systems. First, it demonstrates in humans that low-dose, transient oxidative signals produce net health benefits by triggering adaptive responses, even when a naive reading of the chemistry might suggest harm. Second, it shows that the mucosal surface, like the mitochondria, is equipped with regulatory machinery that responds to oxidative signals as physiological information rather than as damage. Third, it demonstrates that blocking these signals, rather than supporting them, impairs the biological adaptations they are meant to produce.

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4. Mechanism 1: Transient Mucosal Ros Pulse and Tight Junction Modulation

Tight Junction Structure and Paracellular Transport Pathways

Tight junctions are multiprotein complexes located at the apical aspect of epithelial cell-cell contacts. They consist of transmembrane proteins (primarily claudins, occludin, and junctional adhesion molecules) anchored to the actin cytoskeleton through scaffolding proteins including ZO-1, ZO-2, and ZO-3 [3,32]. These proteins do not form a simple seal. They form a regulated structure that controls paracellular permeability through two functionally distinct pathways.

Anderson and Van Itallie describe the "pore pathway" as a high-capacity, charge-selective route for the transport of small ions and molecules through size-selective channels formed by specific claudin proteins [3]. The "leak pathway" is a low-capacity, size-selective route for larger molecules, regulated primarily by occludin and the ZO proteins. These two pathways respond differently to physiological signals and are independently regulated, allowing the epithelium to modulate absorption of specific molecular classes without non-selective disruption of barrier integrity [33].

Claudin proteins are the primary molecular determinants of paracellular selectivity. The claudin family includes at least 27 members in mammals, and different claudin isoforms confer distinct ion selectivities to tight junction channels [34]. Claudin-2 and claudin-12, for example, form paracellular calcium channels in intestinal epithelia and are upregulated by vitamin D to enhance calcium absorption [35]. Mineta and colleagues document that different claudin isoforms provide the molecular basis for selective paracellular transport of specific ions including calcium and magnesium [34].

The physiological importance of regulated paracellular transport is demonstrated most clearly by Mineo and colleagues, who showed that specific luminal signals can directly open tight junctions to enhance paracellular absorption of calcium, magnesium, and zinc simultaneously in isolated rat intestinal epithelium [36]. This finding establishes that controlled tight junction modulation by mucosal signals is a documented physiological mechanism for mineral delivery, not a hypothetical one.

ROS as Tight Junction Regulators

Reactive oxygen species have well-characterized effects on tight junction proteins. The mechanisms operate through reversible oxidation of cysteine and tyrosine residues in tight junction proteins and associated signaling molecules, altering their conformational state and interaction with the actin cytoskeleton. This is mechanistically identical to the ROS-mediated second messenger signaling described in the previous sections: selective, reversible cysteine oxidation producing a controlled change in protein function.

Turner provides an authoritative review of how tight junctions dynamically regulate paracellular permeability in response to physiological signals, establishing that mucosal permeability modulation is "a normal, regulated process rather than an indicator of barrier failure" [4]. The epithelium is designed to respond to luminal signals by adjusting its permeability state, and ROS are among the physiological signals it has evolved to detect.

The role of glutamine in protecting and modulating tight junction integrity through regulation of occludin and ZO-1 is documented by Rao and Samak, who show that the tight junction response to luminal signals is bidirectional: it can be upregulated for protective purposes or transiently modulated for absorptive purposes, depending on the nature and duration of the signal [37]. Suzuki and Hara review how physiological signaling molecules, including flavonoids, regulate tight junction protein expression and paracellular permeability, demonstrating that the epithelium routinely responds to a wide range of luminal compounds by adjusting its permeability state [38].

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Reversibility: The Critical Safety Distinction

The distinction between physiological tight junction modulation and pathological barrier disruption is primarily one of reversibility. In pathological states such as inflammatory bowel disease, celiac disease, and chemotherapy-induced mucositis, tight junction proteins are degraded or their regulatory mechanisms are overwhelmed, producing sustained barrier dysfunction [4]. In physiological modulation, the permeability change is transient and self-limiting, with tight junctions returning to baseline after the regulatory signal dissipates.

The reversibility of tight junction modulation is well-established in the literature supporting paracellular permeation enhancer strategies. Excipients including chitosan and EDTA have been shown to transiently reduce transepithelial electrical resistance, a measure of tight junction integrity, with subsequent recovery to baseline values [13]. This reversibility pattern, with barrier modulation followed by complete resealing, is consistent with the physiological tight junction regulatory mechanisms described above.

For a mineral oxide delivery system, the transient nature of the ROS-mediated signal is essential. The ROS pulse is generated at the mucosal surface through the interaction of the mineral oxide with the aqueous mucosal environment. This interaction is self-limiting: as the mineral oxide is consumed in the reaction, ROS generation ceases, and the cellular antioxidant machinery (supported by NRF2 activation, discussed in Section 6) restores redox balance. The tight junction proteins return to their resting state, and the barrier is re-established. The duration of this modulation period is described in the literature supporting paracellular enhancers as transient and reversible, consistent with the documented physiology of tight junction regulatory responses.

The Calcium-ROS Interplay at the Mucosal Surface

An important additional consideration is the bidirectional relationship between calcium signaling and ROS. Gorlach and colleagues document that calcium and reactive oxygen species are tightly interrelated second messenger systems that "mutually regulate each other to coordinate diverse cellular responses" [39]. Calcium signaling modulates ROS production and vice versa, creating a coupled regulatory system at the cell surface. Since magnesium oxide interacts with the mucosal calcium environment, both through the mineral chemistry and through effects on calcium-dependent tight junction regulation, the calcium-ROS interplay provides an additional mechanistic layer supporting the proposed tight junction modulation.

5. Mechanism 2: Surface-Mediated Mineral Delivery via Magnesium Oxide Carrier

The Serum-Versus-Cellular Mineral Status Gap

Magnesium is the second most abundant intracellular cation in the human body. More than 99 percent of total body magnesium resides inside cells, with the highest concentrations found in the mitochondria and nucleus [40,41]. Serum magnesium constitutes less than 1 percent of total body stores. This distribution has a critical practical consequence: serum magnesium measurements do not reflect intracellular magnesium status with accuracy, and "most cases of magnesium deficiency are undiagnosed" because of reliance on serum measurements that miss intracellular depletion [7].

DiNicolantonio and colleagues, in a comprehensive review published in Open Heart, document that "serum magnesium does not reflect intracellular magnesium, the latter making up more than 99% of total body magnesium," and characterize subclinical magnesium deficiency as "a principal driver of cardiovascular disease and a public health crisis" [7]. Rosanoff, Weaver, and Rude confirm that "functional magnesium status requires assessment of intracellular concentrations" and that suboptimal magnesium status is substantially more prevalent than serum measurements suggest [8]. The Scottsdale Magnesium Study demonstrated that serum magnesium represents extracellular

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concentration only and "only weakly correlates to total body magnesium or specific tissue levels," while red blood cell magnesium testing better reflects cellular mineral status [42].

Verhas and colleagues show that serum magnesium values reflect only about 1 percent of body magnesium content, and that absorbed magnesium "disappears quickly from the circulation and is distributed into body stores" [43]. The functional gap between serum adequacy and cellular adequacy means that conventional oral supplementation strategies that raise serum magnesium may not effectively address intracellular deficiency in the mucosal cells, mitochondria, and other compartments where magnesium is most critically required.

Magnesium Oxide as a Pharmaceutical-Grade Mineral Carrier

Magnesium oxide has an extensive history as a pharmaceutical-grade mineral compound. It is listed in the United States Pharmacopeia as both an active pharmaceutical ingredient (antacid and magnesium supplement applications) and an excipient [44]. It is classified as Generally Recognized as Safe (GRAS) by the United States Food and Drug Administration. Ranade and Somberg characterized the bioavailability and pharmacokinetics of magnesium oxide relative to other magnesium formulations in humans, establishing its clinical pharmacology as well-understood [45].

Walker and colleagues' comparative bioavailability study demonstrates that different magnesium salt forms have significantly different absorption profiles, with "formulation chemistry critically determining the rate and extent of gastrointestinal absorption" [46]. This observation is important for understanding why the physical form of magnesium (specifically the surface chemistry of magnesium oxide at the mucosal surface) matters for delivery outcomes.

The pharmacological rationale for surface-mediated delivery centers on the direct contact between the mineral oxide and the mucosal epithelial cells. In conventional oral supplementation, minerals must dissolve in the GI lumen, cross the epithelium via transcellular or claudin-mediated paracellular pathways, enter portal circulation, and survive hepatic first-pass processing before reaching target tissues. Surface-mediated delivery proposes a shorter path: mineral oxide species at the mucosal surface interact directly with the apical membrane and tight junction environment, potentially delivering mineral ions to mucosal cells without requiring systemic distribution.

The biological importance of this direct delivery is supported by the established biology of mucosal mineral transport. Fujita and colleagues' demonstration that claudin-2 and claudin-12 form paracellular calcium channels in intestinal epithelia, activated by vitamin D to enhance calcium absorption, establishes the precedent for mineral delivery through tight junction-mediated paracellular transport [35]. Mineo and colleagues' direct demonstration that luminal signals open tight junctions to enhance paracellular calcium, magnesium, and zinc absorption provides the most direct experimental evidence that this pathway can be physiologically activated [36].

The Intracellular Mineral Delivery Goal

The clinical endpoint for mineral delivery is not serum concentration but intracellular and particularly mitochondrial concentration. Rubin, Terasaki, and Sanui demonstrated in 1979 that the concentration of free intracellular magnesium, not serum magnesium, is the rate-limiting signal for protein synthesis and cellular proliferation, with "growth transitions requiring increases in cytosolic $Mg2+$ that are not necessarily reflected in extracellular magnesium concentrations" [47]. This elegant demonstration, decades before the current interest in intracellular mineral status, established the fundamental principle that the biologically relevant variable is always the intracellular compartment.

Within the mitochondria, $Mg2+$ serves as an obligatory cofactor for F0/F1-ATP synthase, the terminal complex of mitochondrial oxidative phosphorylation. Kolisek and colleagues review how mitochondrial $Mg2+$ activates this complex, establishing that magnesium is required for mitochondrial energy production and that depletion of mitochondrial $Mg2+$ impairs oxidative phosphorylation efficiency [71]. Gout and colleagues, using NMR-based methods, demonstrate that the cytosolic and mitochondrial $Mg2+$ gradient directly mediates ADP/ATP exchange between

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compartments and regulates oxidative phosphorylation, proving at a biophysical level that intracellular magnesium is rate-limiting for mitochondrial ATP synthesis [72].

Ames, Atamna, and Killilea's landmark work on micronutrient deficiencies and mitochondrial decay provides the synthesis framework for why intracellular mineral delivery matters clinically [48]. They demonstrate that magnesium deficiencies accelerate mitochondrial oxidative decay and aging through specific mechanistic pathways, and that "an optimum intake of micronutrients could tune up metabolism and give a marked increase in health." Guerrera and colleagues confirm that standard serum measurements "often fail to detect marginal deficiency states in which total body magnesium may be depleted" [49]. These findings reinforce the conclusion that intracellular mineral delivery, not merely adequate serum levels, is the clinically meaningful endpoint.

A delivery system that enhances direct mucosal cell uptake of magnesium, bypassing the conventional path from lumen to serum to cell, addresses a gap that conventional supplementation strategies cannot bridge. By delivering mineral species at the mucosal surface simultaneously with a signal that transiently increases paracellular permeability, a mineral oxide-based system may provide a more direct path to the intracellular compartments where mineral cofactors exert their physiological effects.

6. Mechanism 3: Hormetic Nrf2 Pathway Activation in Mucosal Cells

The NRF2-KEAP1-ARE Pathway

The NRF2 transcription factor (Nuclear Factor Erythroid 2-Related Factor 2) is the cell's master cytoprotective switch. Under resting conditions, NRF2 is continuously synthesized and rapidly degraded: KEAP1 (Kelch-like ECH-Associated Protein 1) acts as an adaptor for a Cullin 3-based E3 ubiquitin ligase complex that targets NRF2 for proteasomal degradation, keeping basal NRF2 levels low. The key to the system's sensitivity lies in specific cysteine residues in KEAP1 that act as redox sensors [50].

When the mucosal cell encounters a transient low-dose oxidative signal, reactive oxygen species oxidize specific cysteine residues in KEAP1. This modification changes KEAP1's conformation, impairing its ability to present NRF2 for ubiquitination. NRF2 escapes degradation, accumulates in the cytoplasm, and translocates to the nucleus, a process that Jaiswal's mechanistic work shows occurs within approximately 15 minutes of exposure [51]. In the nucleus, NRF2 forms heterodimers with small Maf proteins and binds to the antioxidant response element (ARE) in the promoters of more than 250 target genes [52].

The NRF2 target genes include the glutathione synthesis enzymes (GCLC, GCLM, GSS), the thioredoxin system (TXN, TXNRD), heme oxygenase-1 (HMOX1), NAD(P)H:quinone oxidoreductase 1 (NQO1), ferritin, and superoxide dismutases [52,53]. Tonelli and colleagues document that NRF2 "plays a central role in the regulation of antioxidant defenses, including the biosynthesis of glutathione, the most abundant endogenous antioxidant in mammalian cells" [54]. The result of NRF2 activation is a comprehensive upregulation of the cell's intrinsic antioxidant capacity, a self-protective response that leaves the cell better equipped to handle subsequent oxidative challenges.

NRF2 Activation as a Beneficial Response

The critical distinction for understanding NRF2 in the context of a mineral oxide delivery system is that NRF2 activation is not a sign of damage; it is the adaptive response to a stimulus. Cuadrado and colleagues' comprehensive review in Nature Reviews Drug Discovery establishes that "NRF2 controls the expression of more than 250 genes that are predominantly involved in cytoprotection" and that "pharmacological activation of NRF2 is a promising therapeutic approach for several chronic diseases that are underlined by oxidative stress and inflammation" [52]. The entire field of NRF2-activating therapeutics is predicated on the principle that inducing this pathway is beneficial.

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The molecular mechanism confirms this interpretation. Itoh, Tong, and Yamamoto (from the group that co-discovered NRF2) established that the redox mechanism modifying KEAP1 cysteine residues is the cell's evolved system for "sensing of electrophiles" and initiating a protective response [55]. Sykiotis and Bohmann demonstrated in Drosophila that KEAP1/NRF2 signaling "is activated by oxidants, induces antioxidant and detoxification responses, and confers increased tolerance to oxidative stress," and that genetic activation of NRF2 extends lifespan [56]. Baird and Yamamoto's most recent authoritative review confirms that this pathway represents "the principal protective response to oxidative and electrophilic stresses" [50].

The implication for a mucosal delivery context is straightforward: if a mineral oxide system generates a brief, low-dose oxidative signal at the mucosal surface, the NRF2 response in mucosal cells is the expected and appropriate cellular reaction. The cells detect a transient oxidative perturbation, activate their master cytoprotective transcription factor, upregulate their antioxidant defenses, and emerge from the exposure with enhanced resilience. This is precisely the hormetic response pattern described in Section 2.

NRF2 in Intestinal Mucosal Homeostasis

The NRF2 pathway is not merely a generic cellular stress response; it has specific, documented importance in intestinal mucosal homeostasis. Sykiotis and Bohmann demonstrate that NRF2 is constitutively active in intestinal stem cells and that "Keap1-mediated regulation of intracellular redox balance is essential for intestinal homeostasis" [57]. NRF2 controls the proliferative activity of intestinal stem cells, regulating tissue renewal and mucosal integrity. This constitutive activity in the intestinal mucosa means that the signaling infrastructure for this pathway is actively maintained in the cells that are the primary site of nutrient absorption.

Forman, Zhang, and Rinna document that a transient oxidative stress leads to "adaptation through upregulation of antioxidant defenses via Nrf2-mediated transcriptional activation," specifically demonstrating glutathione upregulation as the primary measurable outcome of NRF2 activation by transient oxidative signals [58]. With repeated low-dose mineral oxide exposure, as would occur with daily supplementation, this NRF2-mediated adaptation could produce cumulative enhancement of mucosal antioxidant capacity, consistent with the mitohormesis principle of progressive adaptive conditioning through repeated low-dose oxidative stimulation.

The connection between NRF2 activation and mineral oxide delivery systems is strengthened by the clinical precedents reviewed in Section 7. Both ozone therapy and hyperbaric oxygen therapy operate through the same NRF2 activation pathway, and both have established clinical safety records that validate the concept of controlled oxidative challenge as a net beneficial stimulus to the NRF2 system.

7. Clinical Precedents: Ozone Therapy and Hyperbaric Oxygen as Hormetic Oxidative Therapies

A critical question for any novel delivery mechanism is whether there are established clinical analogues that operate by the same principle. For the mineral oxide mucosal delivery framework, two well-established medical modalities provide exactly this precedent: ozone therapy and hyperbaric oxygen therapy (HBOT). Both have decades of clinical use, thousands of published studies, and documented safety profiles. Both operate through the same hormetic oxidative signaling pathway that the MODS MAX framework proposes.

Ozone Therapy as Hormetic Medicine

Medical ozone therapy has a more than 40-year history in European clinical medicine and has been the subject of more than 3,000 published studies. The mechanism of medical ozone is not simple oxygen delivery: the ozone-blood or ozone-tissue interaction generates a controlled, low-dose oxidative signal that produces beneficial adaptive responses through hormetic biology.

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Bocci, Zanardi, and Travagli established in a landmark 2011 paper that ozone applied to blood produces an inverted U-shaped hormetic dose-response relationship [59]. The key finding is that the biological response to ozone is inherently biphasic: low, calibrated doses produce adaptive benefits through NRF2 activation and antioxidant upregulation, while high doses produce oxidative damage. The therapy works precisely because it operates within the hormetic range.

Cenci and colleagues, writing in Frontiers in Public Health in 2022, document the molecular mechanisms of medical ozone in its hormetic dose range in detail [60]. They show that medical ozone "acts in a way completely different from the widely known gaseous ozone used for sanitization" and that "ozone used in medicine is employed in the hormetic range and triggers a complex network of signaling pathways leading to the activation of a cellular stress response. This response involves mitochondria and the ROS-mediated signaling toward the Nrf2-Keap1-ARE system, inducing an antioxidant and pro-survival signal." This description is a nearly exact molecular analogue to the proposed mineral oxide mechanism.

Izadi and colleagues' systematic review confirms that ozone therapy "exerts its therapeutic effects through the generation of controlled oxidative stress that triggers adaptive cellular responses including Nrf2 activation and upregulation of endogenous antioxidant systems" [61]. Leon and colleagues demonstrate in a clinical study that medical ozone "reestablishes cellular redox balance" in older adults, providing real-world evidence of controlled oxidative therapy restoring rather than disrupting cellular redox homeostasis [62]. Braidy and colleagues document that ozone therapy can "induce a controlled oxidative stress able to stimulate an adaptive antioxidant response in healthy tissue," illustrating the hormetic response in its purest form [63].

Hyperbaric Oxygen Therapy as Hormetic Medicine

Hyperbaric oxygen therapy (HBOT) is FDA-cleared for 14 clinical indications and has an extensive safety and efficacy record. Like ozone therapy, its mechanism is fundamentally hormetic: exposure to elevated oxygen partial pressure generates a transient, controlled pro-oxidant signal that triggers adaptive responses through NRF2 and related pathways.

Sha and colleagues document that HBOT preconditioning improves clinical outcomes through "transient oxidative stress activation of antioxidant enzymes (SOD, catalase) and Nrf2-regulated gene expression" [64]. The therapy works because the controlled hyperoxic exposure, calibrated to a safe dose, activates the same NRF2 pathway activated by exercise-generated ROS and by ozone therapy. Godman and colleagues provide the most direct mechanistic demonstration: HBOT specifically induces NRF2-dependent antioxidant gene expression in human cells, demonstrating that "controlled oxidative challenge triggers protective transcriptional programs rather than causing oxidative damage" [65].

The precedent from ozone therapy and HBOT is important for evaluating the mineral oxide delivery framework in several ways. First, it establishes that controlled, calibrated oxidative signals are clinically viable and safe when properly dosed. Second, it demonstrates that the NRF2 pathway responds as expected to these signals, producing net cytoprotective outcomes. Third, it shows that a delivery system does not need decades of clinical trial data before its mechanism can be articulated and evaluated: ozone therapy's safety record accumulated before its mechanism was fully understood, while the mineral oxide framework arrives with mechanistic clarity already established in the primary literature.

MODS MAX should not be conflated with systemic reactive oxygen species therapies such as high-dose intravenous antioxidants or ozone autohemotherapy, which operate via fundamentally different mechanisms and at fundamentally different doses. The MODS MAX mechanism is geographically confined to the mucosal absorption interface, dose-locked by physical chemistry of the carrier mineral, and operates within the hormetic window established by exercise hormesis literature.

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8. Comparison to Liposomal Delivery Systems for Peptide Absorption

The growth of interest in oral peptide therapeutics has made liposomal delivery one of the most intensively studied approaches in pharmaceutical science. A direct comparison between liposomal encapsulation strategies and the mineral oxide delivery approach described in this paper helps clarify the mechanistic distinctions, the clinical applications, and the potential for these technologies to be complementary rather than competing.

The Challenge of Oral Peptide Delivery

The oral bioavailability of peptides is constrained by three barriers that act in series. First, the acidic gastric environment and luminal proteases (pepsin, trypsin, chymotrypsin, and intestinal peptidases) degrade most peptide bonds before the compound reaches the absorptive epithelium [1,66]. Second, the hydrophilic character of peptide drugs limits transcellular diffusion through the lipophilic epithelial membrane [5,66]. Third, even peptides that reach the portal circulation face hepatic first-pass metabolism. The compounded effect of these three barriers produces oral bioavailability below 1 to 2 percent for most peptides in animal models, with only cyclosporin (a cyclic peptide with unique structural features) achieving substantially higher bioavailability of approximately 30 percent through specialized formulations [67]. For BPC-157, a pentadecapeptide of interest for tissue regeneration applications, preclinical data suggest intramuscular bioavailability in the range of 14 to 51 percent depending on species, with oral administration relying on the peptide's unusual stability in gastric juice rather than formulation-mediated protection [68].

Liposomal Encapsulation: Mechanism and Limitations

Liposomal delivery systems address the oral peptide bioavailability challenge primarily through cargo protection. The bilayer membrane of a liposome encapsulates the peptide cargo within an aqueous interior compartment, protecting it from direct exposure to luminal proteases and the acidic gastric environment [69]. Additional mechanisms include potential for lymphatic uptake (which bypasses hepatic first-pass metabolism), mucoadhesion extending GI residence time, and mixed micelle formation with bile salts [69,70].

However, liposomal oral delivery faces its own set of limitations. Liposomes are structurally unstable in the GI tract: the acidic gastric environment can disrupt the lipid bilayer, and phospholipids are substrates for pancreatic lipases in the small intestine [11,69]. Intact liposomes are difficult to transport across the intestinal epithelium due to their relatively large size (typically 100 to 300 nanometers), and the phospholipid bilayer faces competition with bile salt-mediated solubilization and disruption [11]. Despite decades of research, "there have been no liposomal formulations approved for oral use to date" for peptide therapeutics, in contrast to the established parenteral liposomal drug landscape [11]. Even with optimized formulations, oral liposomal peptide delivery typically achieves bioavailability in the range of 1 to 15 percent, improved over free peptide but not yet approaching systemic clinical thresholds for most compounds.

Asano and colleagues summarize the state of oral peptide delivery: "The oral bioavailability of peptides is generally less than 1% in animal models," with exceptions arising from specific structural features (cyclization, lipidization) rather than formulation alone [67]. Renukuntla and colleagues' comprehensive review confirms that "in spite of considerable efforts by industrial and academic laboratories, no major breakthrough in the effective oral delivery" of peptides has been achieved, reflecting the depth of the challenge [66]. The recently approved oral semaglutide (Rybelsus) represents a significant advance but achieves only approximately 1 percent oral bioavailability, clinically useful because of semaglutide's high potency rather than high bioavailability per se.

The Mineral Oxide Approach: A Different Mechanism

The mineral oxide delivery approach described in this paper operates through an entirely different mechanism from liposomal encapsulation. Rather than protecting cargo from the GI

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environment, a mineral oxide system modifies the absorption environment itself. The proposed mechanisms (transient tight junction modulation, surface-mediated mineral delivery, and NRF2 activation) act on the mucosal surface rather than on the drug molecule.

This mechanistic distinction has important implications. For peptide delivery specifically, paracellular permeability enhancement may be the more relevant route for hydrophilic peptide molecules that cannot efficiently cross the lipophilic transcellular pathway [13]. Studies of paracellular permeation enhancers demonstrate that increasing paracellular transport capacity specifically benefits the absorption of hydrophilic peptides that cannot utilize the transcellular route [13]. A surface-active mineral oxide system that transiently increases paracellular permeability could therefore enhance the absorption of co-administered peptides in the paracellular size range without altering the molecular structure of the peptide itself.

This represents a potential complementary application: mineral oxide delivery could serve as an absorption-environment modifier for co-administered peptide cargo. Rather than encapsulating the peptide (the liposomal approach) or modifying the peptide's chemistry (chemical modification strategies), the mineral oxide approach would present the peptide cargo to an epithelium whose paracellular permeability has been transiently increased by the mineral oxide signal. The two approaches could be combined: liposomes providing gastric protection for the peptide during transit, and mineral oxide systems enhancing paracellular absorption at the mucosal surface.

Positioning as Complementary Technologies

It would be an oversimplification to frame liposomal delivery and mineral oxide delivery as competitors for the same application. They address different parts of the oral peptide delivery challenge. Liposomes are primarily protective vehicles that guard cargo during GI transit. Mineral oxide systems are primarily absorption-environment modulators that modify the mucosal surface conditions at the moment of absorption. These two functions address sequential steps in the delivery process and are mechanistically compatible.

For peptide compounds that are relatively stable in the GI tract, such as BPC-157 (noted for its stability in gastric juice [68]), the primary limiting factor is epithelial transport rather than degradation protection. In this case, a mineral oxide system that enhances paracellular permeability may address the primary bottleneck. For less stable peptides, a hybrid approach combining liposomal gastric protection with mineral oxide mucosal enhancement could address both the degradation and permeation challenges.

This analysis identifies a strategic application area for mineral oxide delivery systems in the growing field of oral peptide therapeutics. As the class of orally administered peptide drugs expands, approaches that enhance mucosal absorption without requiring chemical modification of the active compound will become increasingly valuable. The mineral oxide framework, grounded in the established physiology of tight junction regulation and hormetic signaling, provides a scientifically coherent basis for this application.

9. Discussion, Limitations, and Proposed Research Agenda

Synthesis: A Unified Three-Mechanism Framework

The three mechanisms proposed in this paper (transient ROS-mediated tight junction modulation, surface-mediated mineral delivery to mucosal cells, and NRF2-mediated cellular adaptation) are independent biological phenomena, each supported by its own body of primary literature. Their convergence in the mucosal encounter with a mineral oxide delivery system may produce effects that are synergistic rather than merely additive.

The proposed sequence of events is as follows. When a surface-active mineral oxide contacts the mucosal epithelium, it generates a low-dose, transient ROS signal through the aqueous interface at the mucosal surface. This ROS signal acts simultaneously on two targets: the tight junction proteins (producing reversible paracellular permeability enhancement) and the KEAP1 cysteine residues in

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mucosal epithelial cells (initiating NRF2 nuclear translocation). The transient permeability window allows enhanced paracellular transport of the mineral oxide species and any co-administered compounds. The NRF2 activation in mucosal cells upregulates endogenous antioxidant defenses, restores redox balance, and protects the epithelial cells from any potential oxidative burden. The tight junctions reseal as the ROS signal dissipates, re-establishing baseline barrier integrity.

With repeated daily exposure, this cycle may produce adaptive conditioning of the mucosal epithelium analogous to the mitohormesis observed with exercise: the cells become progressively better equipped to handle oxidative signals, with higher baseline NRF2 activity, elevated glutathione levels, and maintained barrier integrity. This adaptive response is distinct from, and the opposite of, the progressive barrier dysfunction seen in inflammatory mucosal diseases.

What This Paper Establishes and What It Does Not

This paper establishes the biological plausibility of the proposed mechanisms based on well-documented, independent bodies of primary literature. Each mechanism is drawn from established physiology, and each is supported by multiple independent research groups using different experimental approaches in different model systems. The convergence of these independent lines of evidence on a common mechanistic framework strengthens the overall plausibility case.

What this paper does not establish is the clinical efficacy or specific magnitude of bioavailability enhancement achievable with any specific formulation of a mineral oxide delivery system. The paper does not present pharmacokinetic data, human clinical trial results, or quantitative bioavailability measurements. It is a mechanistic framework paper and a hypothesis generation document that proposes specific mechanisms based on established biology and identifies the specific studies needed to test those mechanisms.

Limitations

Several limitations of this mechanistic framework must be acknowledged. First, the three mechanisms are proposed on the basis of established biology from in vitro studies, animal models, and indirect human evidence. Direct pharmacokinetic evidence of mechanism-mediated bioavailability enhancement for specific mineral oxide delivery systems has not been published in peer-reviewed literature. The framework remains hypothesis-generating until such evidence is produced.

Second, the dose-response relationship for ROS-mediated tight junction modulation at the mucosal surface is not fully characterized for mineral oxide-generated ROS specifically. The literature on paracellular permeation enhancers and on physiological tight junction regulation establishes that such modulation occurs and is reversible, but the precise threshold between beneficial modulation and damaging disruption in the specific context of mineral oxide surface chemistry requires characterization.

Third, the relative contributions of the three proposed mechanisms to any observed bioavailability enhancement are unknown. Each mechanism is individually plausible, but whether all three operate simultaneously, whether one predominates, and how they interact are empirical questions that require experimental investigation.

Fourth, variability in mucosal physiology across individuals, including differences in tight junction protein expression, baseline redox status, NRF2 pathway activity, and GI microbiome composition, may produce variable responses to mineral oxide delivery systems. Clinical pharmacokinetic studies will need to characterize this interindividual variability.

Fifth, this framework addresses primarily the oral and sublingual mucosal surfaces. The relative contributions of different mucosal sites to overall absorption, and how this varies with formulation type (liquid drops, tablets, films), require site-specific investigation.

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Proposed Research Agenda

The mechanistic framework proposed in this paper generates specific, testable hypotheses that can be addressed through a defined program of preclinical and clinical studies.

Study 1: Paracellular Permeability Characterization. In vitro studies using Caco-2 and T84 cell monolayers should characterize the transepithelial electrical resistance response to mineral oxide exposure, including the dose-response relationship, time course of permeability modulation, and reversibility kinetics. Fluorescent tracer (FITC-dextran 4 kDa) transport assays would quantify the magnitude of paracellular permeability enhancement. Immunofluorescence microscopy should document claudin, occludin, and ZO-1 localization during and after mineral oxide exposure.

Study 2: NRF2 Pathway Activation Confirmation. The same in vitro system should be used to measure NRF2 nuclear translocation, ARE-reporter gene activation, and downstream targets (glutathione, heme oxygenase-1, NQO1) following mineral oxide exposure. Time course studies should characterize the onset and duration of NRF2 activation relative to the permeability modulation.

Study 3: Pharmacokinetic Study in Healthy Volunteers. A crossover pharmacokinetic study in healthy adult volunteers should compare absorption of a well-characterized tracer compound (for example, labeled magnesium or an established oral reference compound) administered with and without the mineral oxide delivery system. Red blood cell magnesium measurement should be used alongside serum measurement to capture intracellular delivery. The study should include collection of mucosal biopsy samples for ex vivo tight junction protein and NRF2 pathway analysis in a willing subset of participants.

Study 4: Peptide Co-delivery Pharmacokinetic Study. A pharmacokinetic study should evaluate whether the mineral oxide delivery system enhances oral absorption of a stable peptide tracer when co-administered. BPC-157 or a well-characterized oral reference peptide would be appropriate candidates. The study should compare co-administration with mineral oxide delivery versus peptide alone and versus a liposomal formulation to establish relative bioavailability and characterize the complementary potential of the two approaches.

Study 5: Repeated-Dose Safety and Mucosal Adaptation Study. A 90-day repeat-dose study in human volunteers should evaluate mucosal integrity by endoscopic assessment, tight junction protein expression in mucosal biopsies, and markers of NRF2 pathway adaptation over time. Safety endpoints should include mucosal inflammatory markers, barrier integrity indices, and standard clinical chemistry panels.

Study 6: Phosphatidylcholine and Methylation Cycle Co-Benefit Assessment. The proposed magnesium-dependent mineral oxide carrier may have downstream effects on the methylation cycle that produces S-adenosylmethionine (SAM), which in turn supports phosphatidylcholine synthesis via the PEMT pathway. Recent multi-omics work in C. elegans and human GTEx and UK Biobank cohorts has identified declining SAM-dependent phosphatidylcholine synthesis as a previously unappreciated, evolutionarily conserved driver of natural mitochondrial aging, particularly in post-menopausal women (Aging-associated decline of phosphatidylcholine synthesis is a malleable trigger of natural mitochondrial aging, 2026). A clinical study should evaluate whether mineral oxide delivery system supplementation produces measurable shifts in serum phosphatidylcholine, lysophosphatidylcholine, and methylation-cycle markers (homocysteine, SAM/SAH ratio, betaine) in adults over 60. This would establish whether the proposed mucosal mechanisms translate into improved cellular substrate availability for downstream lipid signaling pathways implicated in mitochondrial aging.

Context for Preprints.org Submission

This paper is submitted to Preprints.org as a preprint to invite scientific community review of the proposed mechanistic framework before formal peer-reviewed journal submission. The preprint format is appropriate for a mechanism review paper that synthesizes established biology into a novel framework. The author acknowledges that formal clinical data specific to mineral oxide delivery

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systems are not yet available in the peer-reviewed literature, and invites colleagues with expertise in mucosal physiology, tight junction biology, redox signaling, and oral drug delivery to engage with this framework.

Conclusion

This paper proposes a three-mechanism framework for understanding how surface-active mineral oxide delivery systems may enhance oral and sublingual bioavailability of nutrients and peptide compounds. The three mechanisms (transient mucosal ROS pulse and tight junction modulation, surface-mediated mineral delivery to mucosal epithelial cells, and hormetic NRF2 pathway activation) are each individually supported by extensive primary peer-reviewed literature, independent of any proprietary formulation data.

The framework situates the proposed mechanisms within the well-established biology of hormesis, draws on the exercise physiology precedent for beneficial ROS signaling in human biology, and aligns the approach with the mechanistic principles of two clinically established oxidative therapies (ozone therapy and hyperbaric oxygen). The comparison with liposomal delivery systems identifies the mineral oxide approach as mechanistically distinct and potentially complementary, with a specific strategic application in oral peptide co-delivery.

The paper's primary contribution is providing a citation-supported biological plausibility case for this class of delivery systems, translating an empirically observed delivery phenomenon into the language and framework of peer-reviewed mechanistic biology. Controlled pharmacokinetic and clinical studies, following the proposed research agenda, are the necessary next steps to confirm the mechanisms and establish the clinical utility of this approach.

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