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PERSPECTIVE

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Beyond nutrients: Inositol as a signaling architect of the gut-host axis and a global health imperative

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Inositol is a naturally occurring hexahydroxycyclohexane that participates in a wide range of physiological processes, including signal transduction, glucose and lipid metabolism, osmotic regulation, and communication between the gut microbiota and the host. Among its isomers, *myo*-inositol (MYO) and D-*chiro*-inositol (DCI) are the most biologically active. They play central roles in insulin signaling and metabolic homeostasis. When inositol metabolism is disrupted, it has been linked to conditions such as metabolic syndrome, polyendocrine metabolic ovarian syndrome (PMOS; conventionally termed polycystic ovary syndrome, PCOS), neurodegenerative disorders, and cancer. This perspective summarizes the challenges and future development trends related to inositol research, providing a comprehensive understanding of its application in public health and clinical settings.

METABOLIC NETWORK OF INOSITOL

Inositol is not a single metabolite but a distributed "signaling currency" that links membranes, metabolism, and microbes. The inositol metabolic network is a key signaling hub that supports cellular homeostasis. Centered on the principal isomer *myo*-inositol (MYO), it coordinates diverse physiological processes through tightly regulated synthesis, interconversion, degradation, and crosstalk with other metabolic pathways (Figure 1).

Classical biosynthesis

Humans "make" MYO on demand, but D-*chiro*-inositol (DCI) is a hormonally gated product—so insulin regulates isomer identity, not merely glucose flux. Endogenous inositol synthesis proceeds via the Loewus pathway: glucose-6-phosphate is first isomerized to inositol-1-phosphate by inositol-3-phosphate synthase (ISYNA1), then dephosphorylated by inositol monophosphatase (IMPA-1) to yield free MYO.[1] This route is dynamically modulated by glucose availability, insulin status, and osmotic stress, enabling demand-driven inositol production. Notably, another bioactive isomer, DCI, cannot be synthesized *de novo* in humans; it arises only through NADPH-dependent epimerization of MYO, the activity of the epimerase is regulated by insulin in a tissue-specific manner.

Extrinsic acquisition pathways

Diet supplies inositol, but microbes and food chemistry decide whether to absorb a signaling molecule or excrete a phosphate-locked reserve. Extrinsic inositol derives primarily from diet and gut microbiota–mediated conversion. Dietary inositol occurs as free inositol and bound forms. Gut-associated Bacteroidetes (e.g., *Bacteroides*, *Prevotella*, and *Parabacteroides*) can extensively synthesize inositol lipids, potentially contributing meaningfully to the intestinal lipid milieu.[2]

In animal organs, egg yolk, and many fruits and vegetables, inositol is largely present as free inositol with high bioavailability. Citrus fruits (especially grapefruit and orange) are among the richest plant sources of MYO, while *Solanaceae* (e.g., eggplant, tomato) and *Brassicaceae* (e.g., cabbage, broccoli) vegetables also contain abundant inositol. In cereals and nuts, however, inositol mostly exists as phytic acid, namely inositol hexaphosphate, which has poor bioavailability and can only be absorbed after hydrolysis by phytase.[3] Beyond MYO, legumes provide methylated inositols such as pinitol and ononitol.

Currently, MYO and DCI are the most common forms used in dietary supplements. Furthermore, green and efficient biomanufacturing of MYO and rarer derivatives can be achieved by building microbial cell factories, optimizing biosynthetic routes, and engineering chassis strains. Engineered *E. coli* strains with dual-promoter regulation and multi-copy genomic integration have achieved high inositol yields, while yeast strains can utilize low-cost carbon sources such as starch owing to their inherent inositol synthesis capacity.[4]

Decomposition and transformation

Inositol catabolism proceeds through three primary pathways: participating in the phosphatidylinositol cycle, transforming into DCI via epimerase, and being oxidized by MIOX to D-glucuronic acid, which is further converted into glucose or excreted by the kidneys. The catabolism of inositol remodels insulin signaling, and the kidneys maintain the overall metabolic balance of inositol. Inositol and its derivatives are core components of intracellular signal transduction, especially in the insulin pathway.

After inositol enters the cell, it gradually generates phosphatidylinositol (PI), phosphatidylinositol monophosphate (PIP), and phosphatidylinositol diphosphate (PIP_2). Upon receptor activation, PIP_2 is hydrolyzed to generate two key second messengers: inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG).[1] IP_3 can be gradually dephosphorylated and converted into inositol diphosphate (IP_2), inositol monophosphate (IP), and inositol. IP_3 triggers calcium release from the endoplasmic reticulum, while DAG activates protein kinase C (PKC), together modulating glucose uptake, glycogen synthesis, and lipid metabolism.[5]

Dysfunction of the inositol signaling network may contribute to insulin resistance (IR), partly through alterations in tissue-specific MYO-to-DCI balance and impaired inositol phosphoglycan signaling. Such imbalance emerges prior to glycometabolic disorders and acts as a key driver of subsequent pathological changes. Inositol pyrophosphates (PP-IPs) serve as the central node for cellular energy sensing. Synthesized by inositol hexakisphosphate kinase, these molecules contain high-energy pyrophosphate bonds and can rapidly respond to fluctuations in intracellular ATP levels. Evidently, inositol is far more than a common nutritional supplement; it is a core signaling coordinator that maintains cellular homeostasis.

Microbial metabolism

Gut microbiota metabolize inositol into different products that exert distinct effects on host health. Beneficial commensal bacteria such as *Anaerostipes rhamnosivorans* break down inositol via a newly identified coenzyme A transferase-dependent pathway to generate propionate and acetate, a newly discovered route for propionate synthesis in gut bacteria.[6] *Dysosmobacter welbionis* and *Intestinibacillus massilensis* ferment inositol into butyrate, while *Mitsuokella* species produce 3-hydroxypropionate (3-HP) that inhibits *Salmonella typhimurium*. These metabolites jointly improve glucose

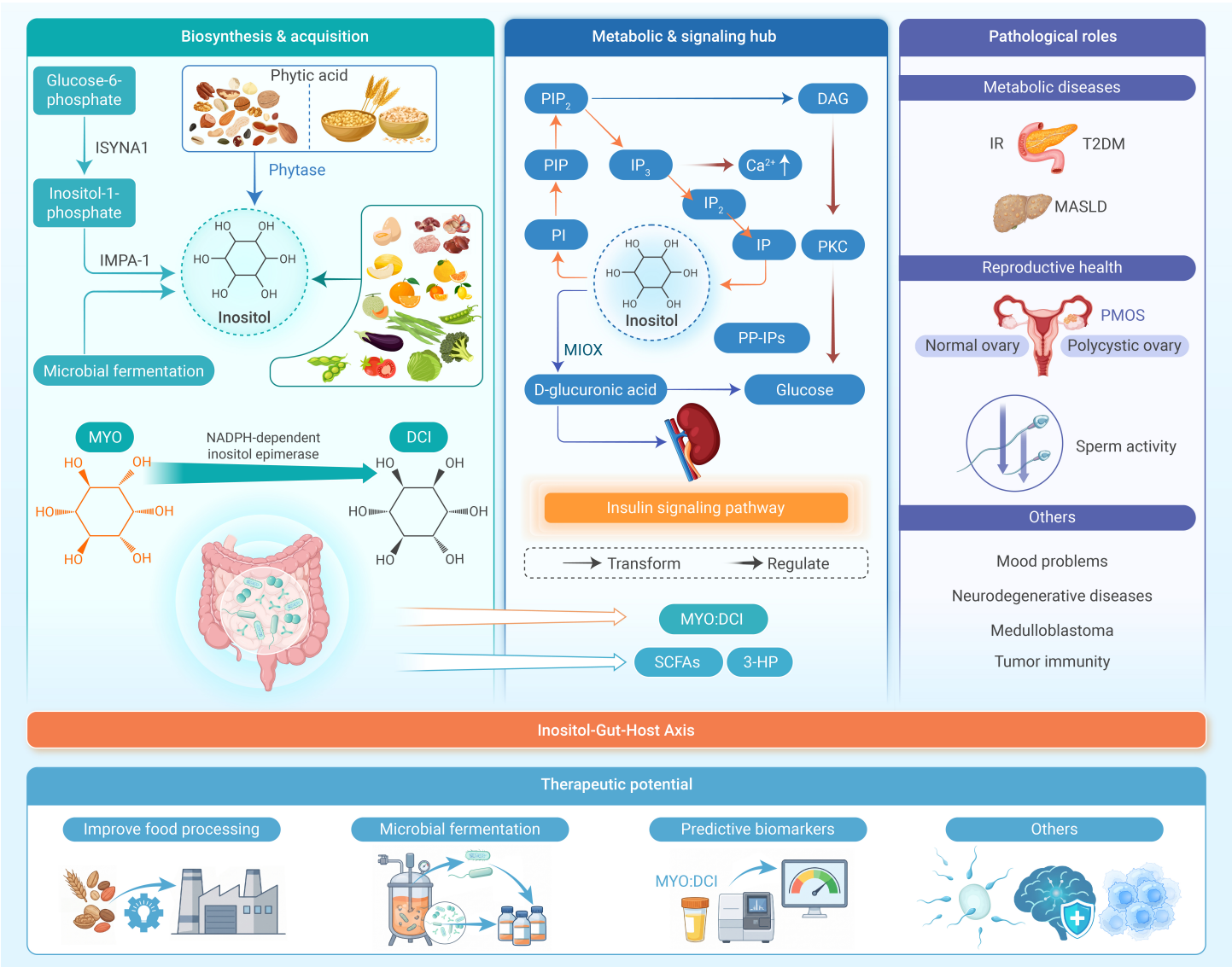

Figure 1. Beyond Nutrients: Inositol as a Signaling Architect of the Gut-Host Axis and a Global Health Imperative

metabolism and protect intestinal barrier function. Conversely, obesity-related microbes such as *Megamonas rupellensis* carry a complete inositol degradation gene cluster (*iolGIEDB*) to decompose inositol excessively, promoting lipid absorption and fat accumulation. The gut microbiota also exhibits synergistic metabolic effects: *Mitsuokella jalaludinii* first dephosphorylates phytic acid to release free inositol, which is then fermented by *Anaerostipes rhamnosivorans* to produce propionate.[6]

Short-chain fatty acids (SCFAs) enter systemic circulation through the portal vein and regulate bone marrow hematopoiesis. Propionate induces bone marrow monocyte precursors to differentiate into anti-inflammatory alveolar macrophages, alleviating allergic airway inflammation and enhancing antiviral immunity via the gut-lung axis. In the gut-brain axis, SCFAs modulate the development and function of microglia, regulating neuroimmunity and neuroinflammation. SCFAs suppress neutrophil chemotaxis and pro-inflammatory cytokine release to reduce systemic inflammation, which has been verified to alleviate sepsis, rheumatoid arthritis and type 1 diabetes in animal models. 3-HP activates the Nrf2/Keap1 pathway to enhance antioxidant capacity and inhibit the NLRP3 inflammasome. Under metabolic stress or intestinal dysbiosis, impaired PP-IPs signaling leads to excessive mitochondrial fragmentation, weakened oxidative phosphorylation and reduced ATP production. PP-IPs link gut microbial inositol metabolism to host energy metabolism and mitochondrial function. Collectively, gut microbiota construct the inositol-gut-host axis, a critical hub for regulating systemic inflammation and connecting dietary phytic acid intake with immune modulation.

PATHOLOGICAL SIGNIFICANCE AND CLINICAL APPLICATION PROGRESS

Inositol-related disorders are mainly caused by disrupted signaling pathways resulting from abnormal distribution and ratios of isomers, rather than simple nutritional deficiency. Impaired inositol metabolism is closely linked to various diseases, especially IR and PMOS. Inositol supplementation can improve insulin sensitivity and liver function in metabolic diseases, relieve reproductive endocrine disorders in PMOS, and also shows promising potential for neuroprotection and tumor therapy.

Metabolic diseases

For metabolic syndrome, MYO functions to restore insulin signaling rather than acting as a hypoglycemic agent. IR and type 2 diabetes mellitus (T2DM) are most strongly associated with inositol metabolic disorders. Preclinical and clinical studies confirm that MYO supplementation restores IP_3/DAG signaling, improves insulin sensitivity, stabilizes postprandial blood glucose and reduces body fat.[5] For metabolic dysfunction-associated steatotic liver disease (MASLD), MYO reduces hepatic fat deposition, postprandial triglycerides and AST levels, mitigates lipid peroxidation and elevates glutathione peroxidase activity, making it a promising adjuvant therapy for metabolic syndrome.[7] The urinary MYO/DCI ratio has been proposed as a potential biomarker for evaluating insulin sensitivity. Its abnormality occurs earlier than hyperglycemia, enabling early screening and long-term monitoring of T2DM, PMOS and other metabolic disorders.

Reproductive health

PMOS reframes inositol as an ovary-specific "isomer-ratio" disease, and inositol metabolic dysfunction contributes to its pathogenesis through several mechanisms. First, it reinforces a vicious cycle of IR: DCI-IPG deficiency impairs glucose transporter translocation, reducing glucose uptake and driving hyperinsulinemia; hyperinsulinemia then enhances ovarian androgen production and promotes adiposity and hepatic gluconeogenesis, further worsening IR. Second, it disrupts ovarian steroidogenesis: excess DCI suppresses aromatase, limiting conversion of androgens to estrogens, while activating key enzymes in androgen biosynthesis, aggravating hyperandrogenism; MYO deficiency perturbs the follicular fluid microenvironment, compromises oocyte mitochondrial function, and contributes to ovulatory dysfunction and reduced embryo quality.[8] In addition, inositol deficiency can lower cellular antioxidant capacity, activate inflammatory pathways, amplify oxidative stress and inflammation, and thereby worsen ovarian injury and metabolic derangements. In male infertility, MYO can support sperm mitochondrial function and provide antioxidant benefits, improving abnormalities in sperm motility, count, and morphology, suggesting value as a nutritional adjunct in assisted reproduction.[9]

Clinical trials suggest that MYO supplementation modulates follicle-stimulating hormone (FSH) signaling, promote oocyte maturation, and improve ovulatory dysfunction and menstrual irregularity in PMOS.[9] Nevertheless, the "ovarian paradox" exists: in PMOS patients complicated with IR, overactive epimerase in ovarian tissue causes excessive DCI accumulation, which impairs oocyte maturation and ovulation. We propose the urinary MYO/DCI ratio as a predictive biomarker. Patients with a low ratio can take pure MYO to repair ovarian signaling pathways, while those with a high ratio need compound preparations of MYO and DCI at 40:1 to avoid the ovarian paradox. Individualized dosage regimens adjusted according to menstrual cycles can optimize follicle recruitment and insulin sensitivity, realizing precise targeted intervention.

Neurodegenerative diseases and tumors

Inositol does more than support basic metabolism. It also affects gene regulation and immune responses, which makes several of its derivatives candidates for use alongside existing treatments for brain disorders and cancer. In the central nervous system, inositol derivatives may be neuroprotective. They take part in the phosphatidylinositol cycle and can also influence serotonin receptor activity, so low levels have been associated with mood problems such as anxiety and depression. Recent studies further suggest possible roles in neurodegenerative disease and oncology. For example, phytic acid has been reported to suppress medulloblastoma growth in preclinical models by limiting epigenetically driven metabolic adaptation, and it may increase the cytotoxic effect of cisplatin.[10] In addition, the gut microbiota–inositol–metabolite pathway may shape anti-tumor immunity: propionate produced during microbial fermentation of inositol can affect T-cell function. These findings fit with broader evidence that interactions among metabolites, microbes, and the immune system contribute to tumor development and progression.

CHALLENGES AND FUTURE DIRECTION

Global health initiatives have consistently centered on macronutrients and prevalent micronutrients, while inositol has remained overlooked. Moreover, the inadvertent consequence of modern industrialized food processing has been the emergence of hidden MYO deficiency. Whole grains are abundant in MYO derived from phytic acid; however, refined processing eliminates the bran and germ, the primary repositories of phytic acid. Even when individuals ingest phytic acid, the scarcity of dietary phytase in diets predominantly composed of ultra-processed foods hinders the absorption and utilization of this form of MYO by the human body. This deficiency subsequently contributes to the elevated global prevalence of PMOS and metabolic syndrome. Public health policies must address this challenge, potentially through the fortification of foods with MYO or the promotion of food processing methods that preserve the bioavailability of phytic acid.

Notably, in low- and middle-income countries, the incidence rates of metabolic syndrome and gestational diabetes are on a continuous upward trajectory, imposing substantial strain on local healthcare systems. Inositol represents an intervention strategy with significant potential for widespread application and demonstrates exceptional cost-effectiveness. In contrast to costly biologics such as glucagon-like peptide-1 receptor agonists, inositol can be economically produced via microbial fermentation and disseminated on a broad scale, thereby offering a feasible approach for the extensive prevention and management of metabolic disorders.

Overall, inositol stands at the nexus of nutrient sensing, microbial ecology, and systemic physiological functions, and its medical relevance is becoming clearer. With continued advances in multi-omics and precision medicine, inositol-based approaches may become more useful for preventing and managing chronic disease in everyday care.

REFERENCES

1. Michell R. H. (2011). Inositol and its derivatives: Their evolution and functions. *Adv Enzyme Regul.* **51**:84–90. DOI:10.1016/j.advenzreg.2010.10.002
2. Heaver S. L., Le H. H., Tang P., et al. (2022). Characterization of inositol lipid metabolism in gut-associated bacteroidetes. *Nat Microbiol.* **7**:986–1000. DOI:10.1038/s41564-022-01152-6
3. Schlemmer U., Frølich W., Prieto R.M., et al. (2009). Phytate in foods and significance for humans: Food sources, intake, processing, bioavailability, protective role and analysis. *Mol Nutr Food Res.* **53 Suppl 2**:S330-375. DOI: 10.1002/mnfr.200900099.
4. Zhuang Y., Wang Y., Tu Q., et al. (2025). Synthetic biology: Revolutionizing animal breeding and biomanufacturing. *Innov. Life* **3**:100169. DOI:10.59717/j.xinn-life.2025.100169
5. Li J., Huang Q., Nie Q., et al. (2024). Effects of myo-inositol on regulating glucose and lipid metabolism and alternative splicing events coexpressed with lncrnas in the liver tissues of diabetic mice. *Heliyon* **10**:e32460. DOI:10.1016/j.heliyon.2024.e32460
6. Jessen H. and Bui T.P.N. (2025). Metabolism of inositol derivatives by the gut microbiome. *Gut Microbes.* **17**:2564765. DOI:10.1080/19490976.2025.2564765
7. Pani A., Giossi R., Menichelli D., et al. (2020). Inositol and non-alcoholic fatty liver disease: A systematic review on deficiencies and supplementation. *Nutrients* **12**. DOI:10.3390/nu12113379.
8. Laganà A.S., Forte G., Bizzarri M., et al. (2022). Inositols in the ovaries: Activities and potential therapeutic applications. *Expert Opin Drug Metab Toxicol.* **18**:123–133. DOI:10.1080/17425255.2022.2071259
9. Etrusco A., Laganà A.S., Chiantera V., et al. (2024). Myo-inositol in assisted reproductive technology from bench to bedside. *Trends in Endocrinology & Metabolism.* **35**:74–83. DOI:10.1016/j.tem.2023.09.005
10. Badodi S., Pomella N., Zhang X., et al. (2021). Inositol treatment inhibits medulloblastoma through suppression of epigenetic-driven metabolic adaptation. *Nat Commun.* **12**:2148. DOI:10.1038/s41467-021-22379-7

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AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.