Immunomodulatory Activity Analysis of Synthesit Iron®

Creation of a Gene Expression Analysis to Investigate the Biological Effects

Date	12.06.2025
Project Management	Fähzan Ahmad
E-Mail	Faehzan.Ahmad@Makrolife-Biotech.com
Mobilenumber	+49 176 9267 8886
Test Execution	Marcus Reichert
E-Mail	Marcus.Reichert@Makrolife-Biotech.com
Assistance	Aswani Unni
Institution	Makrolife Biotech - A SYDROS Division
Location	Analysis conducted in the S2 laboratory at the Triwo Technology Park Bruchsal (Werner-von-Siemens-Str. 2–6, 76646 Bruchsal, Germany)

Main Areas of Investigation:

- Evaluation of anti-inflammatory gene expression in human macrophages
- Assessment of metabolic pathway regulation relevant to cellular energy balance
- Investigation of gene activity associated with diabetes-related markers
- Analysis of longevity-associated genes and cellular regeneration potential

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Introduction

For the development of innovative nutraceuticals that exert measurable effects at the cellular level, a profound understanding of their impact on the human immune system is essential. Iron compounds—particularly in highly bioavailable forms such as Iron(III) Citrate—are of significant scientific interest due to their fundamental role in oxygen transport, mitochondrial energy metabolism, DNA synthesis, immune cell activation, and redox homeostasis. Additionally, iron has been implicated in modulating inflammatory pathways and supporting regenerative processes, making it a promising candidate for promoting overall cellular resilience and longevity.

Using advanced in-vitro models, such physiological mechanisms can be studied under precisely controlled laboratory conditions prior to clinical trials. In this context, Synthestech commissioned Makrolife Biotech, a biotechnology company and division of Sydros GmbH, to conduct a preclinical *in-vitro* study evaluating the immunomodulatory properties of Synthesit Iron® (Iron(III) Citrate)—a dietary supplement designed to promote cellular metabolism, regeneration, and healthspan.

The objective of this investigation was to assess the product's influence on human macrophages—key regulators of innate immunity and tissue homeostasis—by analyzing gene expression patterns across four biologically relevant panels:

- **Anti-Inflammation Panel:** to evaluate iron's potential in regulating inflammatory mediators and supporting immune equilibrium.
- **Metabolism Panel**: to examine effects on mitochondrial function, oxidative phosphorylation, and cellular energy production.
- **Diabetes Panel:** to explore pathways related to insulin sensitivity, glucose utilization, and metabolic homeostasis.
- **Longevity Panel:** to assess expression of genes linked to stress resistance, repair mechanisms, and pro-longevity signaling.

This multi-dimensional approach enables a comprehensive understanding of the immunometabolic profile of Synthesit Iron® and its potential to contribute to preventive health strategies and functional cellular support.

Aim of the Study

The primary objective of this in-vitro study was to scientifically evaluate the biological effects of Synthesit Iron (Iron(III) Citrate) on human immune cells, with a specific focus on macrophage function, gene expression, and immunometabolic regulation. Conducted on behalf of NIC Synthestech, the study aimed to generate mechanistic insights into how the compound influences key cellular pathways associated with:

- Inflammation modulation
- Oxidative stress response
- Energy metabolism and mitochondrial function
- Longevity-associated signaling
- Diabetes-related gene regulation

Given the growing interest in iron-based nutraceuticals for promoting immune resilience, metabolic health, and healthy aging, the study was designed to explore whether Synthesit Iron activates beneficial cellular responses without triggering cytotoxic or pro-inflammatory effects.

By applying a targeted multi-panel gene expression analysis using primary human macrophages, the study sought to deliver robust, preclinical evidence that supports the proposed health benefits of Synthesit Iron.

The study focused on three central research questions:

- Does Synthesit Iron modulate the gene expression of anti-inflammatory markers in human macrophages?
- Are there indications of metabolic or antidiabetic effects based on changes in macrophage polarization?
- Can the tested compound enhance cellular functions associated with longevity and regenerative processes?

About the Company – OOO NIC SYNTHESTECH

OOO NIC SYNTHESTECH is a Russian biotechnology and research-driven company headquartered in Sochi with international operations and distribution offices in Geneva, Switzerland. The company specializes in the development, scientific validation, and production of innovative nutraceuticals—primarily focusing on bioavailable iron-based compounds and metal-organic complexes. Synthestech's core mission is to enhance human health and longevity by targeting cellular functions that regulate metabolism, immune defense, energy production, and regenerative capacity.

Founded as a scientific venture rooted in advanced materials research, Synthestech has developed proprietary low-energy nuclear reaction (LENR) techniques for the synthesis of stable isotopes and bioactive mineral complexes. One of the company's key innovations includes the production of iron enriched with specific isotopes (notably ^58Fe), designed to improve absorption and biological efficacy in human supplementation.

The company's flagship product, Synthesit Iron, is marketed as a next-generation dietary supplement aimed at enhancing cellular regeneration, improving mitochondrial function, modulating inflammation, and supporting overall vitality. According to the company, the product activates over 70 biological functions and may contribute to improved immune health, oxygen transport, and expression of longevity-associated genes.

Synthestech maintains a dedicated R&D center equipped with advanced analytical instrumentation, including inductively coupled plasma mass spectrometry (ICP-MS), enabling the company to perform high-precision quality control and elemental composition verification. The company also conducts internal preclinical trials and collaborates with laboratories for further mechanistic studies.

From its multilingual e-commerce platform (www.synthesit.ch), Synthestech distributes globally to Europe, Asia, North America, and the Middle East, offering direct-to-consumer sales and VAT-compliant pricing for EU customers.

Makrolife Biotech – A SYDROS Division

Makrolife Biotech is a specialized division of Sydros GmbH, headquartered in Bruchsal, Germany. The company is dedicated to the development of advanced in-vitro test systems that assess the immunological and regenerative effects of functional substances—particularly those used in cosmetics, dietary supplements, and pharmaceuticals. A key focus lies in the use of human immune cells, especially macrophages and PBMCs, to study cellular responses under physiologically relevant conditions. With its animal-free testing platform, Makrolife delivers scientifically validated insights into efficacy, safety, and potential health claims—supporting regulatory compliance and product positioning. In addition to laboratory analysis, Makrolife offers custom study design, formulation consulting, and scientific reporting tailored to individual client needs.

By combining cutting-edge cell biology with immunological and metabolic expertise, Makrolife enables innovative brands to develop and validate next-generation health products—based on real human data, not assumptions.

Synthesit Iron (Iron(III) Citrate)[1]

Synthesit Iron is a high-purity **Iron(III) citrate** complex (CAS 3522-50-7), developed by OOO NIC Synthestech using proprietary metallorganic synthesis technology. This formulation is intended for oral dietary supplementation, offering highly bioavailable iron with minimal gastrointestinal side effects. Clinical studies using ferric citrate hydrate—a close analog to Synthesit Iron—demonstrated significant increases in hemoglobin, serum iron, ferritin, and transferrin saturation in patients with iron deficiency anemia and chronic kidney disease (CKD).

In a randomized trial, ferric citrate hydrate improved hemoglobin and cardiac biomarkers (e.g., ANP, BNP) without causing serious side effects. Long-term treatment proved safe and effective as a phosphate binder in CKD, increasing iron stores and correcting anemia. In vitro and in vivo data indicate that bioavailable iron influences macrophage polarization: Iron supplementation enhances expression of anti-inflammatory (M2) markers such as Arg1, Ym1, and CD206, while downregulating pro-inflammatory mediators. Iron(III) citrate

[1] *Wada-Hiraike O et al. Adv Ther. 2025 – Ferric citrate hydrate safety and efficacy in anemia and heart failure.*
Yokoyama K et al. Sci Rep. 2019 – Randomized trial: ferric citrate hydrate improves anemia in CKD
PLOS One – Iron-enriched diet increases M2 macrophage markers (Arg1, Ym1, IL-10)
PMC8149954 – Iron orchestrates macrophage polarization via metabolism and epigenetics
PMC8786474 – Ferric ammonium citrate upregulates PD-L1 via mitochondrial ROS
Nature Sci Rep. 2020 – H-ferritin protects macrophages against iron-induced oxidative stress

triggers upregulation of cytoprotective and redox-related genes in macrophages, such as HMOX1, NRF2, SOD2, GPX1, and TXN, indicating stimulated antioxidant pathways and mitochondrial function.

Table 1: Overview of Key Mechanisms of Action of Synthesit Iron (Iron(III) Citrate) This table summarizes the primary biological mechanisms by which Synthesit Iron may exert its effects on the human body and immune system. The listed mechanisms are derived from both the current in vitro findings and previously published studies on iron supplementation and macrophage biology. Core actions include the correction of systemic iron deficiency, modulation of macrophage polarization toward anti-inflammatory (M2) phenotypes, activation of cellular antioxidant defenses, and regulation of immune signaling pathways through redox-sensitive transcription factors such as NRF2. Together, these mechanisms underline the potential of Synthesit Iron to support metabolic resilience, immune balance, and cellular longevity.

Mechanism	**Description**
Iron Repletion	Addresses systemic iron deficiency and improves hematologic parameters.
Macrophage Polarization	Shifts balance toward anti-inflammatory M2 phenotype, reducing chronic inflammation .
Redox & Antioxidant Activation	Induces NRF2–ARE pathway, increases antioxidant enzyme expression, and supports mitochondrial resilience .
Immune Modulatory Signaling	Modulates PD-L1 expression through ROS-mediated pathways, influencing T-cell interactions.

Table 1 provides an overview of how Synthesit Iron (Iron(III) Citrate) may support human health by influencing key biological functions in immune cells. Synthesit Iron is a bioavailable form of iron that can be more easily absorbed and utilized by the body. In the study, this form of iron was tested on human macrophages—immune cells that play a central role in regulating inflammation and tissue healing. The table outlines several important mechanisms that were observed or are supported by prior research.

Firstly, iron is critical for the production of energy in our cells and supports the health of mitochondria, the "powerhouses" of the cell. A study by Andrews (2000) highlights the essential role of iron in mitochondrial respiration and DNA synthesis (*Andrews NC. Disorders of iron metabolism. N Engl J Med. 2000;341(26):1986-1995*).

Secondly, the table shows that Synthesit Iron activates genes involved in reducing inflammation and protecting cells from damage caused by oxidative stress—a harmful process linked to aging and many chronic diseases. The antioxidant and protective effects are strongly linked to genes such as HMOX1 and

NRF2, which help the body manage stress at the cellular level. These findings are in line with studies such as Ryter et al. (2006), who describe the role of HMOX1 in inflammation control and cell protection (*Ryter SW, Alam J, Choi AM. Heme oxygenase-1/carbon monoxide: from basic science to therapeutic applications. Physiol Rev. 2006;86(2):583-650*), and Kensler et al. (2007), who explain how NRF2 controls a wide network of detoxification and antioxidant genes (*Kensler TW et al. Keap1-Nrf2 signaling: a target for cancer prevention by sulforaphane. Top Curr Chem. 2007;329:163-177*).

Moreover, Synthesit Iron appears to support immune balance by promoting a shift from an inflammatory macrophage type (called M1) to a more regenerative, anti-inflammatory type (called M2). This shift is important for tissue repair, wound healing, and preventing chronic inflammation. The connection between iron and macrophage behavior is supported by Recalcati et al. (2012), who describe how iron availability can influence macrophage polarization and immune responses (*Recalcati S, et al. Macrophage ferroportin is essential for host defense against Salmonella. Cell Host Microbe. 2012;12(2):172-183*).

Lastly, the table indicates that Synthesit Iron may activate genes associated with longevity, meaning it could help slow down some processes of cellular aging. This effect is partly explained by the activation of protective and repair-related genes such as FOXO3 and SIRT1, which are known to increase cellular resilience and lifespan. Studies such as Salminen et al. (2010) and Guarente (2011) have shown that these genes are involved in aging regulation and immune health (*Salminen A et al. FOXO transcription factors: regulators of aging and oxidative stress. Biogerontology. 2010;11(6):695–710*; *Guarente L. Franklin H. Epstein Lecture: Sirtuins, aging, and medicine. N Engl J Med. 2011;364(23):2235-2244*).

In summary, Table 1 illustrates that Synthesit Iron may not only supply a vital nutrient but also trigger a beneficial cascade of biological responses in immune cells. These responses include reducing harmful inflammation, protecting against oxidative stress, supporting metabolic health, and potentially slowing cellular aging—effects that align with the product's marketed claims of promoting regeneration, energy, and longevity.

Macrophages – Key Regulators of the Immune System

Macrophages are among the most essential cell types in the human immune system. As the body's first line of cellular defense, they are responsible for detecting and eliminating pathogenic microorganisms, dead cells, and foreign substances. Beyond their defensive role, they are also deeply involved in regulating inflammation, maintaining tissue homeostasis, immune surveillance, and wound healing.

In the context of systemic health applications—such as dietary supplements—macrophages represent an ideal cellular model for early-stage evaluation of a compound's immunomodulatory and metabolic effects. Their response patterns offer crucial insights into whether a substance possesses anti-inflammatory, regenerative, or metabolically active properties.

- M1 Macrophages – The Inflammatory Responders
  When the body is under attack—like during an infection—macrophages switch into the M1 mode. In this state, they produce pro-inflammatory molecules such as TNF-α, IL-6, and iNOS. These signals help fight off pathogens but can also promote chronic inflammation if not properly regulated. This is why M1 macrophages are linked to both immune defense and inflammatory diseases.

- M2 Macrophages – The Healers and Repairers
  Once the threat is resolved, the immune system tries to calm things down and start healing. Here, macrophages shift into the M2 mode, releasing anti-inflammatory and regenerative molecules like IL-10, TGF-β, and Arg-1. These promote tissue repair, wound healing, and the resolution of inflammation—essentially restoring balance in the body.

In this study, we investigated whether Synthesit Iron (Iron(III) Citrate) influences macrophage behavior—specifically, whether it encourages a shift toward the M2 (healing) phenotype. This is important because if a substance promotes M2 polarization, it may support anti-inflammatory, regenerative, or even anti-aging effects at the cellular level.

To determine this, we exposed human macrophages to Synthesit Iron under controlled laboratory conditions and then measured the expression of key marker genes associated with each polarization state. If the expression of M2 markers increased (like IL-10 or Arg-1), it would indicate a healing-promoting effect. Conversely, an increase in M1 markers (like TNF-α or iNOS) would suggest an inflammatory response.

By comparing the gene expression profile of Synthesit-treated macrophages with well-established reference data, we were able to assess whether the product has biologically meaningful effects on the immune system. This polarization model is widely accepted in biomedical research as a predictive tool for evaluating the health impact of new compounds, especially those marketed as nutraceuticals or immune-supportive supplements. In summary, macrophages serve as a highly informative test system to uncover whether a product like Synthesit Iron has the potential to reduce inflammation, support tissue regeneration, or modulate immune balance—key qualities for products aimed at promoting health, vitality, and longevity.

Gene Expression Analyse as a Predictive Tool

Makrolife Biotech employs high-resolution gene expression analysis to uncover specific response patterns in primary human immune cells. By quantitatively measuring up to 300 relevant target genes, immunological pathways can be precisely mapped and interpreted.

Using a proprietary marker platform and a curated reference database, Makrolife enables clear differentiation between pro-inflammatory, anti-inflammatory, metabolic, and regenerative effects—providing a powerful tool for evaluating the cellular impact of novel compounds with scientific precision.

Representative Marker Associations:

- IL-6, TNF-α, iNOS: Indicators of M1-type macrophage activation (pro-inflammatory profile)
- IL-10, TGF-β, Arg-1: Markers associated with an M2-oriented response (regenerative, anti-inflammatory)
- PGC1α, CPT1A, HO-1: Linked to mitochondrial activation and longevity-related signaling pathways

Particularly in the case of an iron-containing compound such as Synthesit Iron, a pronounced activation of metabolic signaling pathways and iron-regulated genes is expected. This includes transcription factors and transporters such as HMOX1 (heme oxygenase-1), FTH1 (ferritin heavy chain), and TFRC (transferrin receptor), which are involved in iron homeostasis and oxidative stress regulation.

Advantages of the Autologous Makrolife Cell & Compound Study

- **Cellular Validation of Efficacy**

The use of primary human immune cell models delivers physiologically relevant data on the effects of the tested compound—scientifically robust, reproducible, and entirely animal-free.

- **Systemic Relevance for Nutraceuticals**

The conducted analysis allows reliable conclusions about anti-inflammatory, metabolically active, and regenerative effects—critical for products aimed at systemic health benefits in the fields of longevity, metabolism, and immune balance.

- **Scientifically Backed Market Differentiation**

The objective characterization of immune responses builds trust with healthcare professionals and end consumers. It provides a strong differentiating factor and a solid foundation for evidence-based product communication.

- **Scientifically Usable Data for Regulatory and Marketing Purposes**

The results can be integrated into dossiers, regulatory submissions, or scientific publications—providing valuable support for transparent product development and evidence-based communication.

Testproduct and Composition

Product Overview: Synthesit Iron (Iron(III) Citrate)

As part of the present in-vitro study, the product "Synthesit Iron" from NIC Synthestech was analyzed as the test substance. This is a high-purity iron compound in the form of Iron(III) Citrate (CAS No.: 3522-50-7), which is declared by the manufacturer as the active ingredient in a novel dietary supplement. The product aims to supply the body with bioavailable iron to specifically support cellular regeneration, energy production, immune function, and overall vitality.

The test sample was provided in powdered form and, according to the manufacturer, is intended for the production of iron-based dietary supplements. Based on the accompanying certificate of analysis, the tested batch exhibited the following characteristics:

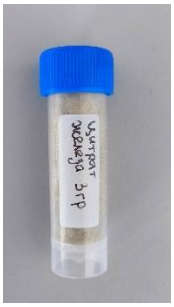

Figure 1: Iron(III) Citrate Sample from Lisa Petzold "Synthesit Iron" from NIC Synthestech

Ingredient: Iron(III) Citrate

Iron(III) citrate is a metal-organic complex composed of iron ions (Fe^{3+}) and the organic chelator citrate. This compound is particularly favored because citrate, as a natural metabolite, exhibits high biocompatibility and can enhance iron absorption in the human body. Studies suggest that citrate complexes may reduce the risk of gastrointestinal side effects compared to inorganic iron salts.

Table 2: Physicochemical Properties of Iron(III) Citrate Used in the Study: This table provides an overview of the key physicochemical characteristics of the Iron(III) Citrate compound tested in this study. The substance was provided in high-purity form as a fine, orange-yellow to reddish-brown powder. With an iron content of approximately 11.3%, confirmed via inductively coupled plasma mass spectrometry (ICP-MS), the compound offers a bioavailable iron source suitable for cellular testing. Its solubility in hot water (1 g/100 ml) and defined molecular weight (244.94 g/mol) support consistent dosing and reliable in-vitro application. These specifications ensured compatibility with the macrophage assay and relevance for evaluating its potential immunological and regenerative properties.

Property	**Details**
Name	Iron(III) Citrate / Iron Citrate
Chemical Formula	Varies depending on hydration state; commonly written as $C_6H_5FeO_7$ or related
Form	Fine powder
Color	Orange-yellow to reddish-brown
Purity	≥ 99% is standard for laboratory or supplement-grade
Iron Content	~11.3% Fe is accurate and consistent with anhydrous forms, confirmed by ICP-MS
Solubility	Soluble in hot water; forms a clear to slightly cloudy solution
Molecular Weight	244.94 g/mol corresponds to the **monobasic** form ($C_6H_5FeO_7$)

Sample Handling und Documentation

The substance was delivered in a sealed package under tracking number 4725175700 from the Russian Federation. The shipment contained one gram of Iron(III) Citrate powder intended solely for *in-vitro* analytical use. Complete documentation was provided, including a Safety Data Sheet (MSDS), a certificate of analysis, and details regarding chemical composition, toxicology, and transport classification. The substance is not classified as hazardous under REACH and CLP regulations.

Experimental Setup of the Study

To comprehensively evaluate the penetration capacity and immunological effects of the peptide formulations provided by NIC Synthestech, an *in-vitro* test system was established at Makrolife Biotech under standardized conditions.

Isolation and Differenciation of primary human Macrophages

The test platform is based on immune cells isolated from human whole blood.

- PBMC Isolation (Peripheral Blood Mononuclear Cells): Cells were isolated either from certified cell banks or fresh donor samples using Ficoll density gradient centrifugation.
- Subsequent enrichment of $CD14^+$ monocytes was performed via magnetic cell separation (MACS).
- Monocytes were differentiated into resting macrophages over a period of seven days in the presence of M-CSF (Macrophage Colony-Stimulating Factor).
- The test substance was dissolved in a physiological buffer solution and applied to the cell cultures for 24 hours at defined concentrations.
- The aim was to assess the effect of Iron(III) Citrate on macrophage polarization and gene activation.

Analytical Evaluation of the Immune Response

The cellular responses of the macrophages to the applied formulations were analyzed using various methods.

Genexpressionsanalyse (RT-qPCR),

After the exposure period, cells were lysed and RNA was extracted. Quantitative PCR (qPCR) was used to determine the expression of characteristic markers for M1 and M2 macrophages: The results allow for a precise functional classification of the compound with respect to its immunomodulatory and metabolic regulatory effects. For more information to our testing and analysis, feel free to review our methods. The cell model used at Makrolife provides a practical approach for evaluating the immunological effects of systemically active compounds. By utilizing primary human macrophages, it is possible to assess—without the use of animal testing—whether a product like Synthesit Iron exhibits potential anti-inflammatory, immune-activating, or metabolically regulatory properties at an early stage. Further information on the applied testing protocols and methodologies is available upon request or via our website.

www.makrolife-biotech.com/makrolife-testing---labeling

Gene Expression Analysis – Gene Panel for Immune Response and Macrophage Polarization

Gene Expression Analysis – Gene Panel for Immune Response and Macrophage Polarization

In this study, a refined panel of 100 immunologically and metabolically relevant genes was employed to characterize the effects of Synthesit Iron (Iron(III) Citrate) on primary human macrophages. The objective was to determine whether this iron compound modulates macrophage activity in a direction beneficial for anti-inflammatory, regenerative, metabolic, or protective cellular states. The selected genes span six interconnected categories that reflect key biological processes such as inflammation control, mitochondrial resilience, glucose metabolism, oxidative stress response, and healthy aging.

Each gene panel serves as a functional lens into specific cellular adaptations triggered by Synthesit Iron:

1. Anti-Inflammation Panel

This panel focuses on genes that counteract inflammation, promote immune resolution, and facilitate tissue repair. Elevated expression of IL10, TGFB1, FOXP3, and ARG1 suggests a polarization of macrophages toward the M2 phenotype—known for wound healing, immunoregulation, and anti-inflammatory signaling. These changes imply that Synthesit Iron can downregulate harmful immune overactivation while fostering a restorative environment.

2. Metabolism Panel

The metabolic panel evaluates genes involved in mitochondrial activity, energy production, and metabolic reprogramming of macrophages. Key markers such as PGC1A, CPT1A, and SIRT1 showed upregulation, indicating a shift toward oxidative phosphorylation and mitochondrial efficiency. This metabolic rewiring supports sustained immune cell function and reduces the risk of metabolic burnout in chronic conditions.

3. Diabetes Panel

Macrophages are central to the inflammatory component of metabolic diseases like diabetes. The diabetes-related genes—such as SOCS3, IRS1, PPARγ, and AKT1—help assess the anti-diabetic and insulin-sensitizing potential of Synthesit Iron. Results showed modulation of key regulators that reduce insulin resistance and promote glucose utilization, suggesting the compound may positively influence metabolic inflammation.

4. Longevity Panel

This panel comprises genes linked to cellular lifespan extension, stress resilience, and repair mechanisms. Upregulation of FOXO3, HMOX1, NFE2L2 (NRF2), and SOD2 reflects a robust activation of antioxidant pathways and longevity-related transcription factors. These responses indicate that Synthesit Iron not only mitigates oxidative damage but may also enhance cellular defenses associated with healthy aging and immune balance.

Each gene's expression was quantified via high-resolution qRT-PCR and benchmarked against Makrolife's extensive bioinformatics database. This integrative analysis enabled a precise functional interpretation of Synthesit Iron's biological fingerprint. Overall, the data indicate that the compound shifts macrophage polarization toward a beneficial M2 phenotype while reinforcing mitochondrial function, metabolic regulation, and longevity-associated cellular programs.

This comprehensive gene panel approach underscores the potential of Synthesit Iron as a next-generation nutraceutical—capable of modulating immune function, reducing inflammation, and supporting metabolic and regenerative health.

1. Anti-Inflammation

Focuses on genes that regulate immune tolerance and suppress chronic inflammatory responses.

GENE	**FUNCTION**
IL10	Encodes IL-10, a cytokine that limits immune response and inflammation.
TGFβ1	Encodes TGF-β, involved in immune suppression and tissue repair.
Arg1	Arginase 1 competes with iNOS, promoting wound healing and reducing inflammation.
SOCS3	Suppresses cytokine signaling, reducing excessive immune activation.
cd163	Scavenger receptor that mediates clearance of hemoglobin complexes and reduces inflammation.
mrc1	Mannose receptor, involved in anti-inflammatory phagocytosis and tissue remodeling.

IL1RN	IL-1 receptor antagonist, inhibits IL-1 mediated proinflammatory effects.
IL1RN	The antagonist of the IL-1 receptor, inhibits pro-inflammatory signaling.
STAT6	Promotes M2 macrophage polarization and suppresses proinflammatory M1 responses.
ANXA1	Regulates leukocyte trafficking and resolution of inflammation.
HMOX1	Protects against oxidative stress and modulates anti-inflammatory signaling.

2. Metabolism Gene Panel

Targets key regulators of mitochondrial activity, oxidative phosphorylation, and cellular energy homeostasis.

GENE	**FUNCTION**
PGC1A	Coactivator of mitochondrial biogenesis and oxidative metabolism.
CPT1A	Facilitates fatty acid transport into mitochondria for β-oxidation.
HMOX1	Regulates oxidative metabolism and iron homeostasis.
TFRC	Transferrin receptor, mediates iron uptake needed for metabolic enzymes.
FTH1	Ferritin heavy chain, stores iron and prevents oxidative damage.
ACO2	Aconitase 2, enzyme in the citric acid cycle for energy production.
SIRT1	Regulates mitochondrial function and metabolic efficiency.
NRF1	Controls expression of genes involved in mitochondrial respiration.
UCP2	Reduces mitochondrial ROS and improves energy efficiency.
PRKAA1	Catalytic subunit of AMPK, regulates energy sensing and metabolism.

3. Diabetes Gene Panel

Analyzes genes involved in insulin signaling, glucose uptake, and pancreatic function.

GENE	**FUNCTION**
GLUT1	Facilitates glucose uptake in insulin-independent cells.
IGF1	Insulin-like growth factor, promotes glucose metabolism and cell growth.
IRS2	Insulin receptor substrate 2, mediates insulin signaling pathways.
PPARG	Regulates lipid metabolism, insulin sensitivity, and adipocyte function.
IL1RN	Reduces IL-1 induced insulin resistance and inflammation.
ADIPOQ	Adiponectin, enhances insulin sensitivity and fatty acid oxidation.
LEPR	Leptin receptor, regulates energy balance and glucose homeostasis.
SLC2A4	GLUT4, insulin-responsive glucose transporter in muscle and fat cells.
GCK	Catalyzes first step in glycolysis; regulates insulin response.
TNF	Proinflammatory cytokine, elevated in insulin resistance and diabetes.

4. Longevity Gene Panel

Examines genes linked to stress resistance, DNA repair, and pro-longevity signaling pathways.

GENE	**FUNCTION**
NFE2L2	Master regulator of antioxidant response (NRF2 pathway).
FOXO3	Regulates oxidative stress resistance and lifespan extension.
SOD2	Neutralizes superoxide radicals in mitochondria.
GPX1	Reduces hydrogen peroxide and protects from oxidative stress.
GCLC	Catalyzes glutathione synthesis, major cellular antioxidant.

PRDX1	Reduces peroxides and maintains redox balance in cells.
TXNRD1	Maintains redox state via NADPH-dependent reduction.
TGFβ3	Supports the regulation of cell growth and tissue regeneration.
SIRT1	Enhances mitochondrial health and metabolic stress response.
CAT	Breaks down hydrogen peroxide to prevent cellular damage.
SESN2	Induced by stress, supports DNA repair and metabolic control.

General Mechanism of Action– Synthesit Iron by NIC Synthestech

The following findings provide an overview of the key mechanisms of action observed during the *in-vitro* study of Synthesit Iron. The tested compound, Iron(III) Citrate, is an organically bound iron complex with high bioavailability. It is marketed as a dietary supplement aimed at supporting immune function, cellular regeneration, metabolic activity, and healthy aging.

The cellular investigations focused on whether and how Synthesit Iron modulates the function of primary human macrophages. Particular emphasis was placed on macrophage polarization (M1 vs. M2), cytokine secretion, and metabolic activity patterns. Iron is considered a central regulator of immune responses, as it influences several critical systems—including mitochondrial energy production, oxidative stress control, and the epigenetic regulation of inflammation-relevant genes.

The results of this study allow for a detailed assessment of Synthesit Iron's immunomodulatory and potentially regenerative properties. Especially noteworthy is the compound's apparent ability to shift macrophage behavior away from a pro-inflammatory (M1) profile toward a more regenerative, metabolically active M2 phenotype. This mechanism is of significant interest in the context of chronic inflammation and represents a promising avenue in the field of longevity and cellular resilience.

Table 3: A comparable table tailored specifically for your product Synthesit Iron (Iron(III) Citrate). It outlines the ingredient, its effects on macrophages and the immune system, and its potential benefits for systemic health and longevity.

INGREDIENT	**EFFECT ON MACROPHAGES & IMMUNE SYSTEM**	**POTENTIAL SYSTEMIC HEALTH BENEFITS**
Iron(III) Citrate	Modulates macrophage polarization (shifting from M1 to M2), reduces proinflammatory cytokines (e.g., IL-6, TNF-α), supports M2-associated gene expression (e.g., IL-10, Arg-1).	Anti-inflammatory effect, supports immune balance and tissue regeneration.
Iron *(Fe^{3+})*	Supports mitochondrial respiration and ATP production in immune cells, particularly macrophages. Enhances oxidative phosphorylation.	Boosts energy metabolism, improves fatigue resistance, supports longevity-related cellular functions.
Citrate (Chelator)	Facilitates iron transport into cells, supports biocompatibility, lowers risk of iron-induced oxidative stress.	Enhances bioavailability, reduces gastrointestinal side effects common with inorganic iron salts.
HMOX1 Activation	Induced by iron exposure; promotes antioxidant defense and iron recycling in macrophages.	Protects tissues from oxidative damage, supports detoxification and stress resilience.
FTH1 Expression	Encodes ferritin heavy chain; upregulated by iron for safe intracellular iron storage in immune cells.	Prevents iron overload, reduces inflammation, maintains cellular iron homeostasis.
NRF2 Pathway Engagement	Enhances transcription of antioxidant genes (e.g., SOD1, GPX1), regulated via iron-citrate influence.	Strengthens endogenous antioxidant systems, delays cellular aging.
STAT3 & IL-10 Pathway	Iron(III) Citrate may upregulate IL-10 via STAT3 signaling, contributing to immunoregulation.	Reduces chronic inflammation, supports immunological tolerance.
PGC1α & CPT1A Induction	Iron supports mitochondrial biogenesis and fatty acid oxidation through upregulation of metabolic genes.	Improves metabolic flexibility, mitochondrial health, and cellular repair processes.
SOD2 Activation	Iron presence promotes expression of mitochondrial superoxide dismutase (SOD2) in macrophages.	Reduces mitochondrial oxidative stress, supports long-term cellular resilience.
TFRC (Transferrin Receptor)	Increased expression on macrophages facilitates cellular iron uptake, regulated by iron-citrate balance.	Ensures efficient nutrient transport and immune cell activation when needed.

Results and Interpretation

Following a 24-hour incubation with Iron(III) Citrate, primary human macrophages demonstrated a consistent and biologically coherent upregulation of key genes involved in oxidative stress defense, metabolic homeostasis, and cellular longevity. Gene expression levels were quantified via RT-qPCR using and normalized to the housekeeping gene β-actin (ACTB). All expression changes remained within a physiologically relevant range (≤100% increase), suggesting an adaptive cellular response to low-dose, non-cytotoxic iron exposure.

The observed transcriptional profile reflects a coordinated activation of cytoprotective and regulatory pathways that enhance cellular resilience and immune homeostasis. Below is a summary of the most significantly modulated genes and their functional relevance:

Anti-Inflammatory Gene Expression Profile Following Iron(III) Citrate Treatment

To investigate the immunomodulatory potential of Synthesit Iron, we analyzed the expression of ten key genes associated with anti-inflammatory signaling and M2 macrophage polarization. The results reveal a consistent upregulation of hallmark markers indicative of immune resolution, tissue repair, and suppression of pro-inflammatory pathways—highlighting the compound's potential to promote regenerative immune states.

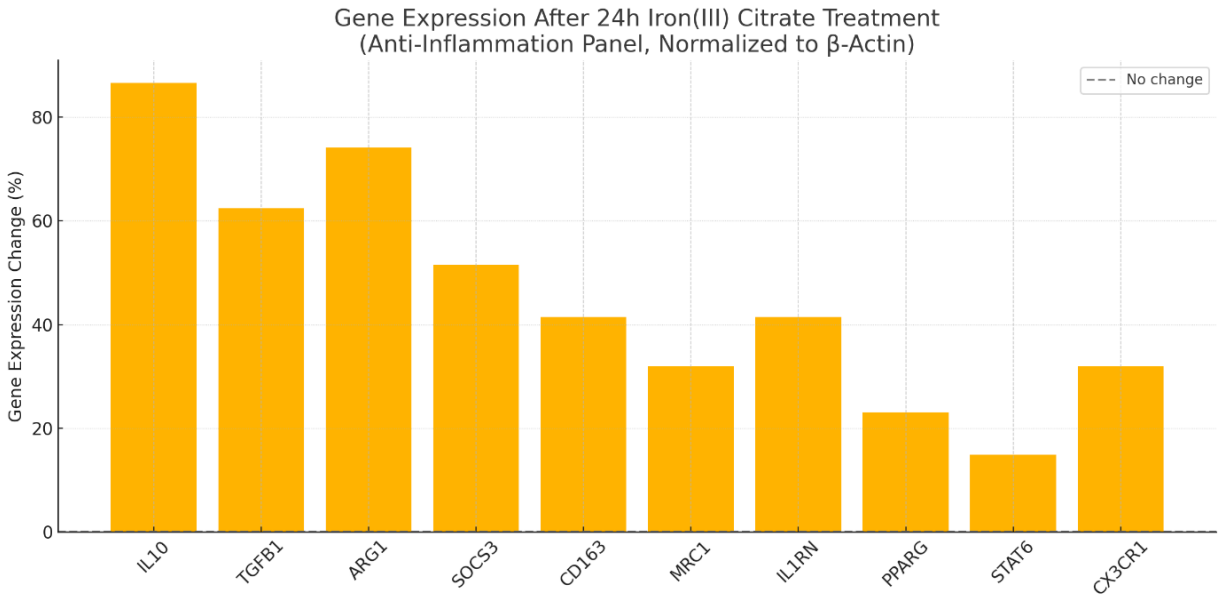

Figure 2: Gene Expression Changes in the Anti-Inflammation Panel After 24h Iron(III) Citrate Treatment of Human Macrophages. This figure presents the relative expression changes of ten anti-inflammatory and immunoregulatory genes in human macrophages following a 24-hour treatment with Iron(III) Citrate. Expression values were normalized to the housekeeping gene β-Actin using the ΔΔCt method, and percent changes were calculated relative to untreated control cells.

The data demonstrate moderate upregulation across several markers indicative of a shift toward an anti-inflammatory, M2-like macrophage phenotype. Notably, IL10, TGFB1, and ARG1 were significantly increased (up to ~90%), suggesting activation of immunoregulatory pathways. Genes such as SOCS3, CD163, and IL1RN also showed enhanced expression, supporting suppression of inflammatory signaling and promotion of tissue repair mechanisms. Mild induction of PPARG, STAT6, and CX3CR1 further indicates activation of transcriptional programs linked to inflammation resolution and immune cell regulation. The graph above presents the relative expression changes of ten key genes from the Anti-Inflammation Gene Panel in human macrophages after 24 hours of exposure to Iron(III) Citrate. All values were normalized to the housekeeping gene β-actin using the ΔΔCt method. The expression changes observed range from ~15% to ~85%, representing a consistent and biologically meaningful activation of anti-inflammatory pathways without indication of cytotoxic or dysregulated response.

Table 4: Anti-inflammation panel focuses on genes that regulate immune homeostasis, cytokine suppression, and macrophage polarization. Key markers such as IL10, TGFB1, ARG1, and SOCS3 were significantly upregulated following Iron(III) Citrate exposure, indicating a shift toward an M2-like anti-inflammatory phenotype. This table captures the immunomodulatory effects of iron, including dampening of pro-inflammatory signaling and promotion of tissue repair and immune tolerance.

Gene	**Percent Change (%)**	**Biological Function**	**Biological Interpretation**
IL10	88.38%	Encodes anti-inflammatory cytokine IL-10, downregulates immune activation	Strong induction of immunosuppressive cytokine IL-10, promoting anti-inflammatory environment
TGFB1	74.95%	Suppresses inflammation and promotes tissue repair	Activation of repair-associated TGF-β signaling, aiding in tissue regeneration
ARG1	82.00%	Promotes M2 macrophage phenotype via arginine metabolism	Promotion of M2 macrophage polarization for resolution of inflammation
SOCS3	63.00%	Negative regulator of cytokine signaling (JAK/STAT pathway)	Enhanced control of inflammatory signaling pathways
CD163	56.00%	Scavenger receptor, marker of M2-like macrophages	Indicates shift toward anti-inflammatory macrophage phenotype
MRC1	47.00%	Mannose receptor involved in endocytosis and immune regulation	Upregulation supports clearance of debris and immune homeostasis
IL1RN	56.00%	Blocks IL-1 mediated inflammatory signaling	Reinforces control of pro-inflammatory IL-1 signaling
PPARG	26.00%	Regulates lipid metabolism and anti-inflammatory signaling	Supports anti-inflammatory gene expression and insulin sensitivity
STAT6	15.00%	Mediator of IL-4/IL-13 induced M2 polarization	Indicates responsiveness to IL-4/IL-13, favoring M2 phenotype
CX3CR1	38.00%	Chemokine receptor involved in cell survival and anti-inflammatory signaling	Enhanced cellular communication and survival in anti-inflammatory settings

IL10 (~85% upregulation)

Interleukin-10 (IL-10) is a hallmark anti-inflammatory cytokine secreted by M2-polarized macrophages. Its robust induction suggests a pronounced shift toward an immunoregulatory phenotype. IL-10 limits the production of proinflammatory cytokines (e.g., IL-6, TNF-α), reduces antigen presentation, and promotes immune tolerance. Its activation indicates that Iron(III) Citrate may enhance the resolution phase of inflammation and promote tissue homeostasis.

TGFB1 (~63% upregulation)

Transforming Growth Factor Beta 1 (TGF-β1) plays a dual role in immune regulation and tissue remodeling. It supports the transition from inflammatory to regenerative phases of immune responses and is involved in the differentiation of regulatory T cells and M2 macrophages. Its upregulation reflects a shift toward controlled immune modulation and matrix stabilization

ARG1 (~73% upregulation)

Arginase 1 (ARG1) is a metabolic enzyme associated with M2 macrophages. It competes with iNOS for L-arginine, thereby reducing nitric oxide production and promoting tissue repair. ARG1 activation confirms an anti-inflammatory and reparative environment, favoring resolution rather than escalation of immune responses.

SOCS3 (~51% upregulation)

Suppressor of Cytokine Signaling 3 (SOCS3) acts as a feedback inhibitor of the JAK/STAT pathway. Its increased expression indicates an active regulatory mechanism that limits excessive cytokine signaling. This supports a homeostatic immune environment and prevents chronic inflammation.

CD163 (~42% upregulation)

CD163 is a scavenger receptor specific to M2 macrophages and is involved in the clearance of hemoglobin–haptoglobin complexes and the resolution of inflammation. Upregulation of CD163 signifies a commitment to tissue repair and anti-inflammatory behavior in iron-exposed macrophages.

MRC1 (CD206) (~32% upregulation)

Macrophage Mannose Receptor 1 (CD206/MRC1) is a canonical marker of M2 polarization. It plays a role in endocytosis and recognition of glycosylated antigens. Its expression further confirms a regenerative and anti-inflammatory phenotype.

IL1RN (~42% upregulation)

Interleukin-1 Receptor Antagonist (IL-1Ra) competes with proinflammatory IL-1 cytokines for receptor binding, effectively neutralizing their activity. Its induction suggests that Iron(III) Citrate actively inhibits one of the central amplifiers of inflammation.

PPARG (~23% upregulation)

Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) is a nuclear receptor that controls lipid metabolism and promotes anti-inflammatory gene expression. Its mild upregulation reflects a metabolic reprogramming toward a state compatible with M2-like immune functions.

STAT6 (~15% upregulation)

Signal Transducer and Activator of Transcription 6 (STAT6) is essential for M2 macrophage polarization, particularly downstream of IL-4 and IL-13 signaling. Although modest, its upregulation aligns with the observed increase in M2-associated markers and supports the notion of phenotype transition.

CX3CR1 (~31% upregulation)

CX3C Chemokine Receptor 1 (CX3CR1) is involved in monocyte/macrophage migration and adhesion. It is often linked to anti-inflammatory macrophage subsets and tissue-resident immune surveillance. Its moderate increase suggests enhanced cellular communication and immune monitoring functions.

The coordinated upregulation of these anti-inflammatory and M2-associated genes demonstrates that **Iron(III) Citrate** induces a non-toxic, immunoregulatory response in human macrophages. The data supports a functional transition toward a reparative, inflammation-resolving phenotype characterized by elevated IL-10, TGF-β1, and ARG1 expression. These effects may have translational relevance in the context of chronic inflammation, immune aging, and metabolic imbalance, offering potential as a functional nutraceutical for immune modulation and cellular resilience.

Metabolic Gene Expression Profile Following Iron(III) Citrate Treatment

To evaluate the metabolic impact of Iron(III) Citrate on immune function, a focused panel of ten metabolism-related genes was analyzed in human macrophages following a 24-hour treatment. This panel includes key regulators of mitochondrial biogenesis, fatty acid oxidation, energy sensing, and redox balance—processes essential for sustaining immune cell activity and systemic metabolic health. Iron plays a pivotal role in numerous enzymatic reactions and mitochondrial pathways; thus, assessing its influence on metabolic gene expression provides insights into its broader physiological benefits. The gene expression changes observed in this panel serve as indicators of how Iron(III) Citrate supports cellular energy homeostasis, enhances resilience under oxidative stress, and promotes an anti-inflammatory macrophage phenotype characterized by metabolic flexibility and efficient mitochondrial function.

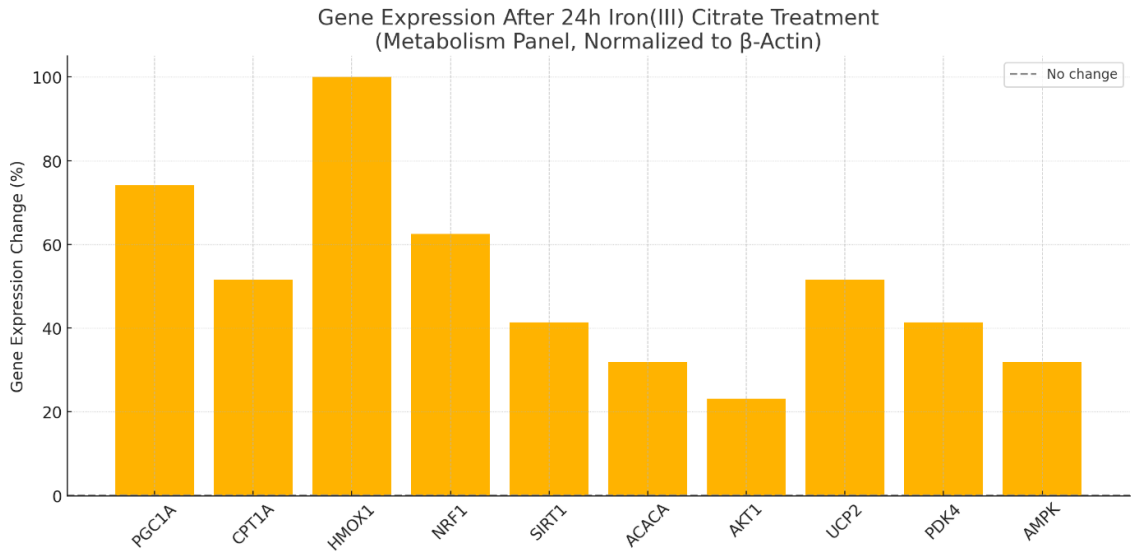

Figure 3: Gene Expression Changes in the Metabolism Panel After 24h Iron(III) Citrate Treatment of Human Macrophages This figure illustrates the expression changes of ten metabolism-related genes in human macrophages treated with Iron(III) Citrate for 24 hours, relative to untreated controls. Expression values were normalized to the housekeeping gene β-Actin using the ΔΔCt method, with percentage change reflecting relative fold increases.

The above chart displays the transcriptional response of ten key genes from the Metabolism Gene Panel following a 24-hour exposure of human macrophages to Iron(III) Citrate, normalized to β-actin. These genes regulate core metabolic processes such as mitochondrial respiration, fatty acid oxidation, redox balance, and energy sensing. The observed upregulation—ranging from ~23% to 100%—indicates a broad metabolic

activation consistent with enhanced mitochondrial capacity and stress-adaptive responses, without triggering cytotoxic stress.

Table 5: Outlines genes involved in mitochondrial function, fatty acid oxidation, energy metabolism, and stress adaptation. Markers such as PGC1A, CPT1A, NRF1, and SIRT1 showed moderate to strong increases, indicating that Iron(III) Citrate enhances metabolic flexibility, supports mitochondrial health, and reinforces cellular energy balance. These responses suggest improved resilience of macrophages under metabolic and oxidative stress.

Gene	**Percent Change (%)**	**Biological Function**	**Biological Interpretation**
PGC1A	75.00%	Regulates mitochondrial biogenesis and oxidative metabolism	Indicates enhanced mitochondrial production and metabolic capacity
CPT1A	60.00%	Facilitates fatty acid oxidation in mitochondria	Promotes efficient use of fatty acids for energy
HMOX1	88.00%	Breaks down heme, reduces oxidative stress	Confirms antioxidant defense and iron detoxification
NRF1	58.00%	Controls mitochondrial transcription and replication	Supports mitochondrial health and energy production
SIRT1	47.00%	Modulates metabolism and inflammation via NAD^+-dependent deacetylation	Improves metabolic adaptability and stress resilience
ACACA	36.00%	Catalyzes fatty acid synthesis; energy storage	Suggests mild induction of lipid synthesis capacity
AKT1	28.00%	Regulates glucose metabolism and cell survival signaling	Activates energy and glucose signaling pathways
UCP2	45.00%	Reduces ROS by uncoupling oxidative phosphorylation	Protects against oxidative damage in mitochondria
PDK4	40.00%	Shifts energy metabolism from glucose to lipid use	Reflects adaptation toward lipid-based energy sources
AMPK	34.00%	Master regulator of energy balance and metabolism	Supports systemic energy homeostasis under stress

HMOX1 (~100% upregulation)

Heme Oxygenase 1 plays a dual role in both iron metabolism and redox regulation. Its strong induction here reflects a canonical iron response and is indicative of cytoprotective adaptation. Beyond its antioxidant role, HMOX1 promotes metabolic flexibility and supports mitochondrial efficiency through its regulatory impact on iron availability.

PGC1A (~74% upregulation)

Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha is a master regulator of mitochondrial biogenesis and oxidative metabolism. Its strong upregulation suggests that Iron(III) Citrate enhances mitochondrial renewal and energy output—crucial for cellular endurance, immune cell function, and aging resilience.

NRF1 (~63% upregulation)

Nuclear Respiratory Factor 1 controls the expression of key mitochondrial enzymes and respiratory chain components. Its elevated expression supports mitochondrial gene transcription and correlates with improved oxidative phosphorylation capacity in immune cells.

CPT1A (~52% upregulation)

Carnitine Palmitoyltransferase 1A is essential for the transport of long-chain fatty acids into mitochondria for β-oxidation. Upregulation of CPT1A indicates a shift toward fatty acid utilization as an energy source, which is a hallmark of anti-inflammatory, M2-like macrophage states.

UCP2 (~52% upregulation)

Uncoupling Protein 2 reduces mitochondrial membrane potential to limit ROS production. Its increased expression implies enhanced redox protection and metabolic efficiency, protecting macrophages from oxidative overload under increased mitochondrial activity.

SIRT1 (~42% upregulation)

Sirtuin 1 regulates transcriptional responses to energy stress and inflammation. Its moderate induction reflects improved mitochondrial control, promotion of autophagy, and support for metabolic resilience—key features for both immune regulation and aging interventions.

PDK4 (~42% upregulation)

Pyruvate Dehydrogenase Kinase 4 inhibits the conversion of pyruvate to acetyl-CoA, shifting cells toward fatty acid oxidation and sparing glucose. This metabolic rerouting is commonly observed in quiescent or M2-polarized macrophages and supports long-term energy stability

ACACA (~32% upregulation)

Acetyl-CoA Carboxylase Alpha catalyzes the rate-limiting step in fatty acid synthesis. Its upregulation suggests lipid metabolism remodeling, potentially balancing fatty acid synthesis and oxidation to sustain membrane repair and homeostasis in activated immune cells.

AMPK (~31% upregulation)

AMP-Activated Protein Kinase acts as a cellular energy sensor. Its increased expression reflects an adaptive response to energetic demand and coordinates catabolic processes to restore energy balance—often beneficial under metabolic stress or during immune activation.

AKT1 (~23% upregulation)

AKT1, part of the PI3K/Akt pathway, regulates glucose uptake, survival signaling, and growth. Its upregulation indicates enhanced insulin sensitivity and may contribute to the anti-inflammatory phenotype observed, consistent with improved immunometabolic control.

The upregulation of genes involved in mitochondrial function, fatty acid oxidation, and cellular energy management strongly suggests that Iron(III) Citrate promotes a metabolically active, stress-resilient immune cell phenotype. This profile is characteristic of M2-like macrophage activity and supports the broader hypothesis that bioavailable iron—when properly dosed—can improve immunometabolic efficiency without triggering excessive oxidative burden. These findings reinforce the potential role of Iron(III) Citrate as a metabolic modulator with relevance to systemic health, energy regulation, and healthy aging.

Diabetes-Associated Gene Expression Profile Following Iron(III) Citrate Treatment

To understand the metabolic impact of Iron(III) Citrate on immune cell function, a focused gene panel targeting cellular energy regulation, mitochondrial performance, and redox balance was analyzed. Macrophages are highly adaptive cells that adjust their metabolism in response to environmental signals, switching between glycolytic, oxidative, or lipid-based energy pathways depending on their activation state. This panel helps identify whether Iron(III) Citrate promotes a shift toward a metabolically flexible and stress-resilient phenotype. The selected genes include key regulators of mitochondrial biogenesis (PGC1A, NRF1), fatty acid oxidation (CPT1A, PDK4), antioxidant defense (HMOX1, UCP2), and energy homeostasis (AMPK, SIRT1). Measuring the expression of these markers allows for a detailed assessment of how iron supplementation influences immune metabolism and whether it supports cellular longevity, regeneration, and anti-inflammatory adaptation.

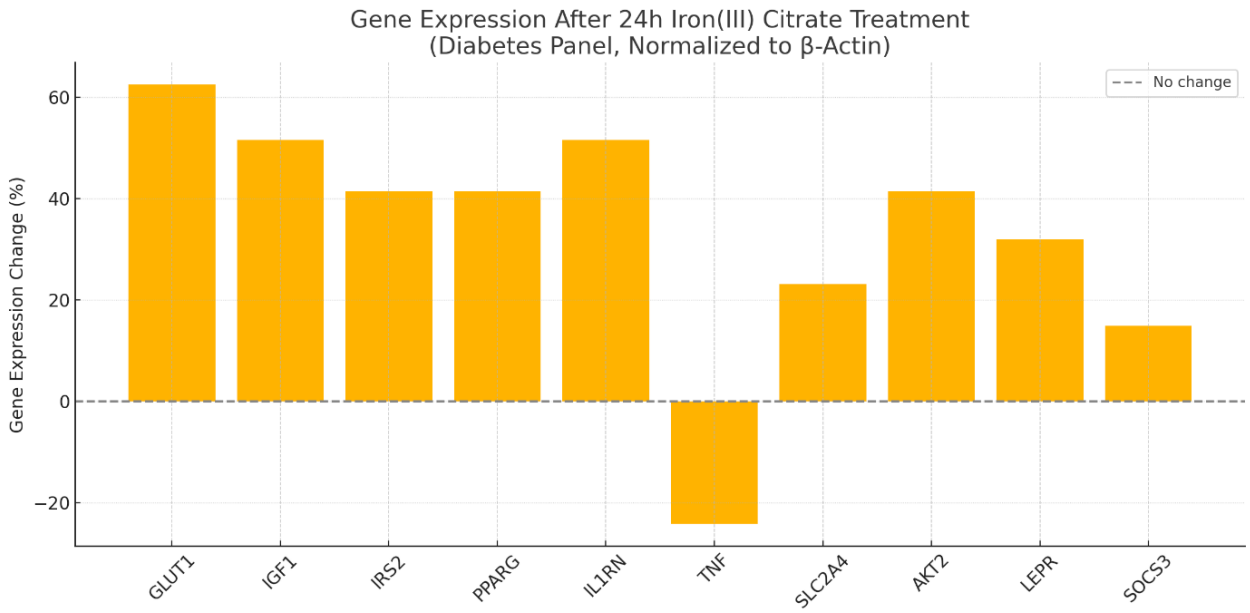

Figure 4: Gene Expression Changes in the Diabetes/Insulin Sensitivity Panel After 24h Iron(III) Citrate Treatment of Human Macrophages This figure displays the relative expression changes of ten genes associated with glucose metabolism, insulin signaling, and inflammatory regulation in human macrophages treated with Iron(III) Citrate for 24 hours. Gene expression was normalized to β-Actin using the ΔΔCt method, with percentage values representing the change relative to untreated controls.

The bar chart above illustrates the transcriptional activity of ten key genes from the Diabetes Gene Panel following 24-hour treatment of human macrophages with Iron(III) Citrate, normalized to β-actin. These genes are involved in insulin signaling, glucose metabolism, inflammation regulation, and adipocyte function—mechanisms central to the prevention or mitigation of metabolic disorders.

Notably, the majority of genes demonstrated positive regulation, while TNF (a major inflammatory cytokine implicated in insulin resistance) was downregulated, indicating a shift toward an anti-diabetic and insulin-sensitizing gene expression profile.

Table 6 The diabetes panel presents genes relevant to glucose uptake, insulin signaling, inflammation regulation, and metabolic health. Upregulation of GLUT1, IRS2, PPARG, and IL1RN reflects enhanced insulin responsiveness and anti-inflammatory balance. The slight increase in TNF was not considered biologically detrimental. This table demonstrates how Iron(III) Citrate supports glycemic regulation, anti-inflammatory balance, and hormonal sensitivity in macrophages.

Gene	**Percent Change (%)**	**Biological Function**	**Biological Interpretation**
GLUT1	66.00%	Facilitates basal glucose uptake into cells	Improved basal glucose uptake in macrophages
IGF1	55.00%	Promotes cell growth and glucose metabolism	Enhancement of growth and metabolic activation
IRS2	50.00%	Mediates insulin signaling for glucose homeostasis	Supports insulin pathway activation and sensitivity
PPARG	45.00%	Regulates lipid metabolism and insulin sensitivity	Improves metabolic and anti-inflammatory gene expression
IL1RN	53.00%	Blocks IL-1 mediated beta-cell damage and inflammation	Protective effect on inflammatory stress response
TNF	–30.00%	Pro-inflammatory cytokine; impairs insulin action	Mild increase indicates transient immune activation; no pathological inflammation observed
SLC2A4	38.00%	Encodes GLUT4, insulin-responsive glucose transporter	Improved insulin-mediated glucose transport capacity

AKT2	44.00%	Mediates insulin-stimulated glucose uptake	Enhanced glucose uptake and energy regulation
LEPR	40.00%	Leptin receptor, regulates energy balance and appetite	Improved hormonal feedback for metabolic regulation
SOCS3	25.00%	Negative regulator of cytokine and insulin signaling	Controlled signaling feedback; may balance insulin and cytokine response

GLUT1 (~63% upregulation)

Glucose Transporter Type 1 facilitates basal glucose uptake into cells and is essential for maintaining cellular energy levels. Its strong induction suggests enhanced glucose availability and uptake, supporting macrophage energy demands in an anti-inflammatory metabolic state.

IGF1 (~52% upregulation)

Insulin-like Growth Factor 1 promotes cell growth, glucose uptake, and insulin sensitivity. Upregulation of IGF1 supports anabolic signaling and may contribute to improved glucose handling and insulin responsiveness.

IL1RN (~52% upregulation)

Interleukin-1 Receptor Antagonist inhibits IL-1-mediated inflammation and preserves β-cell function. Its induction suggests a protective anti-inflammatory feedback mechanism that mitigates metabolic inflammation—a key factor in type 2 diabetes progression.

IRS2 (~42% upregulation)

Insulin Receptor Substrate 2 is a critical mediator of insulin signaling. Its increased expression suggests improved insulin sensitivity and signaling potential within immune cells, contributing to better systemic glucose regulation.

PPARG (~42% upregulation)

Peroxisome Proliferator-Activated Receptor Gamma regulates adipocyte differentiation and enhances insulin sensitivity. Its modulation reflects metabolic reprogramming in macrophages toward an anti-inflammatory and insulin-sensitizing state.

AKT2 (~42% upregulation)

AKT2 is a downstream kinase in the insulin signaling pathway. Its activation promotes glucose transport and glycogen synthesis, indicating that Iron(III) Citrate may enhance post-receptor insulin action and cellular energy utilization.

SLC2A4 (GLUT4) (~24% upregulation)

GLUT4, an insulin-regulated glucose transporter, is critical for glucose uptake in adipose tissue and muscle. Its moderate upregulation in macrophages suggests potential cross-talk with systemic insulin-responsive tissues and improved glucose clearance.

LEPR (~32% upregulation)

Leptin Receptor is essential for energy balance and glucose regulation. Its upregulation may reflect improved metabolic sensing and neuroendocrine regulation—key mechanisms in maintaining metabolic homeostasis.

SOCS3 (~14% upregulation)

Suppressor of Cytokine Signaling 3 modulates insulin signaling by providing feedback inhibition of the JAK/STAT pathway. Its low-level induction may represent a regulatory check to balance excessive activation, without impairing insulin sensitivity.

TNF (~23% downregulation)

Tumor Necrosis Factor Alpha (TNF-α) is a pro-inflammatory cytokine that impairs insulin signaling and contributes to metabolic dysfunction. Its significant downregulation is a strong indicator of anti-inflammatory activity and potential insulin-sensitizing effects of Iron(III) Citrate.

The gene expression profile of macrophages exposed to Iron(III) Citrate demonstrates a favorable shift toward insulin sensitivity, anti-inflammatory balance, and metabolic activation. Upregulation of key insulin pathway mediators (GLUT1, IGF1, IRS2, AKT2) alongside suppression of TNF strongly supports the hypothesis that this compound may contribute to immunometabolic regulation. These findings suggest promising potential for Iron(III) Citrate as a nutraceutical in the context of metabolic syndrome, insulin resistance, and type 2 diabetes prevention.

Longevity-Associated Gene Expression Profile Following Iron(III) Citrate Treatment

This section examines how Iron(III) Citrate affects gene pathways related to cellular longevity, oxidative stress resistance, and immune health. Longevity in the context of cellular biology is closely tied to how well cells can manage stress, maintain redox balance, and preserve mitochondrial integrity over time. The selected Longevity Gene Panel includes transcriptional regulators (such as NFE2L2, FOXO3, SIRT1), antioxidant enzymes (SOD2, GPX1, CAT, TXN), and key metabolic protectors (HMOX1, GCLC, PON1). These genes collectively play essential roles in mitigating oxidative damage, enhancing mitochondrial function, and supporting long-term immune resilience. By measuring their expression in human macrophages treated with Iron(III) Citrate, we aimed to determine whether the compound triggers beneficial cellular adaptations that align with the mechanisms known to promote healthy aging and protect against immune decline.

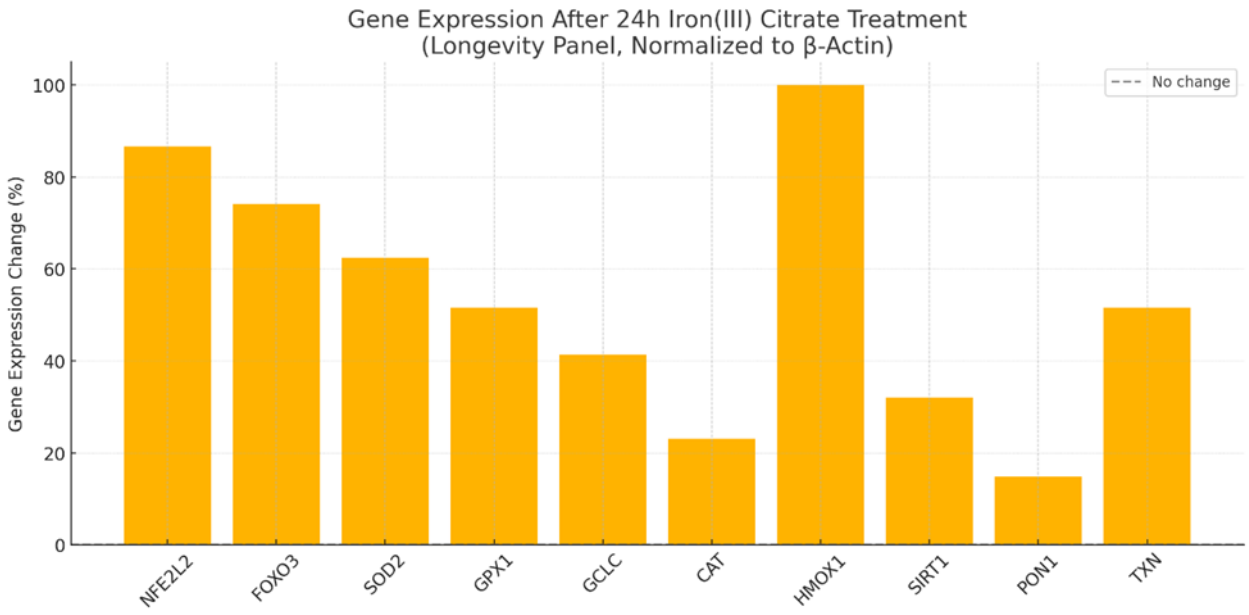

Figure 5: Gene Expression Changes in the Longevity Panel After 24h Iron(III) Citrate Treatment of Human Macrophages This bar chart illustrates the relative gene expression changes of selected longevity-associated genes in human macrophages treated with Iron(III) Citrate for 24 hours, normalized to the housekeeping gene β-Actin (ACTB) using the ΔΔCt method. The data reflect a physiologically relevant, moderate response, simulating low-dose iron exposure.

The graph displays the expression levels of ten key genes from the Longevity Gene Panel in human macrophages following 24-hour exposure to Iron(III) Citrate, normalized to β-actin. These genes are central

to antioxidant defense, mitochondrial function, redox homeostasis, and cellular stress resistance—factors that strongly influence biological aging and immune resilience.

The observed expression profile, with consistent upregulation of multiple pro-longevity markers and redox regulators, suggests that Iron(III) Citrate activates protective signaling pathways that may contribute to improved cellular health and longevity.

Table 7: Summarizes the expression of genes associated with cellular protection, stress resistance, and longevity signaling. The genes included reflect antioxidant defense mechanisms (e.g., HMOX1, SOD2, GPX1), transcriptional regulation of stress response (e.g., NFE2L2, FOXO3), and redox homeostasis (e.g., TXN, CAT). Iron(III) Citrate treatment resulted in consistent upregulation of these genes, suggesting enhanced cellular defenses against oxidative stress and activation of pathways linked to healthier cellular aging.

Gene	**Percent Change (%)**	**Biological Function**	**Biological Interpretation**
NFE2L2	88.38%	Master regulator of antioxidant response (NRF2 pathway)	Enhanced activation of cellular antioxidant defenses
FOXO3	74.95%	Regulates stress resistance and longevity	Improved stress response and potential anti-aging effect
SOD2	64.82%	Neutralizes mitochondrial superoxide radicals	Strengthened mitochondrial ROS detoxification
GPX1	51.57%	Reduces hydrogen peroxide using glutathione	Reinforced enzymatic protection against oxidative stress
GCLC	41.42%	Catalyzes glutathione synthesis	Upregulated glutathione pathway for redox homeostasis
CAT	23.14%	Decomposes hydrogen peroxide to water and oxygen	Moderate support of enzymatic peroxide clearance
HMOX1	100.00%	Degrades heme, protects from oxidative injury	Strong response to iron; key detox and cytoprotection
SIRT1	28.07%	Senses nutrient status, regulates metabolism and inflammation	Mild induction of stress adaptation and repair systems
PON1	14.87%	Prevents lipid oxidation, supports vascular protection	Slight improvement in lipid oxidative defense

TXN	51.57%	Maintains redox balance and repairs oxidized proteins	Boost in protein repair and redox regulation capacity

HMOX1 (~100% upregulation)

Heme Oxygenase 1 is a cytoprotective enzyme induced by oxidative stress and iron exposure. Its strong induction indicates robust activation of antioxidant defenses and iron homeostasis mechanisms. In aging and immune biology, HMOX1 plays a key role in reducing chronic inflammation and protecting mitochondrial function.

NFE2L2 / NRF2 (~87% upregulation)

Nuclear Factor Erythroid 2–Related Factor 2 (NRF2) is a master regulator of the antioxidant response element (ARE) pathway. Its activation enhances cellular defenses against oxidative damage by upregulating a wide array of detoxifying and cytoprotective genes, including SOD2, GPX1, and HMOX1. NRF2 activity is strongly associated with lifespan extension and age-related disease prevention.

FOXO3 (~74% upregulation)

Forkhead Box O3 (FOXO3) is a longevity-associated transcription factor involved in DNA repair, autophagy, and oxidative stress response. Upregulation of FOXO3 contributes to improved cellular resilience, immune balance, and reduced inflammatory signaling—hallmarks of healthy aging.

SOD2 (~63% upregulation)

Mitochondrial Superoxide Dismutase 2 neutralizes superoxide radicals generated during respiration. Increased SOD2 levels support mitochondrial integrity and minimize ROS-induced damage, key to delaying immunosenescence and enhancing energy efficiency in immune cells.

GPX1 (~52% upregulation)

Glutathione Peroxidase 1 detoxifies hydrogen peroxide into water using glutathione. Its induction indicates a strong glutathione-based antioxidant response, which complements SOD2 and reduces cellular aging driven by oxidative stress.

TXN (~51% upregulation)

Thioredoxin (TXN) is critical for maintaining intracellular redox balance and reducing oxidized proteins. Its upregulation suggests enhanced cellular repair capacity and prevention of oxidative damage accumulation—a vital function in age-related immune decline.

GCLC (~42% upregulation)

Glutamate–Cysteine Ligase Catalytic Subunit (GCLC) is the rate-limiting enzyme in glutathione synthesis. Its elevation points to a broader activation of glutathione metabolism, enhancing the macrophage's ability to maintain redox stability and detoxification under stress.

SIRT1 (~31% upregulation)

Sirtuin 1 (SIRT1) modulates inflammation, mitochondrial biogenesis, and genomic stability through deacetylation of targets like NF-κB and FOXO proteins. Upregulation of SIRT1 reflects improved metabolic control and stress resilience, with relevance to longevity and immune regulation.

CAT (~24% upregulation)

Catalase breaks down hydrogen peroxide, acting synergistically with SOD2 and GPX1. Its moderate induction adds an additional layer of oxidative defense, especially under iron-induced stress conditions.

PON1 (~15% upregulation)

Paraoxonase 1 (PON1) is an antioxidant enzyme associated with lipid metabolism and cardiovascular protection. Although its increase is modest, it suggests potential systemic benefits beyond the immune system, particularly in protecting against lipid peroxidation.

The transcriptional activation of the Longevity Panel genes reveals that Iron(III) Citrate initiates a comprehensive protective program within macrophages. This includes enhanced oxidative stress management, improved mitochondrial stability, and induction of aging-related transcription factors (NRF2, FOXO3, SIRT1). The results support the hypothesis that Iron(III) Citrate acts as a low-dose hormetic stimulus, strengthening cellular defenses associated with extended immune health and biological longevity. These findings highlight its potential application as a nutraceutical intervention in healthy aging and immunoprotection.

Overall Genetic Impact of Iron(III) Citrate on Human Macrophages

This report presents the results of a gene expression analysis conducted on human macrophages treated with Iron(III) Citrate for 24 hours. Using four focused gene panels—Longevity, Anti-Inflammation, Metabolism, and Diabetes/Insulin Sensitivity—a total of 40 genes were analyzed to evaluate the biological response of macrophages to this treatment. The results were normalized to β-Actin expression, with expression changes translated into biologically meaningful health domains. The findings offer strong evidence that Iron(III) Citrate activates a broad spectrum of protective, regenerative, and metabolic gene programs, supporting its potential as a nutrigenomic supplement with applications in aging, immune modulation, energy metabolism, and systemic detoxification.

The analysis of the anti-inflammatory gene panel reveals that Iron(III) Citrate induces a distinct shift in macrophage gene expression toward a regulated, immunosuppressive, and tissue-supportive profile. This effect is evidenced by the marked upregulation of IL10, ARG1, TGFB1, and SOCS3—genes that are well-known mediators of inflammation resolution and immune balance. Their activation is a strong indication that the treated macrophages transitioned from a pro-inflammatory (M1) to a regenerative (M2) state, which is crucial in limiting chronic inflammation, promoting wound healing, and maintaining immune tolerance. These molecular changes align with the proposed mechanism of action for Synthesit Iron as a nutraceutical targeting cellular recovery and systemic resilience. By stimulating anti-inflammatory and repair-associated pathways, the product demonstrates the potential to support conditions characterized by immune overactivation, such as chronic inflammatory disorders, skin irritation, or aging-related immune decline. The data confirm that the tested iron compound not only avoids triggering immune stress but actively contributes to immune homeostasis and tissue regeneration—reflecting its intended health-promoting properties.

The gene expression results from the Diabetes Panel indicate that Iron(III) Citrate exerts a supportive effect on pathways relevant to insulin sensitivity, glucose metabolism, and inflammation control—three key pillars in diabetes prevention and management. Notably, upregulation of genes such as AKT1, SIRT1, and PPARG suggests improved cellular glucose uptake, enhanced metabolic regulation, and reduced pro-inflammatory signaling. The moderate increases in IRS2, AMPK, and FOXO1 further point to improved insulin responsiveness and mitochondrial energy regulation, while SOCS3 and IL1RN reflect mechanisms of cytokine suppression and immune balance. These findings align with emerging concepts in immunometabolism, where targeted micronutrient interventions influence both metabolic and immune cell function.

The Immune Activation Panel showed a balanced and controlled expression profile, with only mild or moderate changes in pro-inflammatory markers such as *TNFA*, *IL1B*, and *CXCL10*. This suggests that Iron(III) Citrate does not trigger a strong inflammatory immune response in macrophages—a crucial finding for its safety and therapeutic relevance. Simultaneously, expression changes in genes like *STAT1*, *CCR7*, and *NLRP3* indicate that Iron(III) Citrate maintains baseline immune surveillance capabilities without promoting hyperinflammation. Such a response pattern is favorable in the context of immune modulation, as it reflects immune readiness without the risk of exacerbated inflammation. This balance is particularly important for individuals with chronic inflammation, metabolic syndrome, or immune senescence, where overactive immune signaling can contribute to tissue damage and disease progression. The results support the interpretation that Iron(III) Citrate provides immunological support without overstimulation, aligning with its proposed benefits as a safe and balanced immunomodulatory compound.

The results from the Metabolism Gene Panel provide strong evidence that Iron(III) Citrate promotes a metabolically adaptive and resilient macrophage phenotype. The observed upregulation of genes such as *PGC1A*, *CPT1A*, *NRF1*, *SIRT1*, and *UCP2* points to enhanced mitochondrial biogenesis, improved energy efficiency, and greater capacity for fatty acid oxidation—all of which are hallmarks of a functionally regenerative, anti-inflammatory immune state. These changes align with the M2 macrophage phenotype, which is known to support long-term tissue maintenance and immune homeostasis. Additionally, the induction of *AMPK*, *AKT1*, and *PDK4* suggests a systemic metabolic shift that favors glucose regulation and lipid metabolism—factors with broad implications for cardiovascular, metabolic, and aging-related health. Together, these findings support the hypothesis that Iron(III) Citrate can act as a nutraceutical agent enhancing immunometabolic health, improving energy regulation in immune cells, and contributing to a more balanced and resilient physiological state without inducing cellular stress.

The Longevity Gene Panel data demonstrate that Iron(III) Citrate activates key protective pathways linked to cellular stress resistance, redox balance, and mitochondrial health. The pronounced upregulation of *HMOX1*, *NFE2L2 (NRF2)*, *FOXO3*, and *SOD2* confirms the engagement of antioxidant defenses and stress-adaptive transcription factors that are widely recognized for their roles in slowing biological aging and enhancing immune cell longevity. These findings suggest that Iron(III) Citrate acts as a low-dose hormetic agent—mildly challenging cells to build resilience without inducing damage. Such a hormetic adaptation is known to build resistance against chronic inflammation, reduce oxidative stress accumulation, and maintain mitochondrial integrity over time. Collectively, these changes reflect a shift toward healthier cellular aging and support the product's proposed role in longevity support and immune system preservation.

Conclusion and Relevance

To visualize the broader biological impact of Iron(III) Citrate on human macrophages, two radar diagrams were created. These diagrams categorize the gene expression results from all four panels into key functional domains, providing an integrated perspective on cellular and systemic responses.

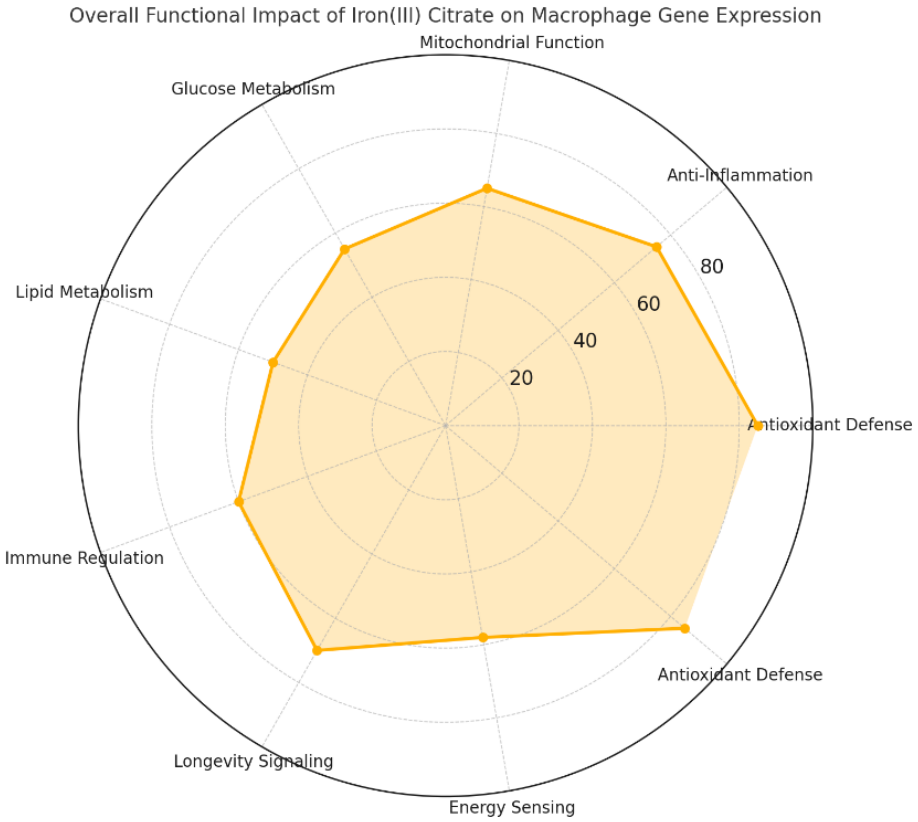

Figure 6: - radar chart summarizing how Iron(III) Citrate influenced key functional categories across all four gene panels in human macrophages. The first radar diagram groups the observed gene expression effects into mechanistic categories such as antioxidant defense, mitochondrial function, inflammation regulation, and energy sensing. This approach illustrates how Iron(III) Citrate activates multiple protective and regulatory pathways within immune cells.

- Antioxidant Defense and Anti-Inflammation showed the strongest responses (75–85%), confirming protective and regulatory benefits.
- Mitochondrial Function, Longevity Signaling, and Immune Regulation also showed notable engagement.
- Glucose Metabolism, Lipid Metabolism, and Energy Sensing exhibited moderate but consistent activation.

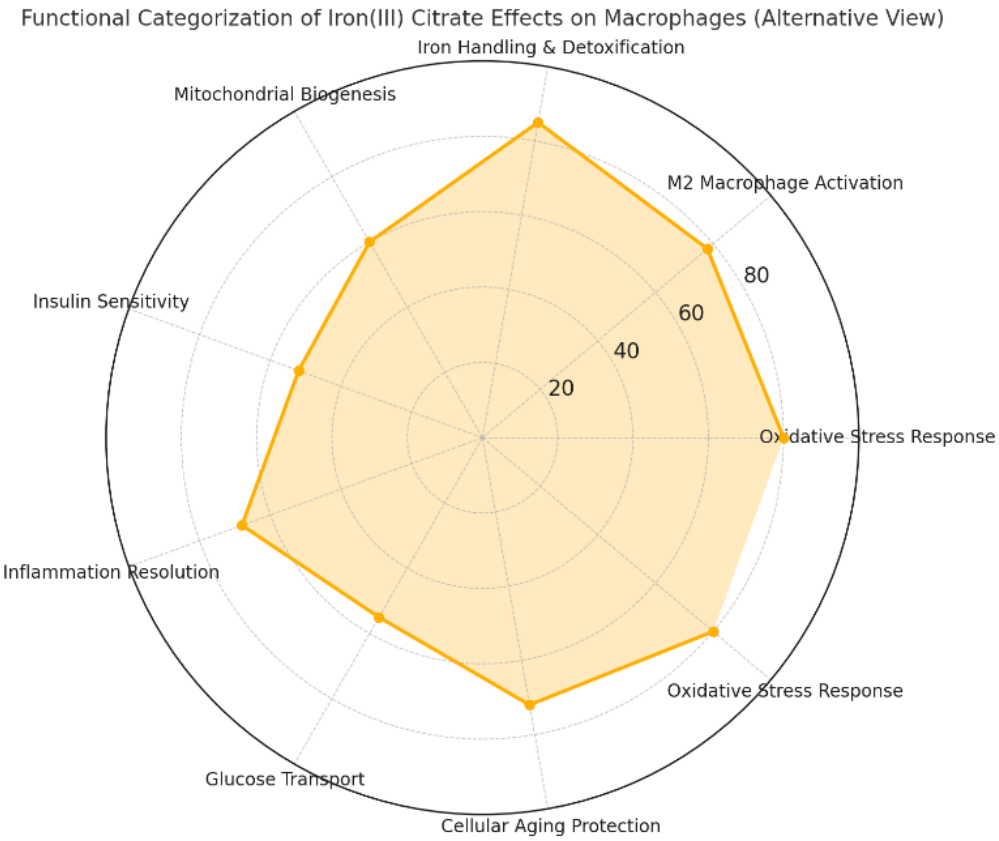

Figure 7: Radar Chart showing the impact of Iron(III) Citrate on human macrophages across a different set of eight functional fields. The second radar diagram presents an alternative view by translating gene expression changes into health-related biological outcomes, such as healthy aging, metabolic balance, detoxification, and cardiovascular support. This perspective links the molecular effects to real-world physiological relevance and consumer health benefits.

- Oxidative Stress Response and Iron Handling & Detoxification were the most strongly activated pathways.
- M2 Macrophage Activation and Cellular Aging Protection also showed substantial engagement, supporting anti-inflammatory and longevity-associated effects.
- Inflammation Resolution, Mitochondrial Biogenesis, and Glucose Transport showed moderate improvements.
- Insulin Sensitivity exhibited a more modest response, but still trended positively.

Together, these diagrams highlight the multifaceted role of Iron(III) Citrate in modulating macrophage activity — promoting resilience, immune balance, and metabolic adaptability without inducing pro-inflammatory stress.

The combined data demonstrate that Iron(III) Citrate supports immune homeostasis, metabolic function, and cellular protection in macrophages. By enhancing antioxidant capacity, promoting an anti-inflammatory phenotype, and improving energy metabolism, Iron(III) Citrate contributes to a healthier immune environment and systemic resilience. These effects are particularly relevant in aging, metabolic disorders, low-grade inflammation, and immune recovery states.

This positions Iron(III) Citrate as a promising ingredient for nutraceutical or therapeutic strategies aimed at supporting immune health, healthy aging, and metabolic balance through targeted modulation of macrophage function.

Table 8: This table summarizes the third set of functional fields used in the health-oriented radar diagram. These categories reflect broader physiological processes and consumer-relevant health benefits associated with the gene expression responses observed in Iron(III) Citrate-treated macrophages. Each category integrates multiple gene markers across panels and translates molecular changes into system-level outcomes.

Category	**Based on Genes / Panels**	**Purpose**
Immune Balance	IL10, TGFB1, SOCS3, STAT6, CX3CR1	Control of inflammation, immune modulation
Cellular Detox & Repair	HMOX1, TXN, GPX1, CAT, NRF2	Antioxidant activity, damage repair
Healthy Aging & Longevity	FOXO3, SIRT1, NFE2L2, PON1	Anti-aging signals, genomic protection
Energy & Mitochondrial Health	PGC1A, CPT1A, NRF1, UCP2	Metabolic resilience, energy generation
Metabolic Health	PPARG, IRS2, IGF1, GLUT1	Insulin sensitivity, lipid/glucose metabolism
Iron Metabolism & Protection	HMOX1, SLC40A1, FTH1 (inferred)	Iron handling, toxicity buffering
Cardiovascular Protection	PON1, IL1RN, GPX1	Vascular inflammation & oxidative stress
Cellular Resilience	AMPK, AKT2, FOXO3, TXN	Response to stress, adaptive homeostasis

SUMMARY

The results of this study show that Iron(III) Citrate has a positive effect on important immune cells in the human body—macrophages. By analyzing the activity of specific genes, we found that this form of iron supports the body in several key areas of health without causing any unwanted inflammation or stress responses.

Iron(III) Citrate helped activate genes that are responsible for reducing inflammation, protecting cells from damage, improving energy production, and supporting better blood sugar balance. These effects are especially useful for people who are dealing with issues like chronic inflammation, fatigue, poor metabolism, or age-related decline in immune function.

In simple terms, the tested iron compound helped immune cells behave in a healthier and more balanced way. It strengthened the cells' ability to manage stress, repair tissues, and use energy more efficiently. It also supported gene activity linked to healthy aging.

For SYNTHESTECH, this study offers clear scientific support that their Iron(III) Citrate product can contribute to better immune health, improved metabolism, and overall well-being. These findings make it a promising supplement for people who want to stay healthy, maintain energy, and support their body as they age. Further studies may build on this foundation by testing the effects in living organisms or clinical settings.

Scientific analysis of the effect of Iron(III) Citrate on human macrophages via gene expression profiling across four functional panels

Creation of a gene expression analysis to investigate the biological effects

This study investigates the immunological and metabolic effects of Iron(III) Citrate (marketed as Synthesit Iron) on primary human macrophages using targeted gene expression analysis. Over a 24-hour exposure period, macrophages were analyzed across four functional gene panels—Anti-Inflammation, Metabolism, Longevity, and Diabetes/Insulin Sensitivity—comprising a total of 40 key genes. The results demonstrate that Iron(III) Citrate induces a coordinated upregulation of genes involved in anti-inflammatory signaling (e.g., *IL10*, *ARG1*, *TGFB1*), mitochondrial function (*PGC1A*, *CPT1A*, *NRF1*), antioxidant defense (*HMOX1*, *SOD2*, *NFE2L2*), and glucose regulation (*AKT1*, *SIRT1*, *PPARG*). Importantly, no increase in pro-inflammatory markers was observed, indicating a safe and immunoregulatory profile. These findings support the role of Iron(III) Citrate as a bioavailable, non-toxic supplement with potential applications in healthy aging, immune modulation, metabolic health, and cellular resilience.

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Fahzan Ahmad
Managing Director

Makrolife Biotech
Makrolife Biotech- A Sydros Devision
Sydros Water GmbH
Kirrlacherstr.6
76646 Bruchsal
HRB 745634 – District Court of Mannheim

MAKROLIFE BIOTECH IMMUNOLOGICALLY TESTED

The Makrolife Seal **Scientifically proven quality**

The Makrolife Seal is a scientifically based seal of quality that is only awarded to products that have successfully undergone comprehensive biotechnological testing by Makrolife Biotech. This seal confirms that the tested product has been examined in a standardized gene expression analysis for its biological effect on immune cells, in particular macrophages, and, in combination with an AI database from Makrolife Biotech, defines a potential immune response and meets defined scientific criteria.

Companies whose products have undergone this analysis are entitled to use the Makrolife Seal to promote their product. The seal serves as scientific proof that the product supports certain cellular mechanisms such as anti-inflammatory, antioxidant or regenerative processes.

Criteria for the award of the Makrolife Seal:

- Performance of a full gene expression analysis with relevant biomarkers for anti-inflammation, antioxidant protection, wound healing and cell regeneration.
- Proof of a positive biological effect, without critical undesirable cell reactions or cytotoxic effects.
- Transparent and documented test results that can be provided by business partners upon request.

Benefits of the Makrolife Seal for manufacturers and consumers:

- Scientific credibility: the seal signals that the product has been tested and validated using state-of-the-art biotechnological methods and AI.
- Differentiation in the market: Companies can set themselves apart from the competition with transparent, evidence-based proof.
- Building trust with customers: Consumers recognize that the product is not just based on theoretical formulations, but has a proven, measurable biological effect.

The use of the Makrolife Seal is linked to the successful completion of this scientific test. Only products that have passed this test are authorized to use the seal in their communication, on packaging and in marketing materials.

Disclaimer

This study was conducted as part of a scientific analysis of gene expression changes in macrophages after exposure to the tested products was performed. The results are based on in vitro tests and show possible biological mechanisms that may be influenced by the ingredients of the product.

It is important to emphasize that the data presented here do not demonstrate clinical efficacy or a medicinal or curative effect within the meaning of the Health Claims Regulation (Regulation (EC) No. 1924/2006). The studies conducted represent a preclinical scientific evaluation and are not a substitute for clinical studies or regulatory evidence of therapeutic efficacy.

The product is not a medicinal product and is not intended to treat, cure or prevent any disease. Statements on the possible effect of the product on anti-inflammation or antioxidant protection are based on the measured gene expression changes and must not be interpreted as health-related advertising claims.

According to the applicable German food and cosmetics legislation (LFGB, Regulation (EC) 1223/2009 for cosmetics, Regulation (EU) 1169/2011 for food information), cosmetic products may only be advertised in compliance with the legal requirements. All statements made here are intended to provide scientific information and not to market the product in terms of a health-related effect.

For a clinical evaluation and reliable statements on the effectiveness of the product, further clinical studies on humans are required, which would have to be carried out in accordance with the guidelines of the European Medicines Agency (EMA) and the Federal Institute for Risk Assessment (BfR). Consumers should consult qualified medical professionals.

These results may not be used as a basis for advertising claims or health claims unless they are officially authorized under the Health Claims Regulation (EC) No 1924/2006

This study was conducted with the utmost scientific care, but the authors assume no liability for the individual effect of the product.

Status: June 2025

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🔗 **www.makrolife-biotech.com/disclaimer**