

# Novel Nutraceutical Combination Restores Hepatic Deiodinase Activity Under Inflammatory Conditions: Evidence from an In Vitro Model

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## Abstract

Thyroid hormones are key regulators of energy metabolism, involved in a systemic conversion of T<sub>4</sub> to T<sub>3</sub>. This reaction is catalyzed by selenoprotein iodothyronine deiodinase type 1 (DIO1). DIO1 protein is overexpressed in the liver and kidney tissue and it is regulated by nutritional factor, cytokines and oxidative stress. The present study aimed to explore, in an in vitro model of LPS-induced inflammation, the effects of a combination of selected nutrients—vitamin A, selenium, taurine, oleic acid, and resveratrol—on the expression and activity of DIO1 (Type 1 Iodothyronine Deiodinase) in Hepatoma cancer cells (HEPG2). The objective was to determine whether these bioactive compounds could mitigate inflammation-induced suppression of peripheral thyroid hormone activation, thereby supporting a more favorable redox and metabolic profile. To summarize, simultaneous treatment with taurine, resveratrol, oleic acid and vitamin A not only prevents DIO-1 suppression, but also positively regulates its levels of expression offering a promising avenue for maintaining endocrine and metabolic health in frail, elderly, or oncologic patients and potentially across a broader spectrum of chronic inflammatory conditions.

**Keywords:** type 1 deiodinase; DIO-1 modulation; nutrients; taurine; resveratrol; retinol; oleic acid; LPS

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## 1. Introduction

Thyroid hormones are key regulators of energy metabolism, redox homeostasis, and protein turnover in multiple tissues. Their biological activity largely depends on the local and systemic conversion of thyroxine (T<sub>4</sub>) to triiodothyronine (T<sub>3</sub>), a reaction catalyzed by the selenoprotein iodothyronine deiodinase type 1 (DIO1). This enzyme is highly expressed in the liver and kidney and plays a central role in maintaining circulating T<sub>3</sub> concentrations and in modulating metabolic adaptation to stress [1,2].

DIO1 activity is tightly regulated by nutritional factors, cytokines, and oxidative stress. Several in-vitro and in-vivo studies have shown that exposure to lipopolysaccharide (LPS) or inflammatory mediators such as interleukin-6 and tumor necrosis factor- $\alpha$  suppresses DIO1 gene expression, leading to a decrease in peripheral T<sub>3</sub> production [3–5]. This mechanism is considered an adaptive metabolic response aimed at reducing energy expenditure during acute stress; however, when persistent, it may contribute to tissue dysfunction, loss of muscle mass, and adverse clinical outcomes [6,7].

Recent evidence highlights that the ratio between free triiodothyronine (fT<sub>3</sub>) and free thyroxine (fT<sub>4</sub>) represents a sensitive biomarker of peripheral deiodination efficiency and overall metabolic resilience. A low fT<sub>3</sub>/fT<sub>4</sub> ratio has been associated with systemic inflammation [8], frailty [9,10], sarcopenia [11], malnutrition [12], and unfavorable clinical outcomes in both medical and oncologic

settings [13–18]. Collectively, these data suggest that the preservation of adequate T4-to-T3 conversion capacity may reflect a fundamental determinant of metabolic health, linking nutritional status, inflammation, and endocrine adaptation.

Inflammation-induced DIO1 downregulation is mediated by the activation of NF- $\kappa$ B-dependent pathways and by the accumulation of reactive oxygen and nitrogen species that alter selenoprotein synthesis and function [19]. In experimental models, the suppression of DIO1 by LPS or cytokines can be attenuated by antioxidants or anti-inflammatory agents [20], supporting the hypothesis that nutritional and redox status modulate thyroid hormone metabolism at the cellular level. Selenium, a structural component of DIO1, is indispensable for its catalytic activity, while other nutrients such as retinoids, taurine, monounsaturated fatty acids, and polyphenols (e.g., resveratrol) exert complementary actions on oxidative balance, mitochondrial biogenesis, and cytokine signaling [21].

From a mechanistic perspective, these compounds may help preserve DIO1 expression and maintain physiological T3 availability in conditions of inflammatory stress. The interplay between nutrient signaling and thyroid hormone metabolism therefore represents a promising area for nutritional intervention, particularly in populations at risk of chronic inflammation, catabolic diseases, or age-related functional decline.

Based on these considerations, the present study aimed to explore, in an in-vitro model of LPS-induced inflammation, the effects of a combination of selected nutrients—vitamin A, selenium, taurine, oleic acid, and resveratrol—on the expression and activity of DIO1. The objective was to determine whether these bioactive compounds could mitigate inflammation-induced suppression of peripheral thyroid hormone activation, thereby supporting a more favorable redox and metabolic profile.

## 2. Material and Methods

### 2.1. Cell Lines

FB789, a human normal fibroblast and Hepatoma cancer (HEPG2) cell lines were used to assess both the cytotoxicity and *DIO1* gene modulation after nutraceutical compounds treatment.

FB789 and HEPG2 cells were cultured in according to Filippi et al. 2008 and Berni A et al.2012, respectively [22,23].

### 2.2. Evaluation of Cell Viability After Nutraceuticals and Lipopolysaccharide (LPS)

Cells were seeded 18h before treatment in a concentration of  $3 \times 10^3$  for each experimental point in a 96 well/plate.

Taurine and Retinol were used in a range of 2.5 to 100  $\mu$ M, Resveratrol was used in a range of 2.5 to 200 $\mu$ M, while Oleic Acid was used at 100  $\mu$ M. LPS (1 $\mu$ g/ml) was added 1 hr before nutraceutical compounds.

Cell viability was evaluated by measuring the mitochondrial-dependent conversion of the yellow tetrazolium salt MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide] to a purple formazan crystal by metabolically active cells. The experiments were conducted in triplicate in according to Botta et al 2019 [24].

### 2.3. Gene Expression Analyses After Nutraceuticals and LPS Treatment

$1 \times 10^5$  were seeded in a 60 mm dishes 18 hr before treatment. RNA was isolated using NucleoSpin RNA kit (Macherey-Nagel, GmbH & CO., Dueren, Germany) according to the manufacturer's instructions. RNA was diluted by adding 40  $\mu$ L of DEPC water and its integrity was checked on a denaturing 1% agarose gel. RNA concentration was measured with Qubit Fluorometer 2.0 cDNA synthesis, which was performed with 1  $\mu$ g of RNA for each sample by using the First Strand cDNA Synthesis kit (Thermo Fisher Scientific, Waltham, MA, USA). Comparative qRT-PCR was carried out with GoTaq qPCR SYBR green master mix (Promega, Madison, WI, USA), using Mx3005P Real-Time

PCR system (Agilent, Santa Clara, CA, USA). Results were normalized to  $\beta$ -Actin. Primer sequences are available on request.

#### 2.4. Protein Expression Analysis by Western Blot

Proteins from the different cell lines were fractionated by SDS-PAGE and transferred to Nitrocellulose membrane (Biorad Laboratories, Hercules, CA, USA), according to Botta et al. 2019 [26]. After blotting, the membrane was incubated with appropriate primary and secondary antibodies. Primary antibodies used were against DIO-1 (Immunological Science) and  $\beta$ -actin (Santa Cruz Biotechnology, Santa Cruz, CA, USA), while secondary antibodies were HRP conjugated.

### 3. Results

#### 3.1. Cytotoxicity Analysis After Nutraceuticals Treatment

Cell viability was measured as a percentage relative to the untreated control (Medium). Figure 1 presents the effects of different nutraceutical concentrations on the viability of two cell lines, FB789 and HEPG2.

The graph (panel A) shows the effect of increasing concentrations of Taurine (2.5, 5, 10, 25, 50, and 100  $\mu$ M) on the cell viability of FB789 and HEPG2 cell lines, compared to untreated control (medium). Cell viability remains close to control levels for both cell lines up to 25  $\mu$ M taurine. At higher concentrations (50 and 100  $\mu$ M), a reduction in cell viability becomes evident, particularly at 100  $\mu$ M, where both FB789 and HEPG2 show a notable, but not drastic, decrease in viability. FB789 cells appear slightly more sensitive at the highest doses compared to HEPG2 (\* $p$ <0.05 and \*\* $p$ <0.01) [25–29].

Panel B shows the resveratrol concentrations tested ( $\mu$ M) were 2.5, 5, 10, 25, 100, and 200. Upon exposure to the compound: FB789 cells exhibited a dose-dependent increase in viability at lower concentrations (2.5–25  $\mu$ M), peaking at 10 (\* $p$ <0.05 and \*\* $p$ <0.01). A gradual decrease was observed at higher concentrations (100 and 200  $\mu$ M), though viability remained elevated compared to the control. HEPG2 cells showed a different profile. After initial slight increase at 2.5  $\mu$ M, viability decreased steadily with higher doses, reaching the lowest values at 200 (\* $p$ <0.05 and \*\* $p$ <0.01).

The graph (panel C) illustrates the impact of increasing concentrations of retinol (2.5, 5, 10, 25, 50, and 100  $\mu$ M) on the viability of FB789 and HEPG2 cell lines, compared to untreated controls. In both cell lines, cell viability increases moderately at low-to-intermediate doses (peaking notably at 5 and 25  $\mu$ M, more pronounced in FB789), followed by a slight reduction at the highest concentrations (50 and 100  $\mu$ M).

#### 3.2. Modulation of Both mRNA Levels and Protein Expression of DIO-1 After Nutraceutical Treatment

Based on the cytotoxicity results and dose response single compound DIO-1 inductions, we selected a single dose for each nutraceutical compound, specifically 2.5  $\mu$ M for taurine and resveratrol, 50  $\mu$ M for retinol for the modulation of DIO-1 after concurrent nutraceutical compound treatments.

The dose of oleic acid (OA) and lipopolisaccharide (LPS) was chosen on the basis of the literature and corresponds to 100  $\mu$ M and 1  $\mu$ g/ml, respectively [30,31].

The results demonstrate differential regulation of DIO-1 expression at both the mRNA and protein levels in HEPG2 cells under various treatments. At the protein level, the “Combined” treatment markedly increased DIO-1 protein expression compared to medium control, indicating a synergistic or cumulative effect of the combined factors in modulating DIO-1 abundance (## $p$ <0.01). At the mRNA level, LPS alone caused a pronounced down-regulation of DIO-1 transcript levels as showed in Figure 2. Simultaneous treatments largely prevented LPS-mediated suppression of DIO-1 mRNA, restoring or even enhancing its expression.

Panel B of Figure 2 presents data on DIO-1 protein expression in HEPG2 cells following a simultaneous treatment. The results show that the concurrent treatment significantly increases DIO-1 protein expression compared to the control.

#### 4. Discussion

This *in vitro* study demonstrates that DIO1 expression in hepatic cells is markedly downregulated in response to lipopolysaccharide (LPS)–induced inflammation. Treatment with a combination of taurine, resveratrol, retinoic acid, and oleic acid effectively restored DIO1 expression at both the gene and protein levels. Cytotoxicity assays confirmed the absence of significant toxicity in both cell lines across the tested concentration range, with cell viability remaining above 75% in all conditions [32].

We selected the concentrations of resveratrol, taurine, and retinol for DIO1 modulation assays by combining cytotoxicity data with single-compound dose–response experiments, in order to identify the most biologically effective but non-toxic range. Notably, the observed DIO1 modulation occurred at concentrations well below the cytotoxic threshold, supporting the physiological relevance of the findings. Previous *in vitro* studies used resveratrol concentrations between 0.5 and 5  $\mu\text{M}$  to achieve biological activity [33], and the mean serum concentration after a 500 mg oral dose in healthy volunteers is about 0.3  $\mu\text{M}$  [34]. Plasma retinol concentrations after 20 mg supplementation reach 1.3  $\mu\text{M}$  [35], while normal taurine plasma levels are around 40  $\mu\text{M}$ —approximately 15-fold higher than the concentration used in our experiments. For oleic acid, typical plasma concentrations range from 0.2 to 5.0 mmol/L (Abdelmagid et al., 2015), and the 100  $\mu\text{M}$  concentration applied here is comparable to postprandial levels following a MUFA-rich meal. Overall, the tested concentrations were within the same order of magnitude as those achieved in humans through dietary supplementation, ensuring translational plausibility.

At the molecular level, LPS exposure significantly reduced DIO1 transcript abundance, in line with prior evidence showing that inflammatory cytokines and oxidative stress suppress deiodinase activity in hepatic and other systems [3,19]. Individually, taurine, resveratrol, and retinoic acid increased *DIO1* mRNA relative to control, consistent with their known antioxidant and transcriptional effects on hepatic metabolism. Importantly, concurrent treatment with all four nutrients fully counteracted the LPS-induced suppression of DIO1 expression, suggesting a synergistic or complementary mechanism that stabilizes thyroid hormone activation under inflammatory stress. The partial discrepancy between mRNA and protein expression may reflect post-transcriptional regulation or differences in protein stability [2]. Mechanistically, these nutrients exert converging antioxidant and anti-inflammatory effects—taurine and oleic acid modulate oxidative tone and cytokine signaling, resveratrol enhances mitochondrial biogenesis, and retinoic acid acts via nuclear receptors—while selenium, although not directly tested, is indispensable for DIO1 catalytic activity.

These findings support the concept that inflammation-driven suppression of DIO1 contributes to impaired fT4-to-fT3 conversion, a frequent event in chronic inflammatory and catabolic states [12,36]. Persistent reduction in peripheral T3 generation correlates with frailty, sarcopenia, and poor clinical outcomes across various conditions [9–11,13–18]. The present study thus provides mechanistic insight into how specific nutrients may counteract this impairment, offering biological plausibility for nutritional strategies that sustain thyroid hormone activation and metabolic resilience.

From a practical perspective, nutritional supplements or food for special medical purposes (FSMPs) enriched with bioactive compounds such as taurine, resveratrol, vitamin A, oleic acid, and selenium could represent innovative tools to address the complex malnutrition frequently observed in older, pre-frail, and frail adults, as well as in cancer patients. In these settings, low-grade systemic inflammation, oxidative stress, and nutrient deficiencies often converge to blunt fT4-to-fT3 conversion, leading to reduced metabolic efficiency, muscle wasting, and poorer tolerance to therapy [9–12,14–18]. By combining antioxidant and anti-inflammatory nutrients capable of supporting

deiodinase activity, next-generation FSMs could provide a new nutritional strategy to preserve muscle integrity, enhance treatment tolerance, and improve outcomes in these high-risk populations.

Similar alterations in thyroid hormone activation have been described in other chronic disorders, including inflammatory bowel disease, Parkinson's disease, dialysis-dependent renal failure, rheumatoid arthritis, and anorexia nervosa, suggesting that deiodinase modulation may be a unifying nutritional target across multiple inflammatory and catabolic diseases [37–40].

A limitation of this study is the use of a single cellular model, which cannot replicate systemic thyroid hormone regulation or tissue cross-talk. Nevertheless, the consistency between these results and clinical observations supports further research into nutritional interventions designed to preserve fT4-to-fT3 conversion and metabolic homeostasis under inflammatory stress.

In conclusion, concurrent exposure to taurine, resveratrol, oleic acid, and vitamin A effectively prevented inflammation-induced DIO1 suppression. These findings reinforce the hypothesis that targeted nutritional modulation can mitigate inflammation-related impairment of fT4-to-fT3 conversion, offering a promising avenue for maintaining endocrine and metabolic health in frail, elderly, or oncologic patients and potentially across a broader spectrum of chronic inflammatory conditions.

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