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A Bio-Fortified Whole Tomato Food Supplement as Potential Dietary Tool for the Management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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Abstract

Background: Western diets, rich in refined fats and carbohydrates, are recognized as a major player in hepatic lipid accumulation in adults and youngsters, leading to the growing prevalence of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), the gate to cirrhosis and cancer. Due to the lack of efficacious therapies, antioxidant-rich dietary regimens targeting different pathologic pathways may be clinically advantageous. **Objective**: As tomatoes are a major available source of antioxidant/inflammatory nutrients, we have investigated whether a novel whole tomato-based food supplement (WTFS), possessing an effective antioxidant activity and hindering multiple metabolic pathways, can interfere with mechanisms fostering MASLD progression. **Methods:** Lipidomic and proteomic analyses were performed in the HepG2 liver human cell line treated with WTSF. Results: WTFS induces a marked reduction in triglycerides and cholesterol ester content, a decrease in the relative levels of diacylglycerols, lysophosphatidylcholine, lysophosphatidylethanolamines, phosphatidylethanolamines, and lower expression of transforming growth factor-α, tumor necrosis factor-like weak inducer of apoptosis (TWEAK), and Fms-related tyrosine kinase 3 ligand (FLT3LG), signaling relevant to MASLD progression. **Conclusions:** WTFS may represent a potential candidate for clinical trials in supplementing antioxidant-rich dietary regimens such as the healthy but hard-to-follow Mediterranean diet, the presently first-line preventive and therapeutic nutritional regimen for MASLD.

Keywords: antioxidants; functional foods; lipids; Metabolic Dysfunction-Associated Steatotic Liver Disease; tomato

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1. Introduction

Epidemiological, experimental, and clinical evidences increasingly support the protective role of antioxidants in liver diseases by regulating lipid homeostasis and inflammation [1]. Oxidative stress, generated by accumulation of free fatty acids oxidation by generating an imbalance of antioxidant defense systems, is a major key force in driving hepatic steatosis, inflammation, and scarring [2] Standing the dismetabolic origins of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) [3] and supported by the results of i*n vitro/vivo* models, functional nutrients and foods [4] capable of modulating fat metabolism and associated inflammation, are currently undergoing scrutiny since they may represent, environmentally sustainable, widely reachable at affordable costs to large populations fractions in reasonable short times [5]. In this regard, increasing attention has been focused on the polyene lycopene, potent antioxidant [6] of the carotenoid family, which also through the induction of other endogenous antioxidants decreases lipid peroxidation [7] possesses anti-inflammatory [8] and lipid-lowering properties [9] which are shared by its metabolites [10]. In this context, it should be underlined that the lycopene fats lowering activity relies on the dual mechanism of HMG-CoA reductase inhibition and downregulation of PCSK-9 mRNA synthesis [11]. Because of its hepatic accumulation [12], where active metabolites, i.e., apo-lycopenals and apo-lycopenones are generated [13], the mitigating effects of lycopene-containing foods are attractive candidates to exploit dietary tools of wide acceptance to control the development and progression of MASLD a disease of increasing incidence and prevalence [14]. To acquire the broad spectrum of its healthy biological properties, the trans isomeric form of the naturally occurring lycopene needs to be modified, metabolically [15] in the cis configuration the only biologically active isomer [6].and by the concomitant uptake of other tomato micronutrients, such other carotenoid [16] and nutrients generated by the cooking of the berry [17]. Indeed, the consumption of whole fruits has been shown to result in dose-dependant healthier effects than single lycopene supplementation in animal [18] and human studies [19]. Therefore, the unique combination of antioxidant and anti-inflammatory nutrients [20] with converging biological activities of the berry [21] which is the primary dietary source of antioxidants, [22] advocates the choice of whole cooked tomato consumption as a functional food for equitable and sustainable healthy diets [21]. Along this line of investigation, a novel whole tomato (98%) food supplement (WTFS) [23], enriched (2%) with olive waste water in the form of an additives/excipients-free powder [24], has been recently described which is characterized by a multi-nutrients composition [25] capable of interfering with metabolic pathways sustaining oxidative stress, chronic inflammation and neoplastic transformation [26] and with the potential of modulating gut dysbiosis, a relevant contributor to fat induced hepatitis [27–29].

To further establish whether this improved functional food is endowed with biological activities relevant to the natural history of MASLD thus a candidate for clinical studies aimed at mitigating lipids liver accumulation, we have performed a lipidomic and proteomic analysis on HepG2 human liver cells exposed to the WTFS.

2. Materials and Methods

2.1. Cell Cultures

The HepG2 human hepatoblastoma cells, a reference target to study liver function including lipid metabolism and hepatotoxicity [30,31] obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA), were plated at 1×10^6 in T-75 cell culture flasks in minimum Essential Media supplemented with 10% heat-inactivated fetal calf serum containing 2 mmol/L L-glutamine, 100 IU/ml penicillin, 100 mg/ml streptomycin, 2.2 mg/L sodium bicarbonate, and 1 mmol/L sodium pyruvate, under a humidified atmosphere of 95% air/5% CO_2 at 37° C, as previously described [32]. WTSF preparation in dimethyl sulfoxide (DMSO) and cells treatment followed the conditions described by Rubini et al. [33], HepG2 cells cultured with only DMSO were used as control (CTRL). Cells were collected as a dry pellet following washing with phosphate-buffered saline and

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subsequent counting. A precipitation solvent composed of water-saturated butanol and 20 mM ammonium acetate in methanol (in a 1:1 volume ratio) was added to achieve a concentration of 3,500 cells/µL. The solution was then sonicated and centrifuged for 5 minutes at 4,500 rpm at room temperature. The supernatant was then frozen at -80° C for later lipidomic analysis.

2.2. Lipidomic Analysis

Lipidomic analysis was conducted using a 5500 QTRAP LC-MS/MS system (AB Sciex, Framingham, MA, USA) equipped with an electrospray ionization source and coupled with an ExionLC HPLC system (AB Sciex). Samples were injected onto an Xbridge BEH C18 precolumn (3.5 µm, Waters Corporation, Milford, MA, USA) and subsequently separated using the Xbridge C18 (3.5 µm, 2.1 × 100 mm, Waters Corporation) analytical column. The injection volume was 1 µL for positive ion mode and 5 µL for negative ion mode. The column temperature was set at 50 °C, and elution was conducted at a flow rate of 0.400 mL/min by incrementally increasing the concentration of organic solvent B from 0% to 97% over 50 minutes. The solvent A was composed of 10 mM ammonium formate in a mixture of water, acetonitrile, and 2-propanol (50:30:20 v/v/v), while solvent B contained 10 mM ammonium formate in a mixture of water, acetonitrile, and 2-propanol (1:9:90 v/v/v). All samples were analyzed in triplicate in both positive and negative modes.

The multiple reaction monitoring analysis involved the detection of 333 transitions in positive ion mode, encompassing various lipid classes, including carnitines, cholesterol esters (CE), ceramides (Cer-d), cholesterol, diacylglycerols (DG), glucosylceramides (GCer), lactosylceramides (LacCer), lysophosphatidylserines (LPS), lysophosphatidylcholine (LysoPC), lysophosphatidylethanolamines (LysoPE), phosphatidylcholines (PC), phosphatidylethanolamines (PE), phosphatidylserines (PS), sphingomyelins (SM), and triacylglycerols (TG). In negative ion mode, 93 transitions were monitored, which included bile acids (BA), fatty acids, cardiolipins (CL), lysophosphatidic acids (LPA), lysophosphatidylinositol acids (LPI), phosphatidic acids (PA), phosphatidylinositol acids (PI), phosphatidylglycerol acids (PG), and sulfatides (Sul-d).

Data processing was conducted using MultiQuant software version 3.0.2 (AB Sciex), and statistical analysis was performed utilizing the R software package (version 4.3.2).

2.3. Olink Analysis

The analysis was conducted by using the Proximity Extension Assay Olink Target 48 Cytokine panel (Olink Proteomics, Uppsala, Sweden), providing absolute (pg/ml) measurements for the selected cytokines. A comprehensive list of the 45 analyzed proteins, along with their respective acronyms and UniProt codes, is provided in Supplemental Table S1. This approach uses specific antibody probes marked with dual oligonucleotides that bind to target proteins. Quantitative DNA detection follows, where the oligonucleotide sequence is amplified, via microfluidic real-time PCR. Quality control procedures and normalization were performed on cycle threshold data from both internal and external controls.

2.4. Gene Ontology Analysis

Protein-protein interaction analysis and functional enrichment for Gene Ontology (GO) categories were performed using the STRING database v12.0 (https://string-db.org/). A set of input proteins was analyzed with the interaction confidence score set to default (medium confidence ≥0.4), and the maximum number of interactors was limited to no more than 5 to ensure a functionally relevant and interpretable network. Functional enrichment was evaluated under the GO Molecular Function category. The significance of enrichment was assessed using STRING's built-in statistical framework, based on a modified Fisher's exact test corrected for multiple testing (false discovery rate).

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3. Results

Targeted lipidomic analysis in positive ion mode was performed to assess the impact of WTFS treatment on the lipid composition of HepG2 cells. **Figure** 1 displays a bubble plot summarizing fold changes in lipid species abundance. Each bubble represents an individual lipid species, colored by lipid class. The *x*-axis denotes the fold change, while bubble size is proportional to statistical significance, represented as 1 minus the p-value. This visualization allows simultaneous assessment of both the magnitude and significance of lipid alterations across different classes.

As illustrated in Figure 1, WTFS exposure resulted in a significant reduction in the relative abundance of multiple lipid classes compared to CTRL. Specifically, the levels of CE, DG, LysoPC, LysoPE, PE, and TG were decreased. Among these, TG and CE exhibited the most pronounced reduction, with an average fold change of 0.71 and 0.56, respectively. Conversely, a significant increase was observed in the levels of GCer, which displayed a mean fold change of 1.40. No appreciable alterations were detected in the abundance of carnitine, PC, or SM, indicating a selective remodeling of the lipid profile upon WTFS treatment.

Figure 1. The bubble plot reports various lipid classes examined through targeted lipidomic analysis in positive ion mode. A notable reduction in the relative levels of cholesterol esters (CE), diacylglycerols (DG), lysophosphatidylcholine (LysoPC), lysophosphatidylethanolamine (LysoPE), and triacylglycerols (TG) was observed in cells treated with WTFS. A significant decrease was recorded in the levels of all TG and CE in the treated cells. The size of the bubbles corresponds to the significance of the fold changes (WTFS vs. CTRL), reported as 1 minus the p-values. The other lipid classes analyzed include glucosylceramides (GCer), phosphatidylcholines (PC), phosphatidylethanolamine (PE), and sphingomyelins (SM).

In negative ion mode, treated cells with WTFS showed a decrease in the levels of fatty acids and LPI compared to CTRL (Figure 2). Conversely, only CL and PG exhibited slight increases in the WTFS-treated cells. There were no measurable changes in the relative abundances of BA, PA, LPA, PI, and Sul-d.

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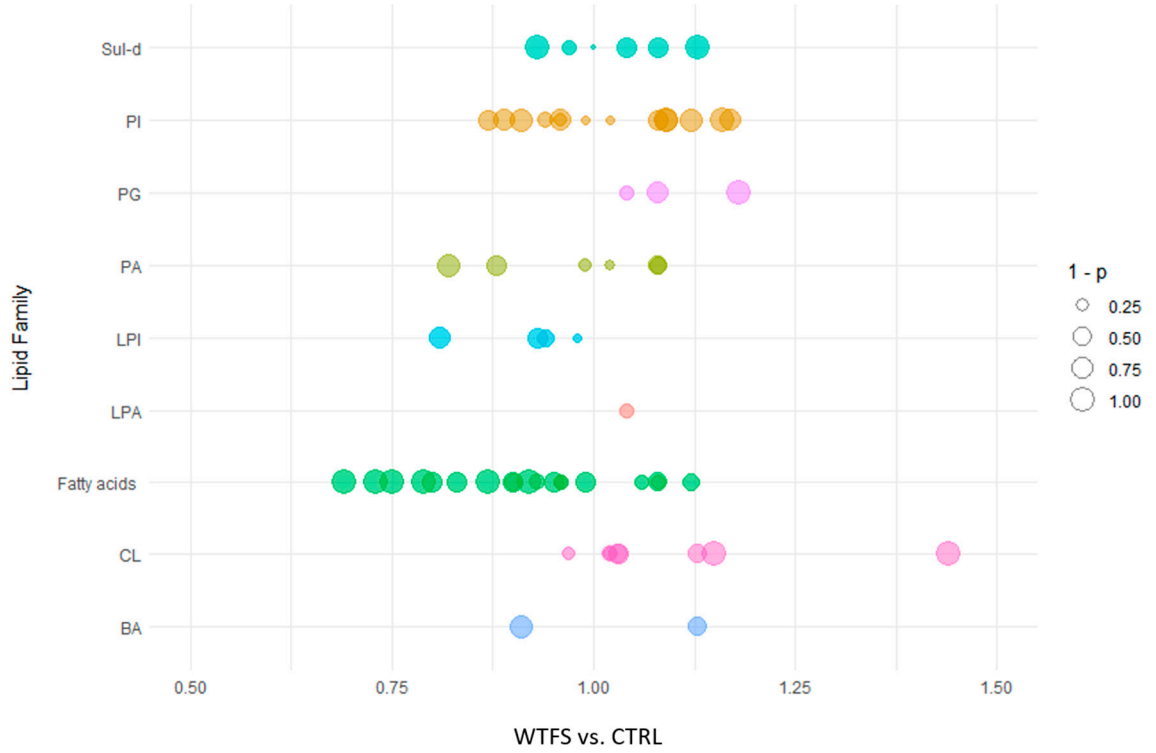

Figure 2. The bubble plot represents different lipid classes measured by targeted lipidomic analysis in negative ion mode. The size of the bubbles corresponds to the significance of the fold changes (WTFS vs. CTRL), reported as 1 minus the p-values. The lipid classes analyzed include bile acids (BA), cardiolipins (CL), lysophosphatidic acids (LPA), lysophosphatidylinositol acids (LPI), phosphatidic acids (PA), phosphatidylinositol acids (PI), phosphatidylglycerol acids (PG), and sulfatides (Sul-d).

Since cytokines and growth factors, known mediators of liver function, can contribute to the onset and progression of various liver diseases [34], we investigated the cytokines' modulatory activity on HepG2 cells treated with WTFS.

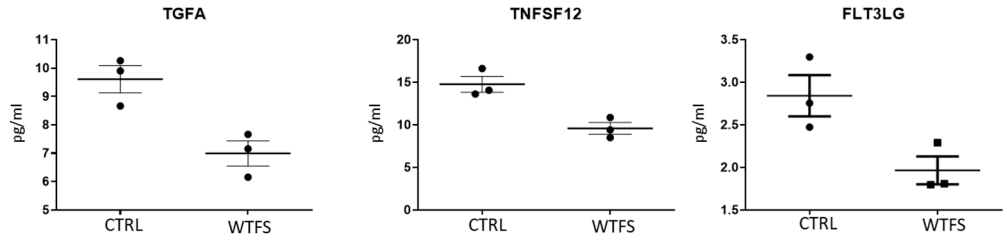

Figure 3. Targeted proteomic analysis was conducted on HepG2 cells treated with WTFS, utilizing the Olink Target 48 cytokine assay.

According to the proteomic analysis (Figure 3), three molecules out of the 45 proteins analyzed (see Table S1) exhibited significant downregulation by the WTFS: a) TGFA, the epidermal growth factor (EGF) family member known as transforming growth factor-α (TGF-α), which plays a crucial role in modulating cell growth, differentiation, migration, and survival [35]; and b) TNFSF12, also referred to as TNF-related weak inducer of apoptosis (TWEAK), a multifunctional cytokine with a diverse array of biological activities [36], which also serves as a ligand for the fibroblast growth factor-inducible 14 (Fn14) receptor; c) FLT3LG, or Fms-related tyrosine kinase 3 ligand, that by binding the Flt3/CD135 receptor, induces dimerization and autophosphorylation of the receptor, and activates multiple downstream signaling pathways, including phosphatidylinositol-3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR), JAK/STAT pathways, and

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RAS/RAF/extracellular signal-regulated kinase (ERK). These pathways are involved in the survival and proliferation of various cell lineages, including hepatocytes [34].

The STRING network analysis, which identified functionally enriched molecular functions among the input proteins (max 5 interactors) showed two enriched GO Molecular Function terms: "cytokine activity" (GO: 0005125) indicating significant involvement of several nodes in cytokine-mediated signaling and "receptor ligand activity "(GO: 0048018), representing proteins with potential to act as ligands for receptor-mediated processes (Figure 4).

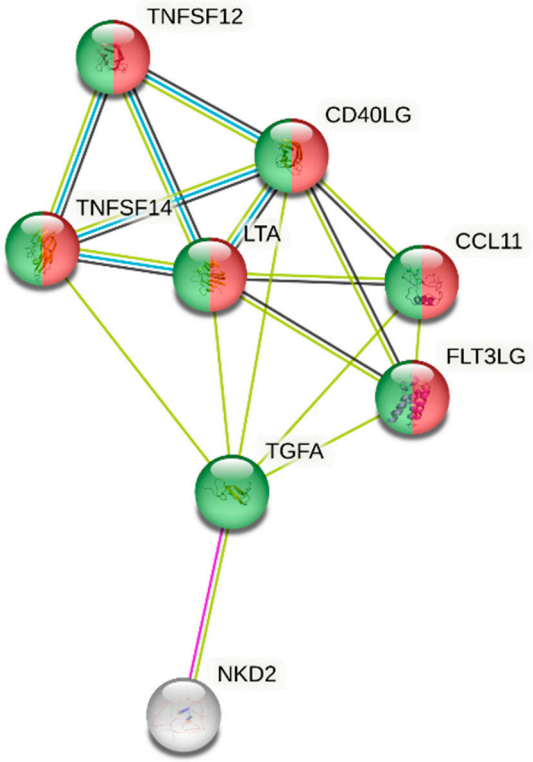

Figure 4. Protein-protein interaction network generated using STRING v12.0. Nodes represent proteins, while edges indicate predicted functional associations. Enriched GO Molecular Function terms are annotated with color highlights: red indicates "cytokine activity" and green indicates "receptor ligand activity". The analysis was performed with a confidence threshold of 0.4 and a maximum of 5 interactors to maintain interpretability. Only significantly enriched categories are shown.

4. Discussion

MASLD is becoming globally a highly prevalent disease in the general population [37], especially in those patients affected by type 2 diabetes mellitus and obesity [38]. Of relevance, MASLD is also the most frequent pediatric liver disease [39,40]. Although established therapeutic regimens are currently unavailable [41], MASLD may be amenable to preventive and therapeutic interventions through the adherence to international guidelines recommending a lifestyle-based approach, relying on healthy diets [42]. This strategy can by variable extent modulate hepatic steatosis and counteract liver damage, preventing and delaying the evolution of MASLD to cirrhosis and cancer [43]. In this context, phytochemical and natural compounds are undergoing an in-depth investigation [44], among which carotenoids are of major interests [45]. Multidisciplinary evidences strongly indicate that lycopene [8], a potent and largely available dietary antioxidant/anti-inflammatory nutrient, may be beneficial in the management of MASLD as it has been proven to be efficacious in the case of alcoholic liver hepatitis [45].

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On the other hand, evidence correlating either the single carotene or lycopene-containing foods, has so far failed to provide conclusive evidence of its protective efficacy on MASLD [46]. This limitation is likely to be multifactorial, as assignable to the wide range of individual variability in the metabolism of lycopene into its bioavailable cis configuration [15] and the need to resort to high consumption of lycopene-containing foods lacking defined nutrients profiles [47], often associated with high calories uptake. It should be underlined that lycopene with a daily requirement of 0.5 mg/kg and a plasma elimination half-life of 5 days [48,49], taken in the range of 5 to 7 mg/day [50] is mainly deriving from lycopene/E 160d red food coloring agent intake [49]. To overcome these limitations, an improved powder formulation [24] of this functional food has been developed using whole tomato fruits, not completely freed from peels and seeds [51]. This WTFS, produced by calibrated heating of the berry and spray drying [26] is biofortified with olive wastewater antioxidants and by the presence of Fru-His Amadori's chelators [52] displaying an overall superior composition compared to available tomato commodities. WTFS has been shown to interfere with metabolic pathways mediating oxidative stress and inflammation, as demonstrated by in vitro, [33] animal models [53], and human conditions of known susceptibility to tomato micronutrients benefits [25].

The information gathered in this study utilizing a transformed hepatocytes cell line [54] which retains the lipid metabolism capacity of the normal counterpart [31] may be informative to explore strategies to contrast liver lipid storage. Indeed, although the progression of MASLD is the result of a stepwise engagement of other parenchymal, i.e Kuppfer cells [55], stellate cells [56], and non-parenchymal, i.e., immune cells [57], the driver of this progressive disease stems from the triglycerides accumulation [58] and lipogenesis [59] in hepatocytes overrunning their dismissal capacity through fatty acid oxidation and/or higher production rates of very-low-density lipoprotein particles [60].

Although the ability of WTFS single components to downmodulate the lipidomic asset of HepG2 cells cannot be fully appreciated, a converging ability of lycopene and other WTFS components ie tocopherol, tyrosol, hydroxytyrosol, oleopeurina, the inhibition of STAT-3 [61], and AhR receptors activation [62], can be hypothesized [33].

Considering that WTFS has been shown to interfere with a several cell signaling, i.e., RTK receptor activation, nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases (MAPK), upregulating the recruiting of inflammatory cells and inhibiting JAK/STAT kinases modulating inflammatory genes [33], the proteomic analysis also identified three major targets of WTFS in HepG2 cells, which, by variably activating different signaling, may foster the progression of MASLD. Indeed, a) TGF-α, by engaging the EGF receptor, triggers multiple downstream signaling, i.e., RTK, PI3K, ERK, and mTOR, which are relevant to liver regeneration [63] thus being a target of WTFS complex of micronutrients. In addition, TGF-α has been identified as an independent indicator of substantial liver fibrosis [64]. TWEAK, a mitogen for liver progenitor cells [65], while undetectable in normal liver, it is significantly upregulated in patients with fatty liver, thus offering a potential therapeutic target [66], also in view that lowering its in vivo signaling may decrease levels of inflammation [36] and unbalanced signaling may lead to altered tissue architecture [67]. Modelling of ligand and receptor interactions at multi cellular level [68] and integrative single-cell and spatial transcriptomic analyses have identified TNFRSF12A [69] as a relevant actor in supporting fibrinogenesis in liver pathology, thus a potential therapeutic target [70].

Activation of FLT3LG, which through binding to the receptor Flt3/CD135, causes dimerization and autophosphorylation of the receptor with activation of iPI3K/Akt/mTOR, JAK/STAT, and RAS/RAF/ERK pathways [71], concurs to fibrosis through epithelial mesenchymal transition [72].

In this regard, WTFS contains a complex of anti fibrogenic nutrients (lycopene, quercetin, narigenin, verbascoside) which can modulate epithelial-mesenchymal transition [73] and reduce platelets aggregation [74] more recently recognized as a relevant co-factor in liver fibrosis [75].

Our STRING network analysis revealed significant functional enrichment in key molecular functions among the input proteins, notably "cytokine activity" and "receptor ligand activity". The

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enrichment of cytokine activity, as evidenced by the clustering of multiple nodes, suggests a prominent role for cytokine-mediated signaling pathways in the biological context under investigation. This aligns with the known involvement of cytokines in modulating inflammatory responses and cellular communication, particularly in pathological states such as immune activation or tissue remodeling. Moreover, the identification of receptor-ligand activity underscores the functional relevance of proteins capable of engaging receptor-mediated mechanisms, which are critical for transducing extracellular signals into specific cellular responses. Together, these enriched terms point toward a functional network characterized by intercellular communication and signal transduction, offering mechanistic insights into the observed phenotypic effects and highlighting potential targets for further experimental validation.

A constant dietary supplementation with WTFS containing a complex of highly bioactive nutrients which share biological activities with lycopene may have in vivo healthy effects that go beyond those produced on hepatocytes since it can modulate high-density lipoprotein [76], and multiple signaling relevant to progression of MASLD because upregulated in variety of cell types contributing to inflammation, angiogenesis, and fibrosis.

It should be noted that WTFS has been shown to interfere with the signaling of some cytokines and chemokines in animal models [53] and to inhibit STAT-3 activation involved in non-alcoholic fatty liver disease progression [77]. Furthermore, the WTFS content of highly bioavailable cis lycopene may be advantageous in patients with MASLD whose liver has impaired ability to generate lycopene active metabolites (i.e., apo-lycopenals and apo-lycopenones [13]. It should be also underlined that an array of lycopene and tomato-based supplements of undefined composition have been shown to be of clinical usefulness in the management of fatty liver associated disease in animals [78] and humans [79–81]. Since available murine models mimicking MASLD do not mirror closely the human condition [82], WTFS at its stage of development, can be regarded as an advanced nutritional candidate for human interventional studies to critically establish the potential costs/benefits [25] of this biofortified side-effects free functional food in the management of MASLD.

These studies can be aimed at improving available therapeutic regimens of not yet optimal performance [83] or still ongoing long-term assessment [84].

From the immediate translational point of view [85], WTFS appears an “ad hoc” supplement to complementing the Mediterranean diet, highly recommended for the prevention/treatment of non-alcoholic fatty liver disease [86–88], but now recognized as hard to follow [89], thus hampering its wide compliance and deriving benefits by large population fractions [90]. These will include individuals with glucose intolerance [91], in whom MASLD is often co-existing [92] but refrain from consuming high-calorie tomato-seasoned dishes, the main source of adequate amounts of bioavailable antioxidants carotenoids whose deficiency has been described in fatty liver [93].

Supplementary Materials. Table S1: List of cytokines analyzed by Olink Proteomics.

Author Contributions: Conceptualization, P.G.N.; Methodology, P.G.N. and E.G.; Validation, P.G.N. and C.B.; Formal Analysis, C.B.; Investigation, P.G.N. and E.G.; Data Curation, E.G. and C.B.; Writing—Original Draft Preparation, P.G.N. and L.I.; Writing—Review & Editing, P.G.N., L.I., M.P., A.S. and E.G.

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Conflicts of Interest: P.G.N. is principal research investigator of Janus Pharma Srl., Rome, Italy. M.P. is co-inventor of Euro patent 3 052 113 B1. The other authors declare no conflicts of interest.

Abbreviations

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The following abbreviations are used in this manuscript:

CTRL	control
DMSO	dimethyl sulfoxide
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease
WTFS	whole tomato-based food supplement

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