ICU Investigación, Ciencia y Universidad ISSN 2525-1783

http://revistas.umaza.edu.ar/index.php/icu/index | Número Temático IV: Desarrollo Sostenible | Año 2026 / Vol 10 - Nº 15

Primer puesto Área Salud y Bienestar

Bioactive compounds from grape pomace contribute to the attenuation of metabolic complications associated with increased adiposity

Compuestos bioactivos del orujo de uva contribuyen a la atenuación de las complicaciones metabólicas asociadas con el aumento de la adiposidad

Muscia Saez, María Victoria[1,2]; Perdicaro, Diahann Jeannette[1,2]; Vazquez Prieto, Marcela Alejandra[1,2]

[1] CONICET-IMBECU; Argentina
[2] Universidad Nacional de Cuyo. Facultad de Ciencias Médicas. Área de Fisiopatología; Argentina

Correo de correspondencia: victoria.muscia@gmail.com

Recepción: 13/11/2025
Aceptación: 13/01/2026
Publicación: 03/03/2026

Palabras clave: polifenoles; obesidad; enfermedad hepática esteatósica asociada a disfunción metabólica; permeabilidad intestinal; economía circular

Keywords: *polyphenols; obesity; metabolic dysfunction-associated steatotic liver disease (MASLD); intestinal permeability; circular economy*

DOI: https://doi.org/10.59872/icuv10i15.593

Resumen

La obesidad es una enfermedad crónica caracterizada por un exceso de adiposidad y frecuentemente acompañada de resistencia a la insulina, dislipidemia, diabetes tipo 2, inflamación sistémica de bajo grado y enfermedad hepática esteatósica asociada a disfunción metabólica (MASLD). Las dietas ricas en grasas (HFD) exacerban estas alteraciones al deteriorar la integridad de la barrera intestinal, aumentar la permeabilidad y promover endotoxemia metabólica, lo que impulsa la inflamación hepática a través de la señalización LPS-TLR4.

En este contexto, la valorización del orujo de uva —principal subproducto de la vinificación— en un extracto rico en polifenoles (GPE) representa una estrategia sostenible que vincula la promoción de la salud con los principios de la economía circular. Evaluamos si la suplementación dietaria con GPE (Malbec; 300 mg/kg/día) mitiga las alteraciones metabólicas inducidas por HFD en ratones macho C57BL/6 alimentados durante 13 semanas. Los animales (n = 9/grupo) recibieron una de cuatro dietas: control (C), control + GPE (C+GPE), dieta alta en grasas (~60 % de las kcal provenientes de grasa; HF) o HF + GPE. Las variables evaluadas incluyeron peso corporal y adiposidad, glucemia e insulinemia en ayunas (HOMA-IR), lípidos plasmáticos y ALT, triglicéridos hepáticos, LPS plasmático, marcadores hepáticos inflamatorios/oxidativos (TLR4, NF-κB) y proteínas de uniones estrechas colónicas (ocludina, claudina-1, ZO-1).

La HFD indujo obesidad, resistencia a la insulina, dislipidemia, aumento de triglicéridos hepáticos y ALT, elevación del LPS plasmático, activación de la señalización hepática TLR4/NF-κB y disrupción de las uniones estrechas intestinales. La suplementación con GPE redujo la ganancia de peso y la adiposidad, mejoró la homeostasis glucémico-insulinémica, disminuyó los triglicéridos y el LPS plasmáticos, atenuó la activación de NF-κB y los marcadores hepáticos proinflamatorios/oxidativos, y restauró la expresión de proteínas de las uniones estrechas intestinales.

En conjunto, el GPE protegió frente a las complicaciones metabólicas y el daño hepático inducidos por HFD, probablemente mediante la modulación del eje intestino-hígado. Además de sus beneficios biomédicos, la reutilización del orujo de uva como ingrediente funcional para la salud respalda la innovación agroalimentaria sostenible y las iniciativas de economía circular.

Abstract

Obesity is a chronic disease characterized by excessive adiposity and frequently accompanied by insulin resistance, dyslipidemia, type 2 diabetes, low-grade systemic inflammation, and metabolic dysfunction-associated steatotic liver disease (MASLD). High-fat diets (HFD) exacerbate these disturbances by impairing intestinal barrier integrity, increasing permeability, and promoting metabolic endotoxemia that drives hepatic inflammation through LPS-TLR4 signaling.

Cómo citar: Muscia, V., Perdicaro, D. J., & Vazquez Prieto, M. A. Bioactive compounds from grape pomace contribute to the attenuation of metabolic complications associated with increased adiposity. Compuestos bioactivos del orujo de uva contribuyen a la atenuación de las complicaciones metabólicas asociadas con el aumento de la adiposidad. Investigación Ciencia Y Universidad, 10(15), 11–15. Recuperado a partir de https://revistas.umaza.edu.ar/icu/article/view/593

In this context, the valorization of grape pomace—the main by-product of winemaking—into a polyphenol-rich extract (GPE) represents a sustainable strategy that links health promotion with circular-economy principles. We evaluated whether dietary GPE (Malbec; 300 mg/kg/day) mitigates HFD-induced metabolic disturbances in male C57BL/6 mice fed for 13 weeks. Animals (n = 9/group) received one of four diets: control (C), control + GPE (C+GPE), high-fat diet (~60% kcal from fat; HF), or HF + GPE. Measured outcomes included body weight and adiposity, fasting glycemia and insulinemia (HOMA-IR), plasma lipids and ALT, hepatic triglycerides, plasma LPS, hepatic inflammatory/oxidative markers (TLR4, NF-κB), and colonic tight-junction proteins (occludin, claudin-1, ZO-1).

HFD induced obesity, insulin resistance, dyslipidemia, elevated hepatic triglycerides and ALT, increased plasma LPS, activation of hepatic TLR4/NF-κB signaling, and disruption of intestinal tight junctions. GPE supplementation reduced body-weight gain and adiposity, improved glycemic–insulinemic homeostasis, lowered plasma triglycerides and LPS, attenuated NF-κB activation and hepatic pro-inflammatory/oxidative markers, and restored the expression of intestinal tight-junction proteins.

Overall, GPE protected against HFD-induced metabolic complications and hepatic injury, likely through modulation of the gut-liver axis. Beyond its biomedical benefits, upcycling grape pomace into functional health ingredients supports sustainable agri-food innovation and circular-economy initiatives.

Introduction

The global burden of obesity is tightly linked to insulin resistance, dyslipidemia, chronic low-grade inflammation, and MASLD (Kim *et al.*, 2021; World Health Organization, 2024). A key pathophysiological driver is compromise of the intestinal barrier, where high-fat diets (HFD) disrupt tight junctions (TJ), increase paracellular permeability, and allow lipopolysaccharide (LPS) translocation into the portal/systemic circulation. LPS activates hepatic TLR4–NF-κB signaling, exacerbating steatosis and inflammatory injury (Lu *et al.*, 2008; Soares *et al.*, 2010).

Grape pomace—skins, seeds and stems remaining after vinification—is typically discarded despite being rich in polyphenols (e.g., anthocyanins, flavonols, flavan-3-ols, phenolic acids) (Antoniolli *et al.*, 2015; Machado *et al.*, 2024). Its valorization can generate functional ingredients, reduce winery waste, and foster circular-economy practices in vitiviniculture (Jofré *et al.*, 2024; Zhu *et al.*, 2015). Polyphenols display antioxidant and anti-inflammatory actions and have been associated with improved epithelial barrier integrity and attenuation of diet-induced metabolic dysfunction(Muscia Saez *et al.*, 2025; Rodriguez Lanzi *et al.*, 2020).

This study evaluated whether dietary grape-pomace extract (GPE) from Malbec attenuates HFD-induced metabolic and hepatic alterations in mice, with emphasis on gut-liver axis mechanisms (endotoxemia, TLR4–NF-κB signaling) and intestinal junctional proteins (Cani *et al.*, 2007; Muscia Saez *et al.*, 2025). We further discuss the sustainable innovation perspective arising from upcycling grape pomace (Abenavoli *et al.*, 2021; Zhu *et al.*, 2015).

Materials and Methods

GPE source and characterization

GPE (single, previously characterized lot) was provided by IBAM–FCA UNCuyo/CONICET. Extraction followed validated solid–liquid methods (ethanol:water 50:50), concentration, lyophilization, and −20 °C storage. Total phenolics were quantified (Folin–Ciocalteu; A280), expressed as gallic-acid equivalents. HPLC-DAD profiling identified anthocyanins (e.g., malvidin-3-glucoside), flavonols (quercetin, myricetin), flavan-3-ols ((+)-catechin, (−)-epicatechin), and phenolic acids (gallic, ellagic), ensuring batch consistency for the entire study (Antoniolli *et al.*, 2015; Kammerer *et al.*, 2004).

Animals and ethical approval

Male C57BL/6 mice (8 weeks, 20–25 g) were housed under standard conditions (12:12 light–dark), with ad libitum access to food/water. Protocols were approved by the institutional animal care and use committee (CICUAL FCM-UNCuyo; approvals No. 185/2020 and 240/2023) (Muscia Saez *et al.*, 2025; Rodriguez Lanzi *et al.*, 2020).

Experimental design and diets

Mice were randomized (n=9/group) to four groups for 13 weeks:
(1) **C:** standard diet (~10% kcal from fat).
(2) **C+GPE:** standard diet + GPE 300 mg/kg/day.
(3) **HFD:** high-fat diet (~60% kcal from pork fat).
(4) **HFD+GPE:** HFD + GPE 300 mg/kg/day.

GPE was incorporated into milled diets weekly (dose adjusted to body weight/food intake) and stored at −20 °C to preserve phenolics (Muscia Saez et al., 2025; Rodriguez Lanzi *et al.*, 2020).

Outcomes

Anthropometric/metabolic: body-weight trajectory; fat depots (visceral/subcutaneous/brown); fasting glycemia and insulinemia (HOMA-IR); plasma lipids (total cholesterol, LDL, triglycerides); ALT.
Hepatic steatosis/injury: hepatic triglycerides; NAS scoring by H&E; macroscopic appearance.
Endotoxemia & barrier function: plasma LPS (ELISA); intestinal permeability by FITC-dextran; colonic TJ proteins (occludin, claudin-1, ZO-1) by Western blot.
Inflammation/oxidative stress: hepatic TLR4 and NF-κB activation (e.g., IKK/p65 phosphorylation), NOX-linked oxidative markers, 4-HNE adducts; macrophage marker F4/80; TNF-α.

Results

HFD induced obesity, insulin resistance, dyslipidemia, endotoxemia and hepatic injury

HFD caused progressive weight gain from week 5 onward and increased visceral and subcutaneous WAT, with whitening of

BAT. Fasting glycemia and insulinemia were elevated, yielding a pronounced HOMA-IR increase. The lipid profile showed higher triglycerides and LDL; ALT and hepatic triglycerides were increased, paralleling macroscopic pallor and histological steatosis with worsened NAS.

Plasma LPS was significantly higher under HFD, indicating metabolic endotoxemia, with levels 45% and 37% higher than in C and C+GPE groups, respectively. In the liver, TLR4 expression and NF-κB activation (IKK/p65 phosphorylation) increased, together with oxidative/inflammatory readouts (e.g., NOX-related markers, 4-HNE adducts; F4/80, TNF-α). In colon, TJ disruption was evident—particularly ↓claudin-1 and ↓occludin—consistent with impaired barrier integrity.

GPE attenuated weight gain and adiposity and improved glycemic-insulinemic homeostasis

In HFD+GPE, body-weight gain and WAT expansion were significantly reduced vs. HFD. GPE supplementation attenuated HFD-induced body weight gain by 36%, and final body weight was 15% lower than HFD-fed mice, with total white adipose tissue mass was reduced by 26% (visceral and subcutaneous depots), while HFD-induced BAT expansion was limited by 28%. In addition, GPE supplementation attenuated fasting glycemia by 20%, insulinemia by 63% and HOMA-IR by 61% compared with HFD-fed mice. Plasma triglycerides decreased vs. HFD, by 46%, while total cholesterol and LDL levels were lower than in HFD-fed mice (18% and 24% reduction, respectively) and shifted toward intermediate or improved values.

GPE reduced endotoxemia, hepatic steatosis/injury, and inflammatory-oxidative signaling

GPE lowered plasma LPS toward control levels and attenuated ALT and hepatic triglycerides. From a quantitative standpoint, HFD induced a significant increase in liver weight, which was prevented by GPE supplementation. This change was accompanied by a marked accumulation of hepatic triglycerides, with increases of 35% and 44% compared with C and C+GPE groups, respectively, consistent with histological evidence of steatosis. Consistently, HFD significantly increased plasma ALT levels, indicating diet-induced hepatic injury, whereas GPE supplementation prevented this increase, evidencing protection against HFD-induced liver damage.

GPE preserved intestinal barrier proteins

In colon, GPE restored TJ proteins, particularly claudin-1 and occludin, aligning with a trend to lower FITC-dextran permeability. These junctional effects are consistent with reduced LPS translocation and improved gut-liver axis homeostasis.

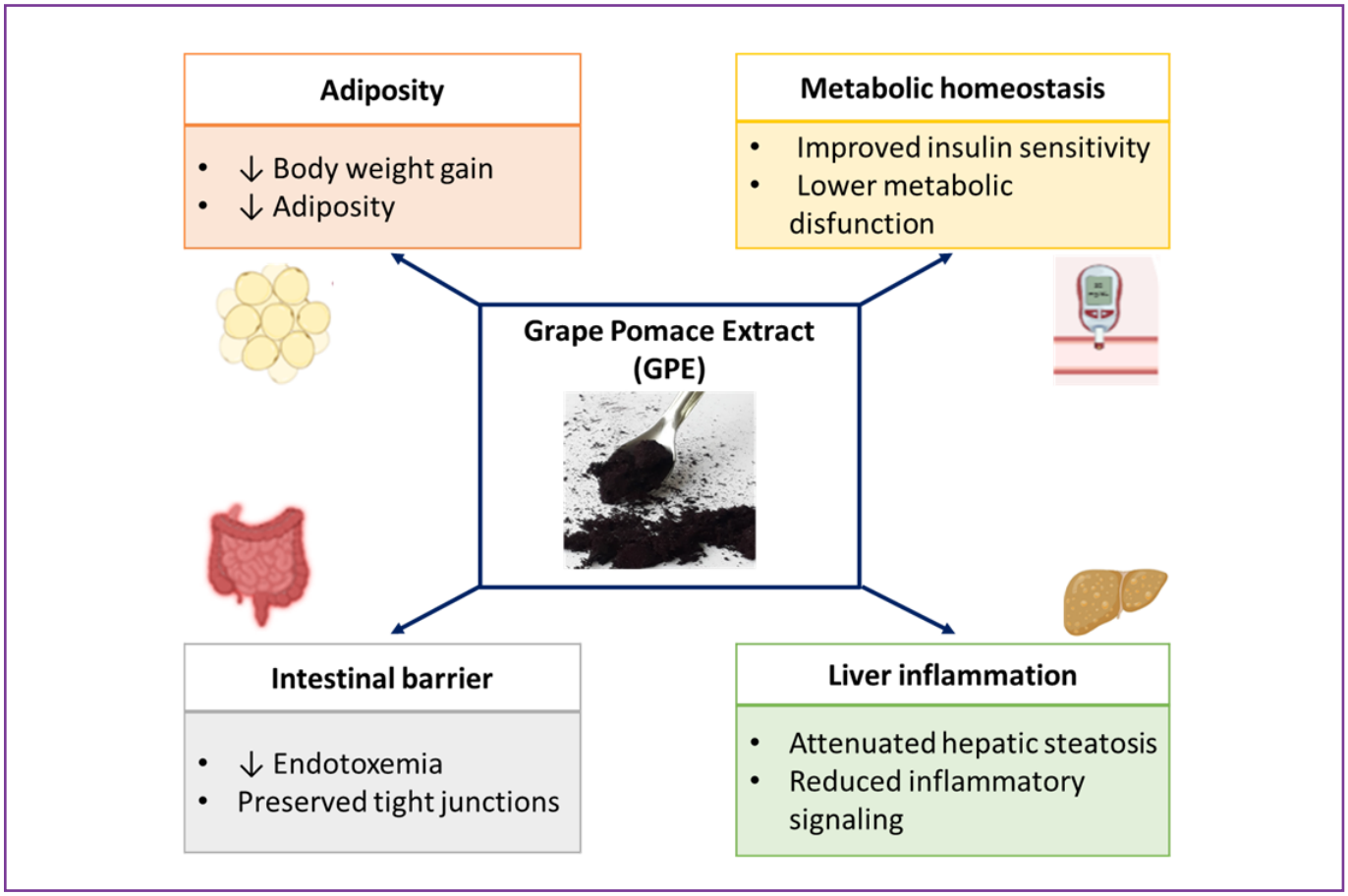

Figure 1. Graphical summary of the main effects of grape pomace extract (GPE) supplementation on adiposity, metabolic homeostasis, intestinal barrier integrity and hepatic inflammation in a high-fat diet model.

Discussion

High-fat diets promote obesity, insulin resistance, dyslipidemia and MASLD through mechanisms involving low-grade inflammation, gut barrier dysfunction and endotoxemia (Di Vincenzo et al., 2024). Consistent with these reports, our HFD model induced marked adiposity, impaired glucose–insulin homeostasis and hepatic steatosis. GPE supplementation significantly attenuated these alterations despite similar caloric intake across HFD groups, in agreement with previous studies showing metabolic benefits of grape polyphenols in diet-induced obesity (Martínez-Maqueda *et al.*, 2018; Muscia Saez *et al.*, 2025; Rodriguez Lanzi *et al.*, 2020).

A major finding of this work is that GPE reduced metabolic endotoxemia and preserved colonic tight-junction proteins, a critical early step in disrupting the gut barrier (Horowitz *et al.*, 2023). Polyphenols such as quercetin, catechins and anthocyanins have been shown to strengthen epithelial junctions and prevent LPS translocation (Cremonini *et al.*, 2017; Nunes *et al.*, 2019). Our results align with this evidence and extend it by demonstrating restoration of occludin and claudin-1 *in vivo*, together with reduced activation of intestinal inflammatory pathways (IKK, ERK), supporting a barrier-protective mechanism.

Hepatic outcomes further confirm gut–liver crosstalk. HFD enhanced TLR4/NF-κB signaling, increased NOX-dependent oxidative stress and elevated inflammatory markers—features characteristic of early MASLD (Serviddio *et al.*, 2013; Singh *et al.*, 2017). GPE markedly reduced hepatic TLR4 expression, IKK phosphorylation, macrophage markers and triglyceride accumulation, consistent with previous observations for quercetin, epicatechin and grape extracts (Iglesias et al., 2022; Muscia Saez *et al.*, 2025). These improvements suggest that mitigating endotoxemia and inflammatory signaling is a key mechanism underlying the hepatoprotective effect of GPE.

Importantly, this study provides physiological evidence supporting the valorization of grape pomace—a major by-product of winemaking—as a functional, polyphenol-rich ingredient. Its upcycling aligns with circular-economy principles and has been proposed as a sustainable nutritional strategy with health and environmental benefits (Jofré *et al.*, 2024). Our findings strengthen this concept by demonstrating that a Malbec-derived pomace extract can simultaneously improve metabolic, intestinal and hepatic disturbances in diet-induced obesity.

While translation to humans requires further study, the convergence of metabolic and mechanistic outcomes highlights GPE as a promising candidate for sustainable interventions targeting obesity-related metabolic dysfunction.

Conclusions

Grape-pomace extract attenuates HFD-induced metabolic dysfunction and hepatic damage in mice, likely by preserving intestinal tight-junctions and reducing LPS-driven TLR4–NF-κB signaling along the gut–liver axis. Upcycling grape pomace into health-promoting ingredients offers a sustainable, circular pathway that couples waste valorization with metabolic-health benefits, particularly relevant to obesity-associated complications such as MASLD.

References

Abenavoli, L., Larussa, T., Corea, A., Procopio, A. C., Boccuto, L., Dallio, M., Federico, A., & Luzza, F. (2021). Dietary Polyphenols and Non-Alcoholic Fatty Liver Disease. *Nutrients, 13*(2), 494. https://doi.org/10.3390/nu13020494

Antoniolli, A., Fontana, A. R., Piccoli, P., & Bottini, R. (2015). Characterization of polyphenols and evaluation of antioxidant capacity in grape pomace of the cv. Malbec. *Food Chemistry, 178*, 172–178. https://doi.org/10.1016/j.foodchem.2015.01.082

Cani, P. D., Amar, J., Iglesias, M. A., Poggi, M., Knauf, C., Bastelica, D., Neyrinck, A. M., Fava, F., Tuohy, K. M., Chabo, C., Waget, A., Delmée, E., Cousin, B., Sulpice, T., Chamontin, B., Ferrières, J., Tanti, J.-F., Gibson, G. R., Casteilla, L., … Burcelin, R. (2007). Metabolic Endotoxemia Initiates Obesity and Insulin Resistance. *Diabetes, 56*(7), 1761–1772. https://doi.org/10.2337/db06-1491

Cremonini, E., Mastaloudis, A., Hester, S. N., Verstraeten, S. V., Anderson, M., Wood, S. M., Waterhouse, A. L., Fraga, C. G., & Oteiza, P. I. (2017). Anthocyanins inhibit tumor necrosis alpha-induced loss of Caco-2 cell barrier integrity. *Food & Function, 8*(8), 2915–2923. https://doi.org/10.1039/C7FO00625J

Di Vincenzo, F., Del Gaudio, A., Petito, V., Lopetuso, L. R., & Scaldaferri, F. (2024). Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. *Internal and Emergency Medicine, 19*(2), 275–293. https://doi.org/10.1007/s11739-023-03374-w

Horowitz, A., Chanez-Paredes, S. D., Haest, X., & Turner, J. R. (2023). Paracellular permeability and tight junction regulation in gut health and disease. *Nature Reviews Gastroenterology & Hepatology, 20*(7), 417–432. https://doi.org/10.1038/s41575-023-00766-3

Iglesias, D. E., Cremonini, E., Hester, S. N., Wood, S. M., Bartlett, M., Fraga, C. G., & Oteiza, P. I. (2022). Cyanidin and delphinidin restore colon physiology in high fat diet-fed mice: Involvement of TLR-4 and redox-regulated signaling. *Free Radical Biology and Medicine, 188*, 71–82. https://doi.org/10.1016/j.freeradbiomed.2022.06.006

Jofré, V., Assof, M., Cantoro-Fernandez, E., Trillas, F., & Fanzone, M. (2024). Microencapsulación de compuestos fenólicos derivados de subproductos enológicos. *Investigación Ciencia y Universidad, 8*(10), 73–85. https://doi.org/10.59872/icu.v8i10.509

Kammerer, D., Claus, A., Carle, R., & Schieber, A. (2004). Polyphenol Screening of Pomace from Red and White Grape Varieties (Vitis vinifera L.) by HPLC-DAD-MS/MS. *Journal of Agricultural and Food Chemistry, 52*(14), 4360–4367. https://doi.org/10.1021/jf049613b

Kim, D., Konyn, P., Sandhu, K. K., Dennis, B. B., Cheung, A. C., & Ahmed, A. (2021). Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States. *Journal of Hepatology, 75*(6), 1284–1291. https://doi.org/10.1016/j.jhep.2021.07.035

Lu, Y.-C., Yeh, W.-C., & Ohashi, P. S. (2008). LPS/TLR4 signal transduction pathway. *Cytokine, 42*(2), 145–151. https://doi.org/10.1016/j.cyto.2008.01.006

Machado, T. O. X., Portugal, I., Kodel, H. de A. C., Droppa-Almeida, D., Dos Santos Lima, M., Fathi, F., Oliveira, M. B. P. P., de Albuquerque-Júnior, R. L. C., Dariva, C., & Souto, E. B. (2024). Therapeutic potential of grape pomace extracts: A review of scientific evidence. *Food Bioscience, 60*, 104210. https://doi.org/10.1016/j.fbio.2024.104210

Martínez-Maqueda, D., Zapatera, B., Gallego-Narbón, A., Vaquero, M. P., Saura-Calixto, F., & Pérez-Jiménez, J. (2018). A 6-week supplementation with grape pomace to subjects at cardiometabolic risk ameliorates insulin sensitivity, without affecting other metabolic syndrome markers. *Food & Function, 9*(11), 6010–6019. https://doi.org/10.1039/C8FO01323C

Muscia Saez, V., Perdicaro, D. J., Cremonini, E., Costantino, V. V., Fontana, A. R., Oteiza, P. I., & Vazquez Prieto, M. A. (2025). Grape pomace extract attenuates high fat diet-induced endotoxemia and liver steatosis in mice. *Food & Function, 16*(6), 2515–2529. https://doi.org/10.1039/D4FO06332E

Nunes, C., Freitas, V., Almeida, L., & Laranjinha, J. (2019). Red wine extract preserves tight junctions in intestinal epithelial cells under inflammatory conditions: implications for intestinal inflammation. *Food & Function, 10*(3), 1364–1374. https://doi.org/10.1039/C8FO02469C

Rodriguez Lanzi, C., Perdicaro, D. J., Gambarte Tudela, J., Muscia, V., Fontana, A. R., Oteiza, P. I., & Vazquez Prieto, M. A. (2020). Grape pomace extract supplementation activates FNDC5/irisin in muscle and promotes white adipose browning in rats fed a high-fat diet. *Food & Function, 11*(2), 1537–1546. https://doi.org/10.1039/C9FO02463H

Serviddio, G., Bellanti, F., & Vendemiale, G. (2013). Free radical biology for medicine: learning from nonalcoholic fatty liver disease. *Free Radical Biology and Medicine, 65*, 952–968. https://doi.org/10.1016/j.freeradbiomed.2013.08.174

Singh, A., Koduru, B., Carlisle, C., Akhter, H., Liu, R.-M., Schroder, K., Brandes, R. P., & Ojcius, D. M. (2017). NADPH oxidase 4 modulates hepatic responses to lipopolysaccharide mediated by Toll-like receptor-4. *Scientific Reports, 7*(1), 14346. https://doi.org/10.1038/s41598-017-14574-8

Soares, J.-B., Pimentel-Nunes, P., Roncon-Albuquerque, R., & Leite-Moreira, A. (2010). The role of lipopolysaccharide/toll-like receptor 4 signaling in chronic liver diseases. *Hepatology International, 4*(4), 659–672. https://doi.org/10.1007/s12072-010-9219-x

World Health Organization. (2024). Obesity and overweight: Key facts. Https://Www.Who.Int/News-Room/Fact-Sheets/Detail/Obesity-and-Overweight.

Zhu, F., Du, B., Zheng, L., & Li, J. (2015). Advance on the bioactivity and potential applications of dietary fibre from grape pomace. *Food Chemistry, 186*, 207–212. https://doi.org/10.1016/j.foodchem.2014.07.057