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Effects of Artemisia scoparia Supplementation on Obesity-Associated Molecular Markers in Mouse Adipose Tissue

Mehmet Veysi Cetiz[1], Ramazan Uzen [2]
[1] *Department of Medical Biochemistry, Faculty of Medicine, Harran University, Sanliurfa, 63290, Turkey*
[2] *Department of Medical Biology, Medical Faculty, Erciyes University, 38030 Kayseri, Turkey.*

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Corresponding Author:
Mehmet Veysi Cetiz

Abstract:

Obesity is accompanied by adipose tissue remodeling and immunometabolic dysregulation, creating interest in plant-derived bioactives as potential modulators of obesity-linked molecular pathways. In this study, we focused on the transcriptional footprint of Artemisia scoparia supplementation on a defined panel of obesity-related molecular markers. We re-analyzed a publicly available adipose tissue microarray dataset including inguinal white adipose tissue and epididymal white adipose tissue from control and supplemented groups. After log2 transformation and between-array normalization, differential expression was evaluated using linear modeling with empirical Bayes moderation, supported by global quality checks and contrast-level differential expression landscapes. Across depots, baseline marker expression differed substantially, indicating strong tissue-context effects. Within depots, A. scoparia supplementation was associated with selective, marker-dependent shifts rather than a uniform directional response. Markers linked to inflammatory signaling, insulin and glucose handling, adipogenic regulation, lipid transport, and mitochondrial or thermogenic programs displayed depot-specific patterns, with particularly clear context dependence for UCP1 and consistent divergence between inguinal and epididymal adipose tissue profiles. Overall, the findings suggest that A. scoparia influences obesity-relevant molecular marker programs in a depot-dependent manner, emphasizing the importance of adipose tissue context when interpreting transcriptomic responses to phytochemical interventions and supporting targeted validation in controlled experimental models.

Keywords: Medicinal plant; obesity-related molecular markers; Artemisia scoparia; adipose tissue; transcriptomics

1. Introduction

Obesity has become one of the most pressing global health challenges, largely because it predisposes individuals to a spectrum of metabolic complications, including insulin resistance and type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease (Haslam 2007, Guh et al. 2009, Reaven, Abbasi and McLaughlin 2004). Beyond a simple imbalance between caloric intake and expenditure, obesity is increasingly recognized as a state of chronic metabolic stress in which adipose tissue undergoes extensive remodeling. This remodeling involves adipocyte hypertrophy, immune-cell infiltration, and a sustained pro-inflammatory milieu that collectively disrupt endocrine and metabolic homeostasis (Weisberg et al. 2003, Hotamisligil 2006). In this context, adipose tissue is not merely a

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passive lipid reservoir; it is an active immunometabolic organ whose transcriptional programs shape systemic insulin sensitivity and lipid handling (Rosen, Eguchi and Xu 2009). A key feature of obesity-associated adipose dysfunction is the coordinated dysregulation of molecular pathways governing inflammatory signaling, adipogenesis, lipid uptake/storage, glucose transport, and mitochondrial/thermogenic capacity (Guilherme et al. 2008, Harms and Seale 2013). Canonical mediators such as CCL2 (MCP-1) and TNF (tumor necrosis factor) have been linked to immune recruitment and inflammatory amplification, whereas genes including PPARG (peroxisome proliferator-activated receptor gamma) and CEBPA (CCAAT/enhancer-binding protein alpha) represent major transcriptional regulators of adipocyte differentiation and lipid metabolism (Dommel and Blüher 2021, Hotamisligil, Shargill and Spiegelman 1993, Yeh et al. 1995, Wu et al. 1999). Likewise, alterations in insulin signaling and glucose handling can be reflected by changes in IRS1 (insulin receptor substrate 1) and SLC2A4 (GLUT4; solute carrier family 2 member 4) expression, while mitochondrial/energy-expenditure programs are often captured by markers such as PPARGC1A (PGC-1α; peroxisome proliferator-activated receptor gamma coactivator 1 alpha) and UCP1 (uncoupling protein 1) (Guilherme et al. 2008, Liang and Ward 2006, Kajimura, Spiegelman and Seale 2015).Together, these markers provide a mechanistically interpretable readout of obesity-relevant transcriptional states. Importantly, adipose depots differ substantially in their cellular composition and metabolic roles, and they can respond differently to nutritional or bioactive interventions (Ibrahim 2010, Tchkonia et al. 2013). Inguinal white adipose tissue (IWAT), which has a greater propensity for "beige" remodeling, and epididymal white adipose tissue (EWAT), often considered more inflammation-prone under obesogenic conditions, may therefore display depot-specific molecular signatures (Boudreau et al. 2018, Peppler et al. 2018, Surmi and Hasty 2008, Breitfeld et al. 2020). Capturing such depot-dependent responses at the transcriptional level is critical for understanding how interventions associate with immunometabolic pathways in adipose tissue. Given the complexity of obesity-related transcriptional networks, there is growing interest in plant-derived bioactive compounds as potential modulators of immunometabolic signaling, particularly in preclinical contexts (Subramaniyan et al. 2025, He, Su and Wang 2024). However, interpreting the molecular footprint of such interventions benefits from systematic transcriptomic analysis that combines global screening with biologically grounded marker readouts. Public repositories such as the Gene Expression Omnibus (GEO) enable reproducible re-analysis of well-annotated datasets to address focused mechanistic questions while maintaining transparency and reusability (Barrett et al. 2012).

Here, we re-analyzed the GSE113808 adipose transcriptomic dataset (Illumina MouseRef-8 v2.0; GPL6885) to examine how *Artemisia scoparia* supplementation is associated with transcriptional modulation of obesity-associated molecular markers in IWAT and EWAT (Boudreau et al. 2018). To avoid over-interpretation beyond the available data, our study intentionally focuses on molecular outcomes rather than phenotypic claims. We implemented a two-layer strategy: (i) a global differential expression framework for quality control and discovery, and (ii) a hypothesis-driven marker panel capturing inflammation, adipogenesis/lipid metabolism, insulin signaling/glucose transport, and mitochondrial function. By integrating depot-specific contrasts with marker-level expression profiling, we aimed to delineate adipose-depot transcriptional patterns that align with obesity-related pathways, thereby providing a mechanistic, marker-anchored interpretation of this intervention at the transcriptome level.

2. Materials and Methods

2.1. *Gene Expression Dataset*

Publicly available microarray data were retrieved from the NCBI Gene Expression Omnibus under accession GSE113808 and generated on the Illumina MouseRef-8 v2.0 BeadChip platform

GPL6885 (Davis and Meltzer 2007). The dataset contains transcriptomic profiles from inguinal white adipose tissue and epididymal white adipose tissue of male C57BL/6J mice fed a high-fat diet either alone or supplemented with *Artemisia scoparia* extract. Samples were grouped by depot and supplementation status into four experimental conditions (IWAT_CON, IWAT_SCO, EWAT_CON, EWAT_SCO), each with four biological replicates (Boudreau et al. 2018). For transcriptome-wide inference, differential expression analysis was carried out using GEO2R, which implements the limma linear modeling workflow with empirical Bayes variance moderation and Benjamini–Hochberg false discovery rate adjustment. Contrasts were specified to capture both within-depot supplementation effects and cross-depot differences, matching the global overview comparisons. GEO2R result tables were then exported and used in R for visualization and focused summaries, including expression distribution plots, adjusted P-value diagnostics, volcano plots, and marker-level expression displays (Ritchie et al. 2015)..

2.*2. Bioinformatic Processing, Differential Expression, and Marker-Focused Analyses*

To provide a biologically interpretable readout alongside the global analysis, we performed a marker-focused evaluation using a predefined panel of obesity- and metabolism-associated genes spanning inflammatory signaling, lipid handling, insulin and glucose regulation, adipogenic control, and mitochondrial or thermogenic programs. The marker panel included CCL2, IL6, CRP, TNF, FABP4, SLC27A1, SREBF1, IRS1, SLC2A4, PPARG, CEBPA, RETN, UCP1, and PPARGC1A. Only markers represented in the platform annotation were retained. (Tokgöz and Altan 2025). Marker visualization was performed at the probe level using exported GEO2R outputs. When multiple probes mapped to the same gene symbol, a single representative probe was retained to avoid redundancy in plotting; the representative probe was selected as the probe with the lowest FDR-adjusted P-value in the relevant within-depot contrast. This probe-selection step was used only to generate a single trace per marker in the visualization and does not alter the transcriptome-wide inference. Normalized log2 expression values were then extracted across all samples and visualized across the four experimental groups using gene-wise box-and-jitter plots to highlight group-level shifts and within-group variability.

3. Results and Discussion

3.1. Global transcriptomic quality assessment and differential expression landscape

Prior to marker-focused analyses, the overall statistical behavior of the transcriptomic dataset was evaluated to support robust downstream inference. The distribution of adjusted P-values (Figure 1A) displayed a broad right-skewed pattern with a modest enrichment of lower P-adj values and a gradual tapering toward 1.0, which is consistent with scenarios where differential regulation affects a subset of transcripts while most genes remain near baseline. Importantly, the absence of an extreme pile-up at P-adj $\approx$ 0 supports appropriate multiple-testing behavior and argues against pervasive inflation (Figure 1A). Differential expression landscapes were further summarized using volcano plots across depot- and condition-linked contrasts (Figure 1B–E), where the x-axis represents log2 fold change (log2FC) and the y-axis represents $-\log10$(P-value). Within epididymal white adipose tissue (EWAT), the EWAT_CON-EWAT_SCO comparison showed little to no visually prominent set of threshold-passing transcripts (Figure 1B), suggesting that *Artemisia scoparia* (SCO) supplementation elicits a comparatively weak or more diffuse transcriptional shift in EWAT under the current cutoffs. In contrast, inguinal white adipose tissue (IWAT) exhibited a clearer treatment-associated signal in the IWAT_CON-IWAT_SCO contrast (Figure 1D), with a substantial population of significant transcripts and an apparent asymmetry toward negative log2FC-consistent with higher expression under SCO given the CON−SCO contrast definition. Across the cross-depot contrasts EWAT_SCO-IWAT_CON

and IWAT_SCO-EWAT_CON, the volcano profiles showed the widest log2FC spread and dense clusters of significant transcripts on both sides of the distribution (Figure 1C and Figure 1E), highlighting strong depot-linked transcriptional divergence that can dominate the differential expression landscape. Overall, Figure 1B–E collectively indicates that depot identity is a major driver of transcriptomic variation, while the detectable SCO-associated response appears more pronounced in IWAT than EWAT under the present analysis settings

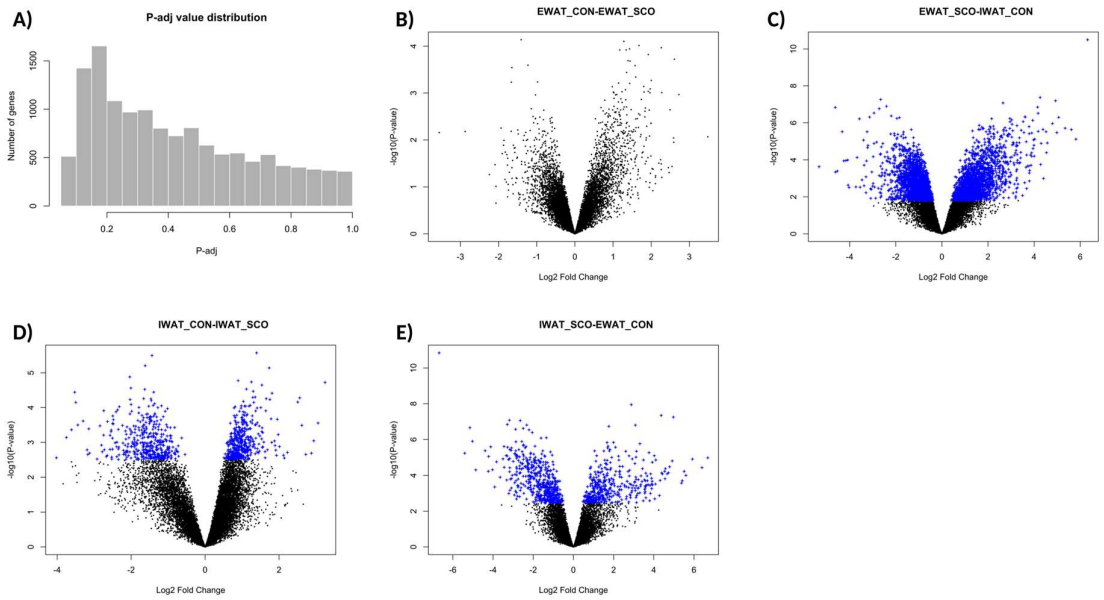

Figure 1. Global statistical behavior and differential expression landscape across adipose depots and contrasts. A) Histogram of adjusted P-values across all tested transcripts, illustrating overall multiple-testing behavior. B) EWAT_CON vs EWAT_SCO. C) EWAT_SCO vs IWAT_CON. D) IWAT_CON vs IWAT_SCO, and E) IWAT_SCO vs EWAT_CON. Blue points indicate genes passing the applied significance threshold, whereas black points denote non-significant transcripts.

3.2. Marker-centric expression patterns across adipose depots and treatments

Following the global transcriptome assessment, the analysis was narrowed to a hypothesis-driven panel of 14 markers representing inflammation (CCL2, IL6, CRP, TNF), lipid handling (FABP4, SLC27A1, SREBF1), insulin signaling (IRS1, SLC2A4), adipogenic regulation (PPARG, CEBPA, RETN), and mitochondrial/thermogenic programs (UCP1, PPARGC1A). Marker-level expression across the four experimental groups (IWAT_CON, IWAT_SCO, EWAT_CON, EWAT_SCO) is shown in Figure 2. Depot identity produced clear baseline separation for multiple markers. In this dataset, CCL2 and IL6 tended to be higher in EWAT than IWAT, whereas RETN, SLC27A1, and SLC2A4 showed higher expression in IWAT than EWAT.

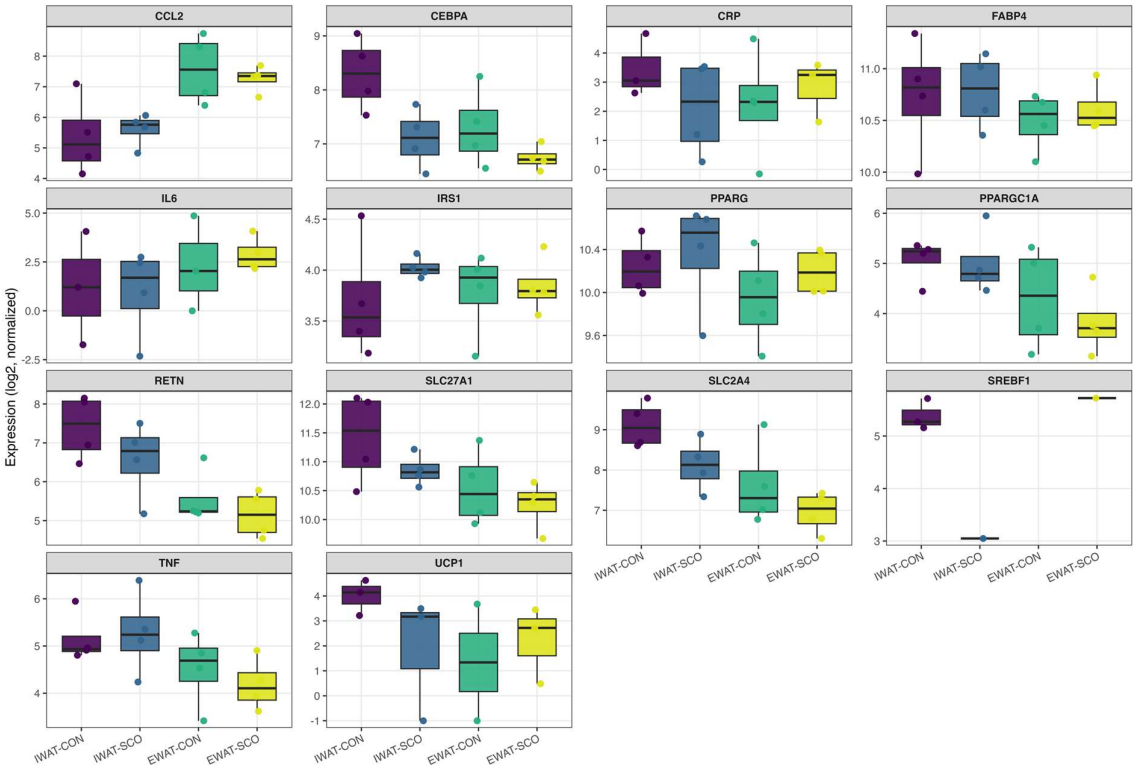

Figure 2. Marker expression profiles across adipose depots and *Artemisia scoparia* supplementation. Box-and-jitter plots show log2-normalized expression of 14 pre-selected markers across four groups (IWAT_CON, IWAT_SCO, EWAT_CON, EWAT_SCO).

These consistent cross-depot differences indicate that, even within a small marker set, depot-specific transcriptional programs are readily detectable. Within each depot, *Artemisia scoparia* (SCO) supplementation was associated with selective and marker-dependent shifts rather than a uniform directional pattern. In IWAT, CEBPA both showed lower central tendency under SCO relative to control, while PPARG appeared modestly higher in IWAT_SCO than IWAT_CON. For insulin-signaling–linked markers, IRS1 trended slightly higher under SCO in IWAT, whereas SLC2A4 showed the opposite direction, indicating that components of the insulin/glucose-handling axis did not move in a single coordinated direction within IWAT under the present conditions. Markers linked to mitochondrial/thermogenic programs displayed a notable depot-dependent directionality. UCP1 was higher in IWAT_CON and showed a drop and increased dispersion in IWAT_SCO, whereas in EWAT the pattern was reversed, with higher UCP1 in EWAT_SCO than EWAT_CON. PPARGC1A tended to be lower under SCO in both depots, most visibly in EWAT. Lipid-handling markers were comparatively stable: FABP4 showed limited separation across groups, while SLC27A1 decreased under SCO in IWAT and showed a smaller shift in EWAT. Finally, SREBF1 should be interpreted cautiously because its panel in Figure 2 shows sparse representation across groups, limiting confident visual inference. Collectively, Figure 2 supports a model in which depot differences dominate baseline marker expression, while SCO supplementation is associated with targeted, depot- and marker-specific shifts (most clearly for UCP1) in opposite directions across depots), rather than a uniform anti-inflammatory or "browning" signature across all markers.

4. Conclusion

Using a publicly available adipose transcriptomic dataset, we show that adipose depot identity is the primary driver of gene-expression variation, with strong divergence between inguinal white

adipose tissue and epididymal white adipose tissue. In contrast, *Artemisia scoparia* supplementation was associated with more selective, depot-dependent shifts rather than a uniform transcriptional signature. Marker profiling supported this context dependence, highlighting clear baseline depot differences and a notable opposite-direction pattern for UCP1 (uncoupling protein 1) across depots. Overall, these data suggest that phytochemical supplementation engages specific immunometabolic nodes in a tissue-context–dependent manner, motivating targeted validation and mechanistic follow-up in controlled experimental models.

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Disclosure Statement

The authors declare no competing financial interests.

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