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Metabolome Alterations in Wild Boars Affected by Sarcoptic Mange

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ABSTRACT

Sarcoptic mange is an extremely infectious parasitic skin disorder that continues to be a serious health challenge for both humans and other mammals around the globe. The disease is produced by the mite *Sarcoptes scabiei*, and its clinical appearance can differ widely in form and severity. Besides visible skin irritation, affected individuals often undergo disruptions in metabolism, immune defense, reproduction, body temperature control, and overall physical condition. Despite this, the full metabolic consequences of the infection remain largely unexplored. Fat loss and alterations in fatty acid composition linked to mange may intensify the pathological effects of the disease. Early detection tools for this parasite are lacking, which frequently leads to significant economic losses in livestock industries and welfare concerns for animals. In this work, we employed a targeted LC–MS/MS metabolomic approach to explore how sarcoptic mange alters the blood serum metabolome in wild boars. Thirteen wild boars were analyzed under three clinical circumstances: during active infection, while undergoing ivermectin therapy, and after complete recovery. Our data showed a pronounced accumulation of long-chain acylcarnitines in the sera of infected animals compared with treated or recovered counterparts. These preliminary outcomes emphasize the importance of further research into how long-chain acylcarnitines influence metabolic stability and their potential use as biomarkers for the early diagnosis of sarcoptic mange.

Keywords: Wild boar, Zoonotic parasite, *Sarcoptes scabiei*, Targeted metabolomics, Acylcarnitines, Disease biomarkers

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Introduction

The microscopic mite *Sarcoptes scabiei* is responsible for sarcoptic mange, a contagious parasitosis affecting a broad spectrum of mammals, including humans, livestock, and wildlife. In humans, the infection manifests as scabies. By burrowing into the skin, this mite causes irritation, discomfort, and substantial welfare concerns in both domestic and wild hosts [1–4]. Cases of mange have been documented in over 150 wildlife species across all continents, where outbreaks can appear in either endemic or epidemic form, often with high mortality [1, 5]. Once infestation occurs, *S. scabiei* can provoke a range of clinical symptoms—from loss of appetite and weakness to sepsis and death [6, 7]. Adult females create tunnels within the stratum corneum, laying eggs between the granulosum and spinosum layers. Waste products such as feces, enzymes, hormones, and molting residues accumulate within these burrows, activating the host's immune defense. The resulting immune reaction depends on the host's physiology and includes Type I hypersensitivity, which releases histamine and recruits eosinophils

and neutrophils, and Type IV hypersensitivity, a delayed T-cell–mediated response. The latter is particularly destructive in immunocompromised animals, where it may lead to hair loss, skin thickening, metabolic imbalance, and secondary bacterial infections [8–10].

Histological research in Iberian ibex, carnivores, and ruminants has revealed that mange triggers early infiltration of macrophages and T lymphocytes, which intensifies during the final stages of infection. This confirms the participation of Th1-type cell-mediated immunity in the disease's progression [10–13]. In severely affected or immunodeficient animals, exaggerated Type IV responses can result in cracked, thickened skin and eventual death [14].

Beyond immune involvement, environmental and physiological factors—such as changes in body weight, habitat conditions, and energy requirements—also influence disease outcomes, making sarcoptic mange particularly problematic in free-ranging populations [15]. For domestic animals, two subcutaneous injections of ivermectin (Ivomec 10 mg/mL; Boehringer Ingelheim Animal Health Italia S.p.A.) at 0.3 mg/kg, administered 15 days apart, remain the standard treatment protocol for eliminating mites and their eggs when topical therapies are impractical [8].

Although ivermectin therapy has proven effective in domestic settings, applying this treatment schedule to wild populations remains largely impractical, making it necessary to develop alternative control strategies and conduct further investigations. Observational data collected across various European regions have revealed significant gaps in surveillance systems for sarcoptic mange in both wild boars and domestic pigs. These deficiencies are mostly related to the absence of highly sensitive diagnostic techniques capable of identifying subclinical or early infections, which likely leads to a gross underestimation of the actual prevalence of this parasitic disease [16–18].

Wild boars, as social omnivores, typically live in family-based groups that include adults and offspring. This close contact environment greatly facilitates mite transmission, especially when populations become overcrowded [17, 18]. During recent decades, alterations in land use and climate shifts have favored a rapid expansion of wild boar numbers, even within urban and suburban landscapes throughout Europe. This demographic shift has introduced new ecological and sanitary challenges, influencing both human communities and wildlife health [19–23].

In areas where domestic herds and wild species coexist, particularly within agroforestry systems, the exchange of mites among species becomes more probable, positioning wild boars as reservoirs of *Sarcoptes scabiei*. A critical event occurred in 2018, when the first confirmed interspecies transmission of mange—from a wild ruminant to a wild boar—was reported in Europe, demonstrating the adaptive capacity of the parasite to infect multiple hosts [18]. Reflecting its global significance, the World Health Organization (WHO) recognized sarcoptic mange as a Neglected Tropical Disease (NTD) in its 2021–2030 roadmap, classifying it as an emerging transboundary infection among wildlife [24].

Despite progress in parasitological diagnostics, reliable early-stage identification of mange remains elusive. Present techniques—such as clinical observation, microscopic evaluation of skin scrapings, and molecular or serological assays—tend to be accurate only at advanced stages of infection [25–32]. Thus, the ability to detect minimal mite loads before symptoms appear remains an unresolved diagnostic challenge.

Modern spectrometric and spectroscopic methodologies enable detailed analysis of molecular fingerprints related to metabolic and energetic states [33–35]. Building upon this, the present research employed a targeted LC–MS/MS metabolomic approach to evaluate how sarcoptic mange influences serum metabolite patterns in wild boars experiencing three sequential conditions: active disease, ivermectin therapy, and clinical recovery.

Materials and Methods

Animals and study site

To address the rising population density of wild boars, the Campania Region (Italy) launched a management initiative entitled *"Plan for the Management and Control of the Species within the Scheduled Hunting Area"* (Regional Decree DGR No. 521, dated 23 November 2021). This initiative regulates boar populations in urban and peri-urban environments where hunting is legally restricted, pursuant to Article 19 of Law 157/92 and Article 18(2) of Regional Law 26/2012, focusing on damage prevention and population containment.

The control program prioritizes population surveys to safeguard public health, maintain environmental balance, and preserve agricultural and cultural assets. Management operations—including capture and selective culling—are implemented through collaboration among forest guards, local authorities, and licensed volunteers, under the direction of official veterinarians.

All animals included in this investigation were wild boars obtained through these regional control efforts, officially owned by the Campania Region, and transported to the "Cerreta Cognole" Regional Forest Facility (coordinates: 40°14′44″ N, 15°89′31″ E). This center is authorized to house live wild boars and conduct health evaluations. Each individual was documented with capture details, sex, estimated age, body mass, clinical findings, and any noted disorders.

The final cohort comprised 13 female boars, aged 7–12 months, selected according to visible dermatological lesions and positive microscopic confirmation of *Sarcoptes scabiei* infestation from skin scraping analysis [22, 36].

Holding environment and health monitoring

Throughout the monitoring period, the animals were kept in a fenced enclosure of about 3000 m², located within a mature beech forest characterized by 15–20-meter-tall trees aged 15–20 years. They had continuous access to feed and water under natural environmental conditions.

For blood collection, each wild boar was calmly guided into a holding pen of roughly 40 m², constructed with chestnut timber panels and wire mesh. From there, animals were moved through a narrow handling corridor ending in a rectangular restraint crate (200 × 100 × 100 cm), ensuring the safety of both handlers and animals during sample collection.

Ethical compliance

All clinical evaluations and blood collections were conducted under the legal framework of the Italian Republic and the regional legislation of Campania, in full adherence to European Union regulations on animal protection and welfare. Throughout the sampling process, no wild boar was injured, mishandled, or sacrificed. Every operation followed international standards for ethical animal research, ensuring the humane treatment of captured specimens during observation.

Capture procedures met all legal requirements under Law 157/1992 (Articles 4, 10.7, 19.2, and 19-bis) and Article 11.4, and were executed exclusively by authorized public veterinarians using approved trapping systems. The entire experimental plan received ethical approval number 139/2020–PR. Animal care and handling followed recognized welfare protocols [37–39].

Blood collection protocol

A group of 13 wild boars was selected from the captured animals for inclusion in this research. Upon their transfer to the monitoring facility, each subject was given a unique microchip ID, inserted beneath the skin of the left shoulder.

Blood samples were obtained by trained veterinarians using a containment crate fitted with mechanical restraint panels to minimize stress. Blood was drawn from the left jugular vein into 9 mL Vacuette® serum tubes (activator type, red cap–black ring, 16 × 100 mm) and promptly placed into portable coolers maintained between 4 and 10 °C.

Within four hours, samples were centrifuged at 2000 × g for 15 minutes using a six-slot portable centrifuge (LW Scientific Zip-IQ TT). Serum was isolated and frozen at –80 °C until biochemical analyses were conducted.

During the March to June observation period, all animals were housed under identical environmental conditions and categorized into three health statuses:

- M – animals exhibiting clinical mange,
- I – animals undergoing ivermectin therapy, and
- R – animals considered recovered.

These codes are used throughout the study for reference.

Cortisol measurement

Serum cortisol levels were quantified in duplicate using a competitive ELISA technique (FineTest® Porcine COR ELISA Kit, Catalog No. EP0254; available at https://www.fn-test.com/). Data analysis was carried out with GraphPad Prism version 10.3.1, applying a repeated-measures ANOVA model to evaluate variations across the three experimental stages.

Targeted metabolomic profiling

To characterize the serum metabolomic composition, a targeted LC–MS/MS approach was used to measure concentrations of amino acids (AA) and acylcarnitines (AC). These analytical platforms provide molecular-level insight into the metabolic energy balance of each specimen [33–35].

Sample preparation followed previously validated procedures [40] with several refinements. A 10 µL aliquot of each serum sample was applied to filter paper, and metabolites were extracted using 200 µL of methanol containing isotope-labeled internal standards for AA and AC. The extracts were derivatized with 80 µL n-butanol/3 N HCl for 30 minutes at 65 °C, then evaporated under nitrogen gas. The residues were redissolved in 300 µL acetonitrile/water (70:30 v/v) containing 0.05% formic acid.

A 40 µL portion of each reconstituted sample was injected four times (technical replicates) using flow injection analysis (FIA) into an Agilent 1260 Infinity II HPLC system, interfaced with an API 4000 triple quadrupole mass spectrometer (SCIEX, USA).

Acylcarnitines were detected in precursor ion scanning mode, while amino acids were identified using neutral loss and multiple reaction monitoring (MRM) scans. Metabolite quantification was achieved by comparing peak areas against those of stable isotope-labeled standards, processed via ChemoView v1.2 software (SCIEX).

Data processing and statistical workflow

All metabolomic data were processed using MetaboAnalyst 6.0, GraphPad Prism v10.2.3, and SRplot for both univariate and multivariate statistical interpretation [41–43].

To explore sample clustering and variability, Hierarchical Clustering Analysis (HCA) and Principal Component Analysis (PCA) were performed based on metabolite concentrations [44]. Profile plots were used to visualize abundance patterns, with membership coefficients (0–1) representing the likelihood that each metabolite belonged to a specific trend cluster.

Differential abundance was further evaluated through volcano plot analyses using $\log_{10}$-transformed and Pareto-scaled concentration data. The statistical thresholds were defined as fold change ≥ 1.0 and $p \leq 0.05$. Three pairwise comparisons were made to reveal infection-related metabolic shifts:

- M vs R,
- M vs I, and
- I vs R.

For overall comparison among the three groups, a mixed-effects model followed by Tukey's correction was applied. To determine functional pathway enrichment, a Metabolite Set Enrichment Analysis (MSEA) was carried out using Over-Representation Analysis (ORA), referencing the Small Molecule Pathway Database (SMPDB) [45], as no comprehensive boar-specific database is currently available.

Results and Discussion

No significant variations in cortisol levels were detected across the clinical groups (repeated measures ANOVA: $F(1.921, 23.05) = 1.753$, $p = 0.1964$) **(Figure 1)**.

Subsequently, a targeted metabolomics analysis was carried out to characterize the serum metabolic responses of wild boars to mange and to monitor metabolic alterations in the same animals following ivermectin therapy. Quantitative metabolomic profiling was generated for three categories—mange-infected, ivermectin-treated, and recovered individuals—designated as "M", "I", and "R", respectively. Using the MS platform, a total of 51 metabolites were detected, including 13 amino acids (AA) and 38 acylcarnitines (AC).

Overall data distribution indicated a distinct separation between the M group and the other two (I and R) **(Figure 2a)**. The PCA accounted for 43.3% of total variance (PC1 = 24.6%, PC2 = 18.7%), showing that I and R groups shared similar metabolic profiles **(Figure 2a)**. Consistent with this, the heatmap clustering aligned with PCA results, clearly grouping M samples together while I and R individuals showed no specific clustering, implying close metabolic resemblance between them **(Figure 2b)**.

Profile plots revealed nine distinct molecular clusters with characteristic quantitative behaviors **(Figure 2c)**. Specifically, clusters 3 and 5 contained metabolites reduced after mange infection and remained low in both treated and recovered animals. Cluster 3 was mainly composed of medium-chain AC (8, 10, and 12 carbon atoms), while cluster 5 included both short- and long-chain AC species **(Figure 2d)**. In contrast, clusters 4, 6, 7, and 8

exhibited opposite trends, with metabolite levels reduced in M compared with I and R; these clusters mainly comprised AA **(Figure 2d)**. Clusters 1, 2, and 9 showed differing patterns between I and R, indicating that some metabolic normalization was still ongoing even after recovery. Recovery was verified ten days after the initial visual assessment through skin scraping and microscopic examination.

The PCA further confirmed that mange-infected boars exhibited a unique metabolomic profile compared with recovered animals **(Figure 3a)**. Volcano plot analysis also highlighted the greatest metabolic divergence between M and R, revealing 24 significantly altered metabolites (17 increased, 7 decreased) **(Figure 3b)**. PCA also distinguished M from I animals **(Figure 3c)**, with 19 metabolites significantly different—13 elevated and 6 reduced in M samples **(Figure 3d)**. This comparison showed a specific rise in AC and a decline in AA, though less pronounced than in M vs. R. The metabolomic overlap between I and R animals **(Figure 3e)** confirmed high similarity, except for three compounds differing in I: Tyr and Met (decreased) and C5 (increased) **(Figure 3f)**.

Fifteen metabolites were shared between the M vs. I and M vs. R comparisons, displaying identical regulation trends in both analyses **(Figure 4a)**.

Statistical evaluation of these fifteen shared metabolites reinforced the AC upregulation and AA downregulation trends noted earlier **(Figure 4b)**. Specifically, Xle, Orn, and ArgSuc were reduced in M individuals, while I vs. R differences were nonsignificant. Concentrations of saturated AC (C4, C6, C8, C10, C12, C14) were higher in M and comparable between I and R. A similar behavior was seen for unsaturated AC (C6:1, C8:1, C10:1, C14:1, C18:1), except for C16:1, whose p-values were nonsignificant **(Figure 4b)**. Pathway enrichment analysis (MSEA) of these shared metabolites identified metabolic routes impacted by mange, including the urea cycle, fatty acid β-oxidation, and spermidine/spermine biosynthesis **(Figure 4c)**. The enriched amino acid pathways comprised arginine, proline, aspartate, glycine, serine, and branched-chain AA (valine, leucine, isoleucine) degradation **(Figure 4c)**.

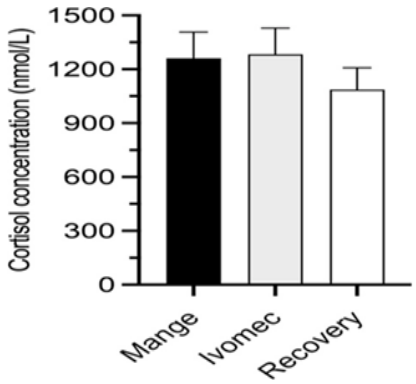
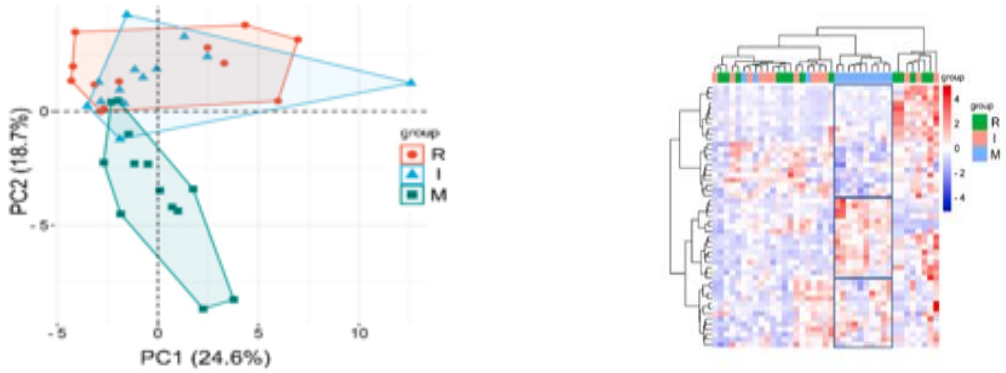
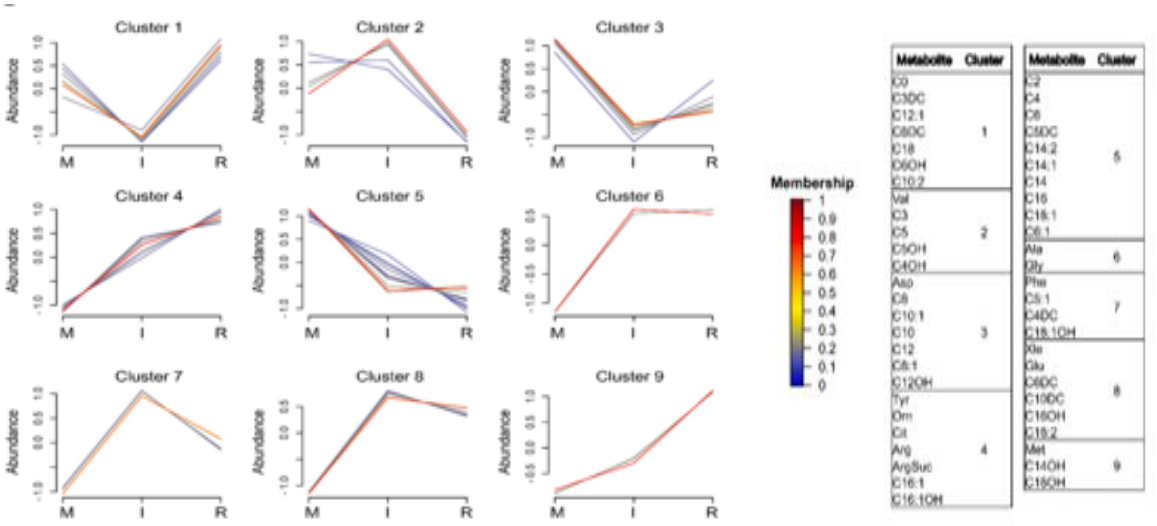


Figure 1. Serum cortisol levels (nmol/L) of wild boars measured under three sequential health conditions—mange infection, ivermectin treatment, and recovery—in the same individuals. Analysis performed using repeated measures ANOVA. Results presented as mean ± SEM.

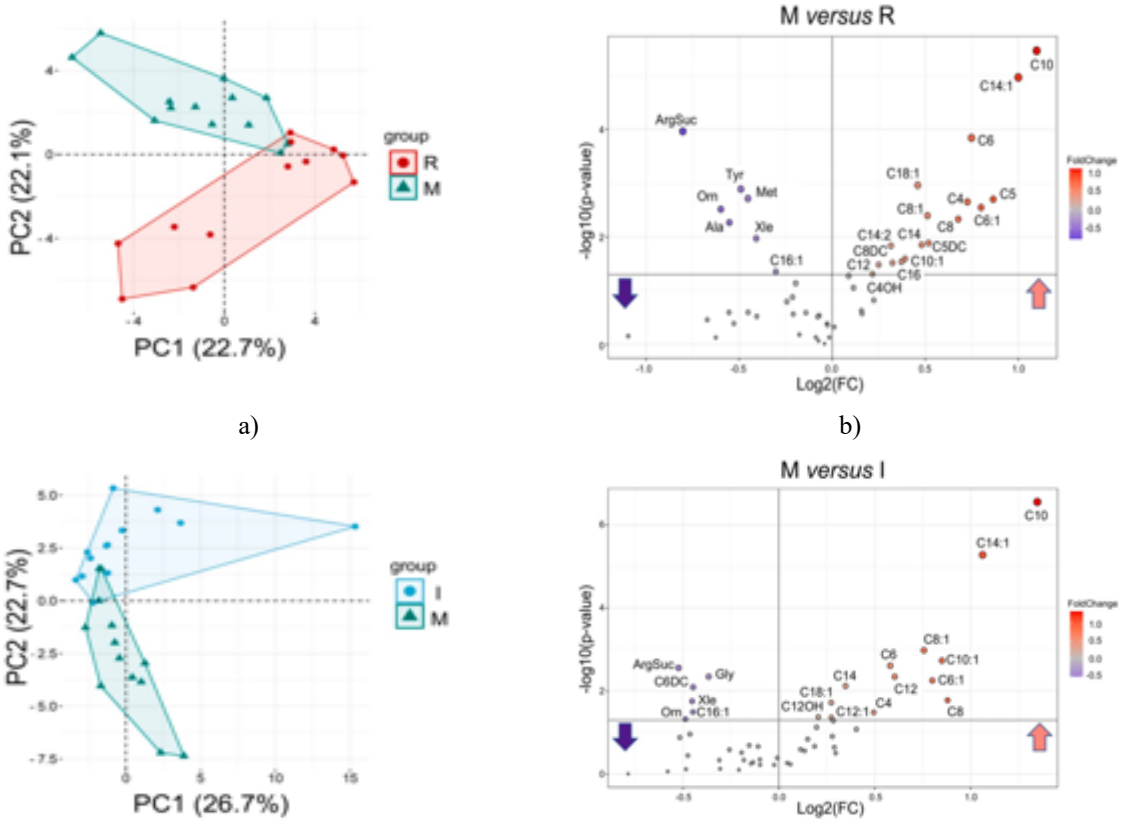


a) b)



c) d)

Figure 2. Comparative metabolomic profiling of mange-infected (M), ivermectin-treated (I), and recovered (R) wild boars. a) Principal Component Analysis (PCA) displaying group distribution along PC1 and PC2 axes. b) Hierarchical Clustering Analysis (HCA) highlighting the clear grouping of M samples in a distinct cluster; shaded boxes emphasize metabolite groups differing from other states. c) Quantitative trends of nine metabolite clusters identified from profile plots, illustrating variations among groups. Line colors indicate molecule association strength with each cluster—from strong (red) to weak (blue) correlation. d) Compounds corresponding to the nine identified clusters.



a) b)

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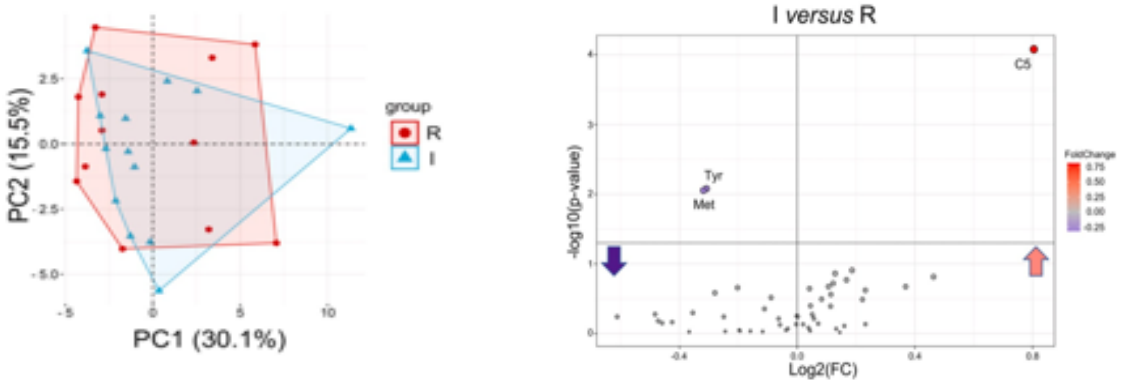
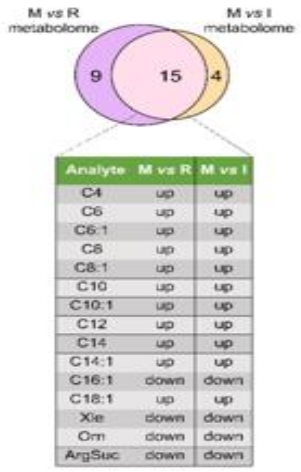


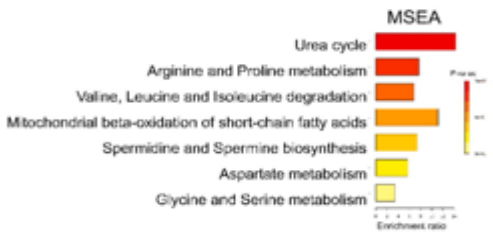
e) f)

Figure 3. Pairwise examination of metabolite regulation between experimental groups. PCA plots (left panels) and volcano plots (right panels) display group separation and significant metabolite changes for: a, b) M vs R, c, d) M vs I, and e, f) I vs R. Upregulated and downregulated metabolites are represented by red and violet arrows. Dashed horizontal and vertical lines denote statistical cutoffs. FC = fold change

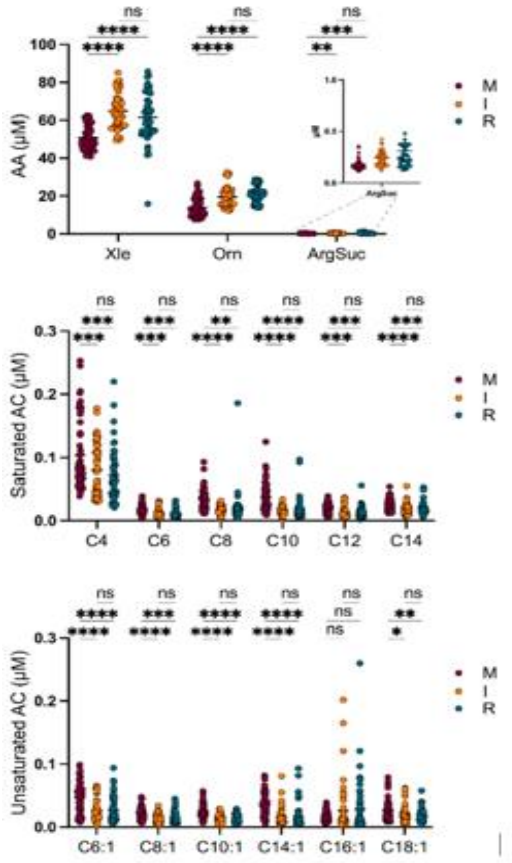


Analyte	M vs R	M vs I
C4	up	up
C6	up	up
C6:1	up	up
C8	up	up
C8:1	up	up
C10	up	up
C10:1	up	up
C12	up	up
C14	up	up
C14:1	up	up
C16:1	down	down
C18:1	up	up
Xle	down	down
Orn	down	down
ArgSuc	down	down

a)



c)



b)

Figure 4. Metabolic features of mange-infected wild boars. a) Venn diagram indicating metabolites significantly shared between M vs R and M vs I comparisons, including compound names and regulation direction. b) Variations in amino acids (AA), saturated acylcarnitines (AC), and unsaturated AC are presented in μM across all pairwise comparisons (M vs R, M vs I, and I vs R). Statistical analysis performed with two-way ANOVA followed by Tukey's test. Data are shown as individual points with mean ± SEM. Significance levels: ****p < 0.0001, ***p < 0.001, **p < 0.01, *p < 0.05, ns = not significant. c) Metabolic pathways significantly enriched according to Metabolite Set Enrichment Analysis (MSEA) derived from shared metabolites.

This work represents the first documentation of cortisol assessment and serum metabolomic mapping in wild boars naturally affected by *Sarcoptes scabiei*, subsequently treated with ivermectin, and later fully recovered—a set of conditions rarely achieved in wildlife studies. Out of 51 identified metabolites, amino acids including alanine, argininosuccinate, methionine, ornithine, tyrosine, and the leucine–isoleucine pair were found in lower abundance in infected individuals. In contrast, elevated levels of saturated (C4, C5, C6, C8, C10, C16, C5DC, C8DC), hydroxylated (C4OH), and unsaturated (C6:1, C8:1, C10:1, C14:1, C14:2, C18:1) acylcarnitines were detected when compared with treated counterparts. The post-treatment metabolic landscape closely resembled that observed six weeks later, coinciding with complete clinical remission.

No measurable variation in cortisol concentration was detected among the three conditions. Nevertheless, since confined wild species may experience stress analogous to domestic animals, cortisol could still serve as a marker of welfare status in such contexts [46–48]. The absence of correlation between cortisol and metabolomic data suggests that acylcarnitine elevation during mange is unlikely linked to hypothalamic–pituitary–adrenal axis activity. Further targeted analysis is required to clarify this point.

Sarcoptic mange is recognized for inducing broad physiological disturbances in host organisms [6, 8, 10, 15, 49–51]. Previous observations in marsupial wombats indicated alterations in adipose fatty acid composition during mange progression, characterized by increased omega-6 and arachidonic acid (C20:4) and reduced oleic (C18:1), α-linolenic (C18:3), and total monounsaturated fats [9]. Loss of fur and compromised skin integrity disrupt thermoregulation, leading to energy expenditure several times higher than in healthy animals.

Studies using non-targeted LC–MS on cold-exposed mice have reported marked rises in acylcarnitines within multiple tissues, such as blood, skeletal muscle, liver, and brown adipose tissue [52]. These metabolites, synthesized in the liver, act as an essential fuel for non-shivering thermogenesis; disruption of their production impairs thermal regulation [53]. Over a thousand acylcarnitine variants are now known, categorized by chain length as short (C2–C5), medium (C6–C12), long (C13–C20), and very long (>C21). Each group contributes uniquely to fatty acid oxidation, energy metabolism, and disorders such as diabetes, cancer, and oxidative stress [54–56].

Long-chain acylcarnitines (LCAC) serve as intermediates in β-oxidation and may compromise mitochondrial function by limiting oxidative phosphorylation and enhancing reactive oxygen species generation [54]. The elevation of medium and long-chain AC observed in infected boars could reflect excessive β-oxidation activity, potentially causing lipid accumulation, mitochondrial overload, and worsened physiological state [56–58].

The current diagnostic tools for *S. scabiei* remain suboptimal, primarily relying on lesion observation and microscopic detection, which can be hindered by concurrent infections [59, 60]. Both microscopy and PCR suffer from low sensitivity due to the limited number of mites present [60, 61], emphasizing the need for more precise diagnostic techniques. Immunoassays such as ELISA have also shown inconsistent performance, likely due to low parasite loads and the lack of available mite culture systems [22, 24, 30, 60]. Future research should further elucidate the physiological significance of acylcarnitines in the development and pathology of sarcoptic mange.

Conclusion

This research represents the first attempt to explore the use of blood metabolomic profiling in wild boars naturally infected with mange. The results revealed that long-chain acylcarnitines (LCAC) were present at higher concentrations in infected animals compared with the same individuals after ivermectin treatment and subsequent recovery. These preliminary observations suggest that acylcarnitines could serve as potential early biochemical indicators of this widespread disease, even before the appearance of clinical symptoms. Furthermore, gaining a more comprehensive understanding of LCAC dynamics and their role in maintaining metabolic balance in livestock and domestic species affected by sarcoptic mange could contribute to improved disease management, better animal welfare, and reduced economic impact.

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Conflict of Interest: None

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Ethics Statement: None

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