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Effect of the sarcoptic mange upon metabolome profiling in wild boars

Nadia Piscopo [a,1], Michele Costanzo [b,c,1], Monica Gelzo [b,c], Luigi Sacchettino [a], Chiara Vitiello [d], Anna Balestrieri [e], Francesco Napolitano [a,c,*], Luigi Esposito [a]

[a] Department of Veterinary Medicine and Animal Production, University of Naples Federico II, 80137 Naples, Italy
[b] Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, 80131 Naples, Italy
[c] CEINGE-Biotecnologie Avanzate "Franco Salvatore", Via G. Salvatore, 80145 Naples, Italy
[d] Department of Clinical Medicine and Surgery, AIF of Endocrinology University of Naples Federico II, Italy
[e] Food Safety Department, Istituto Zooprofilattico Sperimentale del Mezzogiorno, 80055 Portici, Italy

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ABSTRACT

Sarcoptic mange is a highly contagious disease and represents one of the main health concerns for humans and non-human mammals worldwide. It is caused by the mite *Sarcoptes scabiei* and can course with different morphological and physiological presentations. Accordingly, aside from skin inflammation, hosts may experience changes in body condition, immune system, biochemistry, reproduction, and thermoregulation, although the understanding of the downstream metabolic burden is still missing. In this context, mange-derived fat store depletion and following imbalance of fatty acid composition might contribute to the severity of the illness. The lack of a tool for early detection of this etiological agent often results in significant financial losses for farmers and harm to animal welfare. Therefore, using targeted LC-MS/MS-based metabolomics approach, we sought to investigate the impact of sarcoptic mange upon metabolome profiling in the blood serum of mangy wild boars. Thirteen wild boars were analyzed in three different clinical conditions, namely when they were sick, during the therapeutic treatment with ivermectin, and when they were deemed recovered from the disease. We identified specific long-chain acylcarnitines highly abundant in the blood serum of the subjects within the infection phase, when compared to the ivermectin-treated and healthy conditions. Overall, data from our preliminary study highlighted the need for more accurate and broad-based studies, about the potential role of the long chain acylcarnitines in the metabolic homeostasis, to help early diagnose of the sarcoptic mange.

1. Introduction

The burrowing mite *Sarcoptes scabiei* represents the main culprit of the widespread sarcoptic mange in pets, livestock, wild animals, as well as of the scabies in humans. Sarcoptic mange relies on the ability of the mite to infest the host skin, thus impacting the quality of life and welfare across species worldwide (Escobar et al., 2022; Moroni et al., 2022; Niedringhaus et al., 2019; Pence and Ueckermann, 2002). Sarcoptic mange has been reported in about 150 wildlife species over the six continents, affecting health either as epidemic or endemic outbreaks with high death rates (Escobar et al., 2022; Unterkofler et al., 2023). *Sarcoptic scabies* mites can cause serious health issues in infested subjects, ranging from anorexia to lethargy, potentially leading to systemic sepsis and even to death (Martin et al., 2018; Nimmervoll et al., 2013). Adult mites dig tunnels in the lower stratum corneum of the epidermis, where females lay eggs between granulosum and spinosum layers. The waste material accumulated within tunnels, such as excrements, enzymes, hormones, eggshells and moults, can stimulate immune system that, depending on species and individuals, activate both immediate and delayed hypersensitivity reactions. Indeed, the former response system (Type I) causes the release of active substances, including histamine, as well as chemotactic factors for eosinophils and neutrophils. On the other hand, cell-mediated delayed reactions (Type IV), modulated by antigen-specific effector T lymphocytes, are likely to play a key role in the worsening of health conditions in immunocompromised animals, who generally experience alopecia, hyperkeratosis, metabolic disorders and secondary infections (Rowe et al., 2019; Simpson et al., 2016; Valldeperes et al., 2023). In this view, previous studies carried out in Iberian

* Corresponding author at: Department of Veterinary Medicine and Animal Production, University of Naples Federico II, 80137 Naples, Italy.
E-mail addresses: nadia.piscopo@unina.it (N. Piscopo), michele.costanzo@unina.it (M. Costanzo), monica.gelzo@unina.it (M. Gelzo), luigi.sacchettino@unina.it (L. Sacchettino), anna.balestrieri@izsmportici.it (A. Balestrieri), Francesco.napolitano3@unina.it (F. Napolitano), luigespo@unina.it (L. Esposito).
[1] NP and MC share the same authorship.

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ibex, wild carnivores and ruminants, found that skin biopsies of mangy hosts showed macrophage and T lymphocyte infiltrates in the early phases of the disease, which were more pronounced at the terminal stage, thus confirming an involvement of the Th1-dependent and cell-mediated immunity following to the parasitic infection (Browne et al., 2022; Martinez et al., 2020; Mounsey, 2023; Valldeperes et al., 2023). Similarly, in highly susceptible and immunocompromised sick subjects, mites can trigger severe effects downstream type IV hypersensitivity reaction, such as skin thickening and cracking, that eventually bring the infected animals to death (Arlian and Morgan, 2017). Alongside with the well-established knowledge about the role of immune response upon sarcoptic mange onset and progression, growing evidence also highlighted the importance of changes in environmental, body weight and energetic demand conditions, making sarcoptic mange particularly worrying for free-living populations (Carvalho et al., 2015). In domestic animals, two subcutaneous injections of ivermectin (Ivomec 10 mg/mL for bovine and swine BoehringerIng.Anim.H.IT.SpA 0.3 mg/kg) with a fifteen day interval, represent the choice treatment to control and neutralize the pathogen and mite eggs, particularly when the use of topic compounds is not feasible (Rowe et al., 2019). However, such a treatment schedule is still considered an undoable choice for most wildlife species, encouraging more research activity in this field. Collecting data from different European countries raised concerns about the scanning surveillance of the sarcoptic mange either in wild boars or domestic pigs, most likely due to the lack of sensitive tools to detect subclinical symptoms, thus underestimating the extend of such an endemic phenomenon (Haas et al., 2018; Lizana et al., 2024; Valldeperes et al., 2021). Wild boars are omnivorous and generally live grouped together with their offsprings, which represent a key transmission factor of the cosmopolitan arachnid in overcrowded situations (Lizana et al., 2024; Valldeperes et al., 2021). In the last decades, modifications of land use and growing climate change led to an increase of wild boar populations even in urban areas throughout Europe, impacting both animal and human welfare (Castillo-Contreras et al., 2018; Ferrara et al., 2024; Massei et al., 2015; Piscopo et al., 2023; Vetter et al., 2015). In this context, sharing environments (agro-ecosystems) between wild and domestic animals can increase the ability of mites to infect different host species, and attribute to wild boars the liability of such a phenomenon. In 2018, the first case in Europe of interspecific transmission of sarcoptic mange from a wild ruminant host to wild boar raised concerns about the parasite potential to transmit between different species (Valldeperes et al., 2021). Sarcoptic mange has been recently included as part of the World Health Organization (WHO) roadmap for neglected tropical diseases (NTD) 2021–2030 and considered as an emerging panzootic in wildlife (El-Moamly, 2021). Currently, exhaustive diagnostic strategies for sarcoptic mange detection are still lacking, since either clinical signs or microscopic examination of skin scraping, as well as molecular or immunoassay tests on blood sample, are successful only when the pathology is at an its advanced phase (Espinosa et al., 2017a; Espinosa et al., 2017b; Falconi et al., 2009; Haas et al., 2015; Raez-Bravo et al., 2015; Raez-Bravo et al., 2016; Rambozzi et al., 2004; Valldeperes et al., 2019). Therefore, although challenging, identifying very few mites in hosts before clinical conditions get worsened, represents an unmet need. The precise detection and characterization of molecules with spectrometry or spectroscopy techniques may allow to define their functional properties, in terms of energetic metabolic status of subjects (Costanzo et al., 2022a; Gonzalez Melo et al., 2021; Roviello et al., 2014). Accordingly, using targeted metabolomics approach, we sought to investigate the impact of sarcoptic mange upon biochemically annotated metabolites in blood samples of wild boars, who experienced three different clinical conditions, namely at the time of diagnosis, during the systemic treatment with ivermectin, and when deemed recovered.

2. Methods

2.1. Animals and study area

To counteract wild boar population increase the Campania Region (Italy) adopted the "Management and control plan for the species in the scheduled hunting territory" (DGR no. 521 of 23.11.2021), which is aimed at controlling the wild boar in urban and peri-urban areas where hunting is not allowed (art. 19 Law 157/92 and pursuant to art. 18 paragraph 2 - Criteria for the prevention and containment of damage from wild boar - of Regional Law 26/2012). Control activities mainly rely on numerical assessment of wild boars in a particular area, to ensure public health and safety, as well as the protection of soil, zoo-agro-forestry production, and historical-artistic heritage. To achieve a significant impact reduction of wild boars on habitats populated by other species, and minimize damage to crops, political choices are focused on specific containment plans (killing or capture), counting on the collaboration of forest rangers, local police or voluntary game wardens, supervised by public veterinarians.

The present study refers to captured wild boars, owned by the Campania Region, and moved to the "Cerreta Cognole" Regional Forest (Lat 40° 14′ 44" N – Lon 15° 89′ 31 E), which is authorized to welcome live wild boars and carry out veterinary health checks on them. Information about capture, sex, estimated age, weight, clinical examination, and any other health concerns were recorded for each wild boar (see **supplementary material**). Our sample cohort, made up of 13 females, between 7 and 12 months of age, was homogenously chosen for the presence of clinical signs and microscopic examination of skin scrapings (Guldenpfennig et al., 2021; Piscopo et al., 2023).

2.2. Housing and health observation area

The wild boars were confined in a mature beech forest (15–20-m-tall trees, aged between 15 and 20 years) for all the observation time, in a fenced area of approximately 3000 m^2, with access to water and feed *ad libitum*. Blood was collected from each wild boar, taking them to a corral of roughly 40 m^2, made of chestnut wood planks and wire mesh. Subsequently, all the wild boars were directed into a corridor that ended with a rectangular containment cage, safe for both the operators and the wild boars (200 × 100 × 100 cm).

2.3. Ethics statement

Clinical observations and blood samples for health examination were according to the national laws of the Italian Republic and regional laws of the Campania Region, all of them meeting international and institutional guidelines, as well as animal welfare European Union legislation. During the sampling operations, no animals were mistreated, injured, or killed and all the procedures were carried out in compliance with European standards respecting animal welfare, to better manage the animals during the observation period. The welfare of the captured wild boars was compliant with current literature (Barasona et al., 2013; Escobar-Gonzalez et al., 2024; Torres-Blas et al., 2020). The wild boars of the present study were captured by public veterinary with specific traps, according to the current legislation (art. 4; art. 10, paragraph 7; art. 19, paragraph 2; art. 19-bis of the Law no. 157/1992 as well as art. 11, paragraph 4). The study received authorization no. 139/2020–PR.

2.4. Blood sampling

For our study, 13 wild boars from the operations described above were used. Each animal, upon arrival in the housing and health observation area, was identified through the application of a microchip, subcutaneously implanted, at the left shoulder. Blood sampling was performed by veterinarians in standard containment mode (containment cage with a movable side wall equipped with mechanical

immobilization systems). Blood samples were collected in serum tubes (Vacuette® 9 mL tube serum with activator 16 × 100 red cap-black ring), from the left jugular vein, and immediately stored in a portable refrigerator (4–10 °C). Within four hours from the blood collection, the samples were centrifuged at 2000 x*g* for 15 min in a six-place portable centrifuge (LW Scientific Zip-IQ TT). Serum samples were frozen at −80 °C until laboratory testing. During the entire experimental period (March–June), the 13 wild boars, which were kept in the same living conditions, were studied in three different categories, namely mange-infected, ivermectin-treated, and recovered one, respectively labeled as "M", "I", and "R" throughout the manuscript.

2.5. Serum cortisol evaluation

Serum samples were tested in duplicate for cortisol concentrations, using a competitive enzyme-linked immunoabsorbent assay (ELISA) detection method: FineTest® Porcine COR(Cortisol) ELISA Kit Catalog No.: EP0254 (https://www.fn-test.com/). Statistical analysis (repeated measures ANOVA) was performed by using GraphPad Prism software (ver. 10.3.1).

2.6. Serum metabolome analysis

The metabolome of serum samples was profiled by targeted liquid chromatography–tandem mass spectrometry (LC-MS/MS) for the identification and quantification of a set of amino acids (AA) and acylcarnitines (AC) in boars (**Supplementary Table S1**). The precise detection and characterization of molecules with spectrometry or spectroscopy techniques allow to define their functional properties, *e.g.* to describe the energetic metabolic status of subjects (Costanzo et al., 2022a; Gonzalez Melo et al., 2021; Roviello et al., 2014). Sample preparation and metabolome analysis were performed as already published, with some adjustments (Campesi et al., 2023). Briefly, 10 μL of serum were spotted on a filter paper and metabolites were extracted using 200 μL of methanol containing stable isotope-labeled AA and AC standards. The analytes were derivatized with 80 μL of n-butanol/3 N HCl (for 30 min at 65 °C) and dried under nitrogen. The dried samples were resolubilized with 300 μL of acetonitrile/water (70: 30) with 0.05 % formic acid. Each sample (40 μL) was injected four times as technical replicates, *via* flow injection analysis (FIA), into the LC-MS/MS system which consisted of a 1260 Infinity II HPLC (Agilent Technologies, Waldbronn, Germany) coupled with an API 4000 triple quadrupole mass spectrometer (SCIEX, Framingham, MA, USA). Targeted detection of AC was achieved using the precursor ion scan mode, whereas AA were identified by neutral loss scan or multiple reaction monitoring (MRM). The quantification of the analyzed metabolites was obtained through comparison of their areas with those of labeled internal standards using the ChemoView v1.2 software (SCIEX).

2.7. Metabolomics data elaboration

The metabolome dataset was analyzed using MetaboAnalyst 6.0, GraphPad Prism v10.2.3, and SRplot platforms for univariate and multivariate statistics and data visualization (Costanzo and Caterino, 2023; Costanzo et al., 2022b; Costanzo et al., 2024). Metabolite concentration data were used to perform heatmaps for Hierarchical Clustering Analysis (HCA) and Principal Component Analysis (PCA), to assess the distribution of the quantitative data and understand the clustering or the separation of the analyzed groups (Ruiz-Blazquez et al., 2024). Profile plot analysis was carried out to outline the trends of metabolite abundance across the three analyzed conditions. In particular, the membership value of a molecule into a cluster is calculated between 0 and 1, indicating the degree of membership of this molecule for a given cluster. Binary comparisons were performed by volcano plot analysis to deeply determine the metabolic changes depending on mange infection. The concentration data were log10-transformed and Pareto-scaled, the fold change (FC) threshold was set at 1.0, and the *P*-value threshold at 0.05. Precisely, three binary analyses were performed to detect differentially abundant metabolites as follows: M *versus* R, M *versus* I, I *versus* R. Multi-comparison analyses were performed by fitting a mixed-effects model with Tukey correction for multiple testing. Metabolite Set Enrichment Analysis (MSEA) was performed *via* Over Representation Analysis (ORA) using the Small Molecule Pathway Database (SMPDB) as metabolite set library based on normal human metabolic pathways (Frolkis et al., 2010), in the absence of proper databases for boars.

3. Results

No statistically significant differences in cortisol concentrations were observed among the different clinical conditions (ANOVA repeated measures: $F_{(1.921,\ 23.05)} = 1.753$, $p = 0.1964$, Fig. 1).

Then, we used a targeted metabolomics approach to outline the metabolic effects of mange on the serum of wild boars and evaluated the metabolic changes affecting the same animals after ivermectin treatment. Quantitative metabolome profiling was obtained for the three analyzed groups, namely mange-infected, ivermectin-treated, and recovered animals, which were labeled as "M", "I", and "R", respectively. In total, our MS platform allowed the detection of 51 metabolites, 13 amino acids (AA) and 38 acylcarnitines (AC). The global metabolomic dataset is reported in Supplementary Table S2, including the samples analyzed (13 × 3 conditions) and the concentration values (μM) for all the four technical replicates measured. The distribution of the quantitative data for the three groups altogether showed a separation of the M group with respect to I and R (Fig. 2A). The PCA analysis accounted such a separation for a total variance of 43.3 % (PC1 24.6 %, PC2 18.7 %), with the I and R groups being recognized as similar according to their principal components (Fig. 2A). Accordingly, heatmap clustering confirmed the PCA results, spontaneously generating a clustering of the M individuals within one large cluster with metabolites characterized by specific quantitative trends, whereas the I and R groups looked assorted with no clustering, suggesting metabolic similarities between these animals (Fig. 2B). The profile plot analysis identified nine molecule clusters with specific quantitative trends (Fig. 2C), thus bringing to the arrangement of nine clusters of molecules with specific trends. The clusters 3 and 5 contain molecules that decreased after active mange infection both in the ivermectin-treated and recovered wild boars. Cluster 3 comprised several 8, 10 and 12C-atom medium-chain AC, while cluster 5 included some short- and long-chain AC (Fig. 2D). By contrast, the clusters 4, 6, 7, and 8 involved metabolites with opposite trends than the clusters 3 and 5, specifically lowered in M

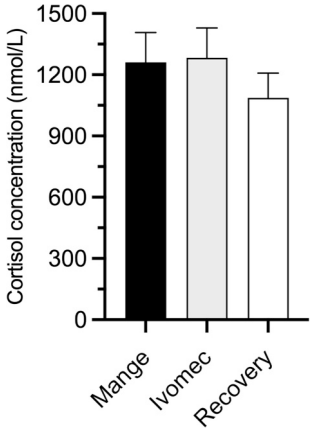


Fig. 1. Cortisol concentrations (nmol/L) in the serum of the wild boars over three different clinical conditions (mange-infected, ivermectin-treated, and recovered animals), experienced by the same subjects. Repeated measures ANOVA. Values are expressed as mean ± SEM.

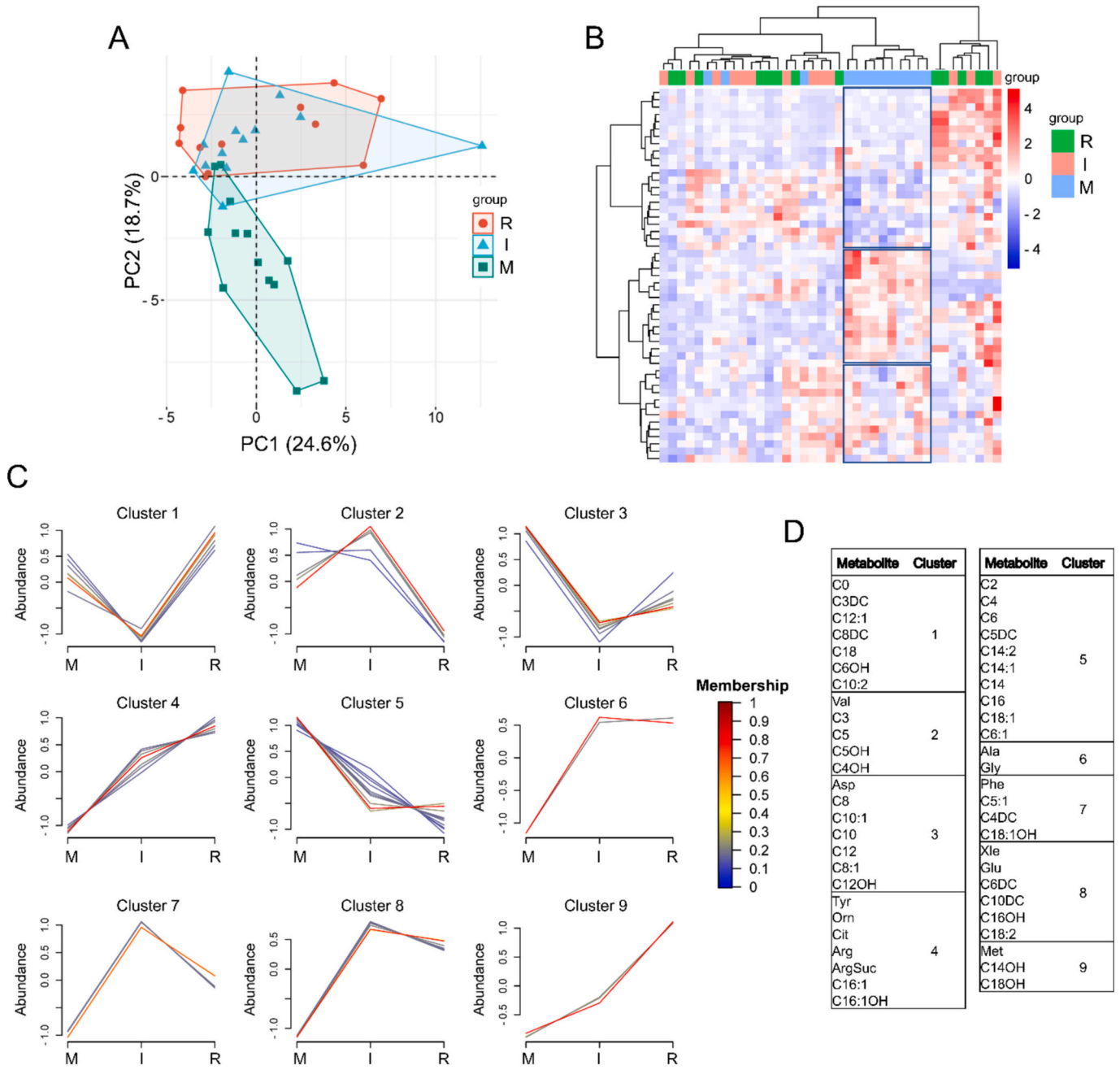


Fig. 2. Characterization of the serum metabolome of mange-infected (M), ivermectin-treated (I), and recovered (R) boars. (A) Principal Component Analysis (PCA) showing the separation of the analyzed groups according to their PC1 and PC2. (B) Hierarchical Clustering Analysis (HCA) showing the specific clustering of the M samples in one large group, with boxes outlining the groups of metabolites changed with respect to the other conditions. (C) Abundance of the nine metabolite clusters for each wild boar group as identified by the profile plot analysis. The colors of the lines refer to the degree of membership of each molecule within a specific cluster, ranging from high (red) to low (blue) membership. (D) Metabolites included in each of the nine clusters identified by the profile plot analysis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

than in I and R. These clusters included AA in their lists (Fig. 2D). Finally, a contrasting behaviour between I and R characterized the clusters 1, 2 and 9, suggesting that the variation in those metabolites might still be in progress, even after recovery from the disease. Recovery was confirmed after a further ten days of the first visual control of healing with skin scarification and verification under an optical microscope.

The PCA analysis confirmed that the mange-infected wild boars had a different metabolome signature when compared to the recovered ones (Fig. 3A). This was also evident from the volcano plot analysis, where the M *versus* R comparison showed the strongest metabolic discrepancy, since we found 24 significantly changed (17 up- and 7 down-regulated) metabolites (Fig. 3B, Supplementary Table S3). The M and I groups also were different according to the PCA (Fig. 3C), and the binary comparison led to the identification of 19 altered metabolites, of which 13 and six were more and less abundant in the M samples, respectively (Fig. 3D, Supplementary Table S3). This analysis also reported a specific increase in AC molecules and a reduction in AA levels, although to a lesser extent than compared to fully recovered animals. The metabolome of I *versus* R wild boars overlapped (Fig. 3E), thus confirming that they were metabolically similar, except for three analytes changed in the I group subjects, namely Tyr, Met (down-regulated), and C5 (up-regulated) (Fig. 3F,

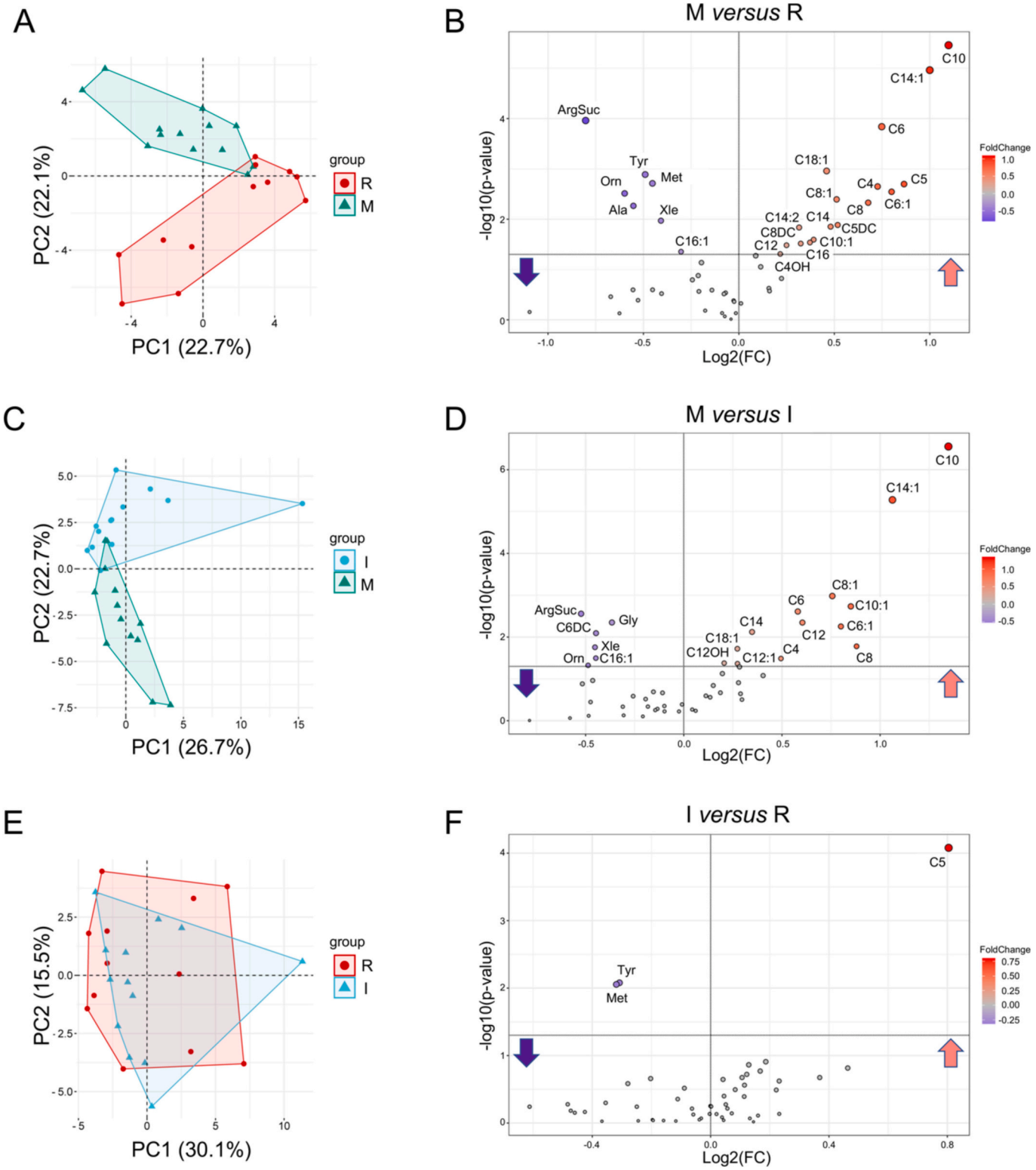
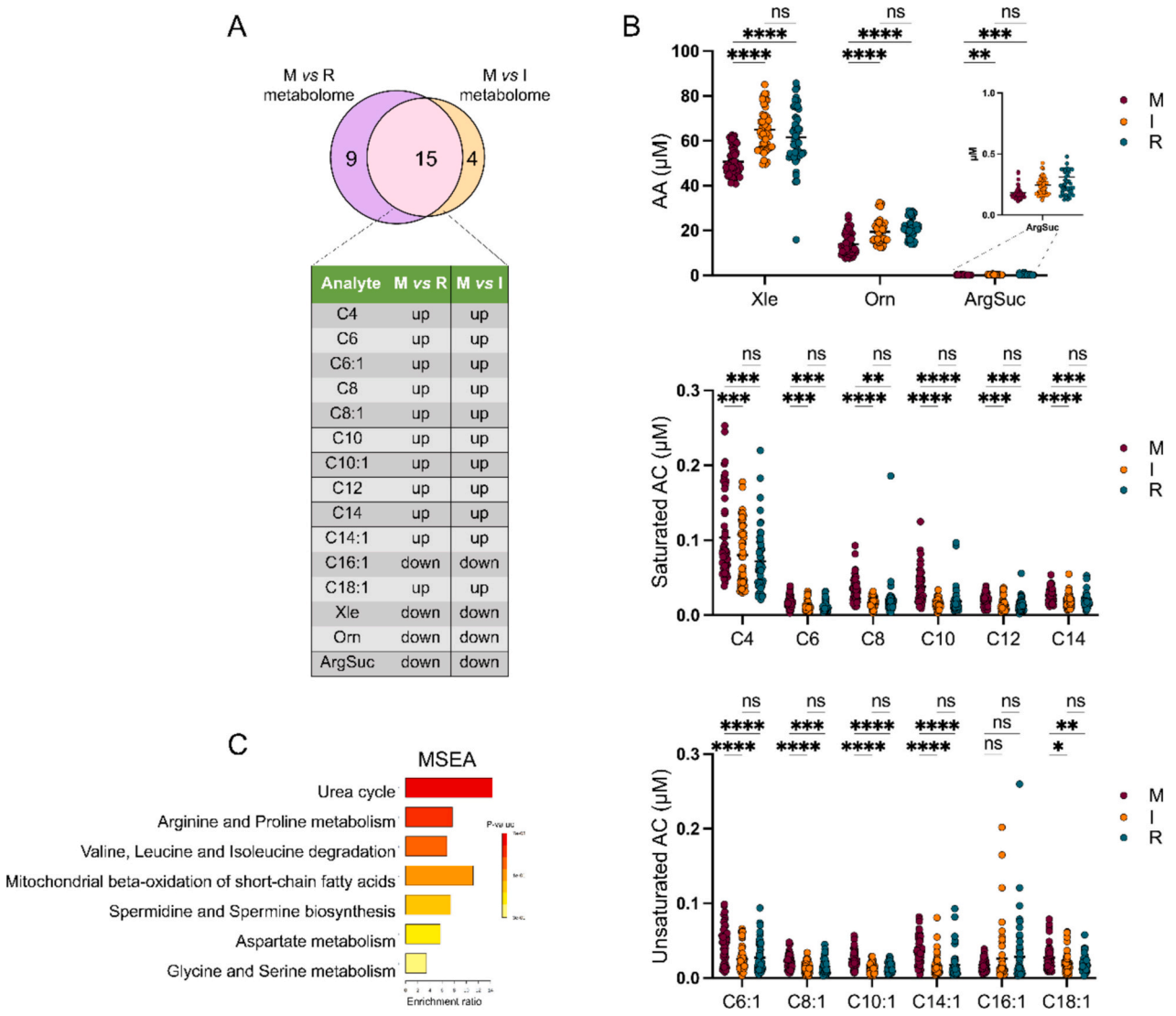


Fig. 3. Binary comparison analysis of differentially regulated metabolites. The Principal Component Analysis (PCA) on the left and volcano plots on the right show the separation of the analyzed groups and the differential metabolites, respectively, in the (A, B) M *versus* R, (C, D) M *versus* I, and (E, F) I *versus* R comparisons. The red and purple arrows indicate up- and down-regulated metabolites. The dashed lines in each plot indicate significance thresholds. FC = fold change. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Supplementary Table S3).

Fifteen metabolites were common when comparing the M metabolome with both the I and R metabolomes, showing the same trend of regulation in both comparisons (Fig. 4A).

The statistical analyses of these fifteen common metabolites agreed with the AC upregulation and AA downregulation identified by the other analyses (Fig. 4B). Accordingly, the selected AA, namely Xle, Orn, and ArgSuc all were lower in the M wild boars, whereas the I *versus* R



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

Fig. 4. Analysis of the metabolic signature of mange-infected wild boars. (A) The Venn diagram shows the common significant metabolites between M *versus* R and M *versus* I comparisons, with detail of the metabolite names and their trend of regulation in both comparisons. (B) The selected AA, saturated AC and unsaturated AC were analyzed using their original concentrations (μM) to test their variation in the multi-comparison M *versus* R, M *versus* I, I *versus* R. Statistical significance was calculated by two-way ANOVA with Tukey correction. The graphs report all the individual replicates of the experiment, with mean values ± SEM; $^{****}p < 0.0001$, $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$, ns = not significant. (C) Significant pathways as detected through Metabolite Set Enrichment Analysis (MSEA) from the common metabolites.

comparison was not significant. The concentrations of the saturated C4, C6, C8, C10, C12 and C14 AC were higher in the M and similar between the I and R groups. An analogous trend was found for the selected unsaturated AC, namely C6:1, C8:1, C10:1, C14:1, and C18:1, except for C16:1 whose *p*-values were not significant (Fig. 4B). The MSEA analysis for pathway enrichment, performed using the set of common metabolites, highlighted pathways affected by mange infection, including urea cycle, beta-oxidation of fatty acids, spermidine, and spermine biosynthesis (Fig. 4C). The enriched pathways related to the AA metabolism included arginine, proline, aspartate, glycine, serine, as well as the degradation of branched-chain (valine, leucine, isoleucine) AA (Fig. 4C).

4. Discussion

We reported for the first time the metabolome profiling and evaluation of cortisol concentrations in wild boars diagnosed with sarcoptic mange, treated with ivermectin, and healed, conditions hard to obtain when studying wild animals. Out of 51 metabolites analyzed, AA like alanine, argininosuccinate, methionine, ornithine, tyrosine and leucine-isoleucine were significantly downregulated in the mangy wild boars, who had higher concentrations 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) AC, when compared to the ivermectin-treated wild boars. The metabolic signature observed in the treated animals almost overlapped with that found in the same subjects six weeks later, when the clinical signs of the mange faded away. On the other hand, we found no significant effect of cortisol concentrations in the wild boars during the different conditions. However, wildlife animals in captivity may have welfare issues similar to those observed in domestic species, so that cortisol might be regarded as a biomarker of the stress-related response also in such a non-domestic species (d'Angelo et al., 2021; Esposito et al., 2017; Ranade et al., 2014). Moreover, the lack of any correlation between metabolome profiling and the unchanged cortisol concentrations found in the wild boars of the present study would allow us to speculate that alterations of acylcarnitines in the mange-affected condition may not be tightly dependent on hypothalamus-pituitary-adrenal axis system. Further investigations to better address this issue are needed. It is well-established that sarcoptic

mange affects a wide range of physiological responses in hosts (Carvalho et al., 2015; Fthenakis et al., 2001; Martin et al., 2018; Perez et al., 2019; Rowe et al., 2019; Valldeperes et al., 2023; Wang et al., 2022) and previous studies highlighted that the disease progression was accompanied by alterations in adipose fatty acid composition in marsupial wombats, with a significant increase of omega-6 and arachidonic acid (C20:4), together with a reduction of oleic (C18:1), alpha linoleic acid (C18:3), and total monounsaturated fats in patients (Simpson et al., 2016). The lack of skin-environment interface, due to the mange-induced alopecia can cause a dysregulated thermoregulation, leading to a six-fold increase of energy loss associated to a higher metabolic rate in the affected animals. Recent findings documented, through a non-targeted LC-MS analysis, a significant AC increase in blood, skeletal muscle, heart, liver, and brown adipose tissue of mice exposed to low temperatures (Simcox et al., 2017). In particular, once synthetized in the liver, AC provide a fuel source for non-shivering thermogenesis, which cannot properly work when the production of such fatty acids is blocked, thus highlighting a physiologic role for AC, among others, as cold-induced metabolites (Wade et al., 2021). Currently, more than one thousands of AC have been identified, and clustered according to the number of carbon atoms in the acyl group, namely short (C2–C5), medium (C6–C12), long (C13–C20), and chain (>C21) AC, which, depending on their length, play crucial roles in several pathophysiological processes, including peroxidation of fatty acids, sugar and lipid metabolism, as well as diabetes and cancer (Dambrova et al., 2022; Li et al., 2019; McCann et al., 2021). Long-chain AC (LCAC) are generally regarded as intermediates of fatty acid oxidation and exert their detrimental effects upon mitochondrial-dependent activity, by inhibiting oxidative phosphorylation and triggering the production of reactive oxygen species (Dambrova et al., 2022). The higher medium and LCAC in our subjects during the pathological condition might be associated to the non-physiological rise of β-oxidation process, which can bring about lipid overload, mitochondrial stress and poor clinical conditions as well (Amaral and Wajner, 2020; McCann et al., 2021; Sarasa et al., 2011). Methods to diagnose *S. scabiei* have limitations, because they mainly rely on clinical signs, as well as microscopic examination of skin scrapings that, unfortunately, are often hidden by other diseases (Rehbein et al., 2003; Walton and Currie, 2007). Thus, based on some limitations about sensitivity of both optical microscopy inspection and polymerase chain reaction (PCR) tools, due to the small number of mites (Bezold et al., 2001; Walton and Currie, 2007), the urge to develop more accurate and viable methods represents a still unmet need. Similarly, immunological assays, such as ELISA test, was proven to be not always high-performing, most likely because of the low numbers of parasites in infected individuals and the absence of an *in vitro* culture method for mites (El-Moamly, 2021; Piscopo et al., 2023; Raez-Bravo et al., 2016; Walton and Currie, 2007). Further studies will be helpful to gain more insights about the role of AC in the sarcoptic mange pathophysiology.

5. Conclusions

This study investigated for the first time the potential role of metabolome profiling in the blood of wild boar hosts, who had higher concentrations of LCAC when compared to the same animals, first treated with ivermectin and later healed from mange. Our preliminary data pave the way for the functional characterization of AC as putative early markers of such an endemic pathology, even in non-symptomatic individuals. Moreover, a deeper understanding of the LCAC in the metabolic homeostasis in livestock and companion animals affected by the sarcoptic mange, might hopefully allow to get more insights into control strategies, enhance animal welfare and economy burden.

Fundings

Not applicable.

CRediT authorship contribution statement

Nadia Piscopo: Writing – original draft, Resources, Project administration, Methodology, Investigation. **Michele Costanzo:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Monica Gelzo:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Luigi Sacchettino:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Chiara Vitiello:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Anna Balestrieri:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation. **Francesco Napolitano:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Luigi Esposito:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rvsc.2024.105505.

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