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DETERMINATION OF SERUM METABOLITES AMONG ASTHMA PATIENTS AFFECTED BY SMOG IN SELECTED URBAN AND RURAL AREAS OF DISTRICT FAISALABAD: A GC–MS-BASED METABOLOMIC STUDY

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Abstract

South Asia is experiencing a rise in the prevalence of smog as an environmental hazard, and the systemic biochemical effects of chronic exposure in asthma patients are not fully described. The present study aimed to explore metabolic changes in the serum of asthmatic individuals living in two different environments of District Faisalabad, Pakistan, by employing gas chromatography–mass spectrometry (GC–MS). Three groups were used for obtaining serum samples: healthy controls, rural asthma patients and urban asthma patients. The differences between the groups were marked in terms of metabolite profile as revealed by GC–MS. The metabolic complexity was higher in the asthma groups than in the healthy group, as represented by the increase in the number of chromatographic peaks and in signal intensity. The number of chromatographic peaks and the abundance of metabolites were highest in urban asthma patients, reflecting the greatest level of biochemical disturbance in association with chronic exposure to urban air pollution. One-way analysis of variance (ANOVA) revealed significant differences between the groups in serum metabolites. Lactic acid rose from 1.76 ± 0.28 µmol/L in healthy controls to 3.08 ± 0.52 µmol/L in urban asthma patients ($F = 9.12$, $p = 0.0008$); palmitic acid increased from 0.89 ± 0.16 to 1.94 ± 0.31 µmol/L ($F = 8.45$, $p = 0.001$); and oleic acid rose from 0.72 ± 0.19 to 1.59 ± 0.33 µmol/L ($F = 7.36$, $p = 0.003$). Conversely, citric acid declined from 2.18 ± 0.36 to 1.48 ± 0.26 µmol/L ($F = 5.72$, $p = 0.008$). The levels of amino acid and glucose derivatives were also markedly increased in the patients with asthma. These findings suggest disruption of energy metabolism together with an increase in oxidative stress and inflammatory activity. Cluster analysis confirmed a clear separation between healthy controls and asthma patients. Altogether, the findings show that smog exposure leads to significant alterations in serum metabolism in asthma patients, and that urban subjects are most strongly affected. The metabolites detected could be used as potential biomarkers for disease monitoring and give mechanistic insights into the biochemical association between air pollution and asthma severity.

1. Introduction

Air pollution has become one of the most critical environmental challenges to human health and ecological balance. Over the last few decades the composition of the atmosphere has significantly changed due to rapid industrialization and unplanned urban expansion, and the combustion of fossil fuels in

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industry and transport systems is the main source of air pollution. The problem is exacerbated by high population density in developing countries, the lack of environmental enforcement and unchecked industrial growth without emission control. In winter, pollution is trapped near the surface, creating more severe smog events than in other seasons of the year, which lead to extended periods of poor air quality and high concentrations of pollutants near the ground and pose significant health risks to millions of people (WHO, 2021).

Smog is a chemically reactive mixture of pollutants consisting mainly of fine and coarse particulate matter (PM2.5 and PM10), ground-level ozone, nitrogen oxides, sulfur dioxide, carbon monoxide and volatile organic compounds. Many of these species are formed through photochemical reactions under sunlight to create secondary pollutants that are more toxic than the primary ones. One of the most concerning components is fine particulate matter, due to its ability to penetrate deep into the respiratory system, where PM2.5 can enter the alveoli and bloodstream, affecting not only respiratory but also cardiovascular and neurological health (Pandis & Seinfeld, 2016; Brook et al., 2010). Air pollution is widely considered to be one of the biggest environmental risk factors for human health, responsible for approximately seven million deaths each year (WHO, 2021).

Asthma is one of the long-term respiratory conditions that is highly affected by air pollution. It is defined by persistent inflammation of the airways, reversible airflow obstruction, airway hyper-responsiveness and excess mucus secretion, which can cause recurrent coughing, chest tightness and difficulty in breathing (GINA, 2023). Excessive exposure to inhaled pollutants triggers a chain of harmful processes in the airways, one of which is oxidative stress, occurring when reactive oxygen species (ROS) are produced in greater amounts than can be neutralized by antioxidant defences, leading to lipid peroxidation, protein oxidation, DNA damage and activation of pro-inflammatory signalling. Airway remodelling is the result of repeated injury, and includes thickening of the airway walls, fibrosis and enlargement of the mucus glands (Guarnieri & Balmes, 2014; Fussell & Kelly, 2011). The clinical relationship of air pollution with asthma has been demonstrated, but the systemic biochemical changes are still poorly understood. This is where the comprehensive analysis of small-molecule metabolites (metabolomics) can help. The metabolome is subject to minute-to-minute changes as a result of the functional state of the organism and responds to environmental changes, making it possible to detect shifts in metabolite concentration in response to even a small environmental exposure (Nicholson et al., 2008). Among the most reliable metabolomic profiling platforms, gas chromatography–mass spectrometry (GC–MS) separates volatile and semi-volatile compounds and, through the resolving power of gas chromatography combined with the sensitivity and repeatability of mass spectrometry, provides both identification and quantification. Serum is a readily available biological matrix that integrates systemic metabolism over extended periods of time (Fiehn, 2016; Lindon & Nicholson, 2008). Although epidemiological studies have shown that exposure to smog is associated with exacerbation of asthma, there is limited comparative metabolomic research that compares serum metabolomic profiles in populations exposed to smog with those in groups that are not exposed, and even fewer regional studies from South Asia (Barnes, 2017; Johnson et al., 2016). In the current study, therefore, a GC–MS metabolomics approach was used to compare the serum metabolites of asthma patients in urban and rural areas of District Faisalabad with healthy controls. The specific objectives were: (1) to measure serum metabolites in asthma patients of urban and rural areas of District Faisalabad; and (2) to compare the metabolites measured in asthma patients with those of healthy people from the same area. The goal of the study is to describe pollution-associated metabolic signatures, to identify potential biomarkers of asthma severity and to elucidate the biochemical mechanisms by which air pollution is associated with respiratory disease.

2. Materials and Methods

2.1 Study design and participants

A comparative metabolomics study was carried out on serum samples of three groups: healthy controls and asthma patients from rural and

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urban areas of District Faisalabad, Pakistan. Grouping was done according to environmental exposure; urban groups had greater exposure to vehicular, industrial and construction-related pollution, while rural groups had greater exposure to biomass-fuel smoke and seasonal burning of agricultural residues. All procedures followed ethical standards for the safety of participants, their dignity and confidentiality.

2.2 Ethical considerations

The relevant institutional ethics review committee gave ethical approval before the experimental work began. All subjects gave written informed consent after being informed of the purpose, objectives and procedures used in the study, and were told that they had the right to withdraw at any time without penalty. All personal and medical information was kept confidential by using coded identifiers instead of names, and all data were used only for research purposes. The research was carried out in compliance with the guidelines for medical research on human subjects of the World Medical Association Declaration of Helsinki (2013) and the World Health Organization (WHO, 2021).

2.3 Sample collection and serum preparation

Trained personnel took blood samples from all participants according to standard clinical and biosafety protocols in order to reduce discomfort to the patients and contamination of the samples. The serum fraction was separated by centrifugation, containing the metabolites generated in cellular processes. Aliquots of serum were stored for appropriate periods of time before analysis. Prior to instrumental analysis, the serum samples were chemically prepared (extraction, derivatization and filtration) to make them suitable for GC–MS analysis (Dunn et al., 2011; Fiehn, 2019).

2.4 GC–MS analysis

The gas chromatography–mass spectrometry system was equipped with a capillary column optimized for metabolites, and the prepared serum extract was injected. The compounds were vaporized and carried down the column by an inert gas, separating according to their volatility and chemical interaction with the stationary phase, and were finally detected by the mass spectrometer. Every metabolite detected yielded a specific peak in the chromatogram with a characteristic mass spectrum (m/z and fragmentation pattern) (Bessonneau et al., 2014; Fiehn, 2019).

2.5 Metabolite identification and evaluation metrics

Agilent MassHunter software was used to compare the acquired mass spectra with the NIST mass spectral library, and only compounds with high similarity scores were reported as metabolites. Three criteria of evaluation were used. Peak area was used as a measure of the relative abundance of metabolites, on the assumption that the peak area is proportional to the amount of metabolite. Retention time was used for identification, and varies for each compound according to the chromatographic conditions. Compounds were identified by matching their mass spectra with the NIST database (National Institute of Standards and Technology, 2020).

2.6 Statistical analysis

Peak area values were used as a relative measure of metabolite concentration. Descriptive statistics were used to summarize metabolite abundance, and one-way analysis of variance (ANOVA) was used to test for differences in metabolite abundance between the three groups at a significance level of $p < 0.05$. Cluster analysis was used to examine patterns of similarity between samples and between metabolites, and to test the ability to separate healthy controls from asthma patients (Smith et al., 2006; Comhair et al., 2015).

3. Results

3.1 Overall metabolic profiling

Several classes of metabolites were detected by GC–MS in the serum of all participants, including organic acids, fatty acids, amino acid derivatives and other small-molecule compounds associated with biochemical signalling, immune response and cellular respiration. The chromatograms varied markedly between the groups. Healthy controls showed a relatively simple profile, with a few low- to medium-intensity peaks, typical of normal physiological metabolism. Rural asthma patients showed an intermediate profile, whereas urban

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asthma patients had the most complex metabolome, with the highest number of peaks and the greatest overall abundance, suggesting substantial biochemical disturbance associated with chronic exposure to urban air pollution. The overall metabolic profiling outcome across the three groups is summarized in Figure 1.

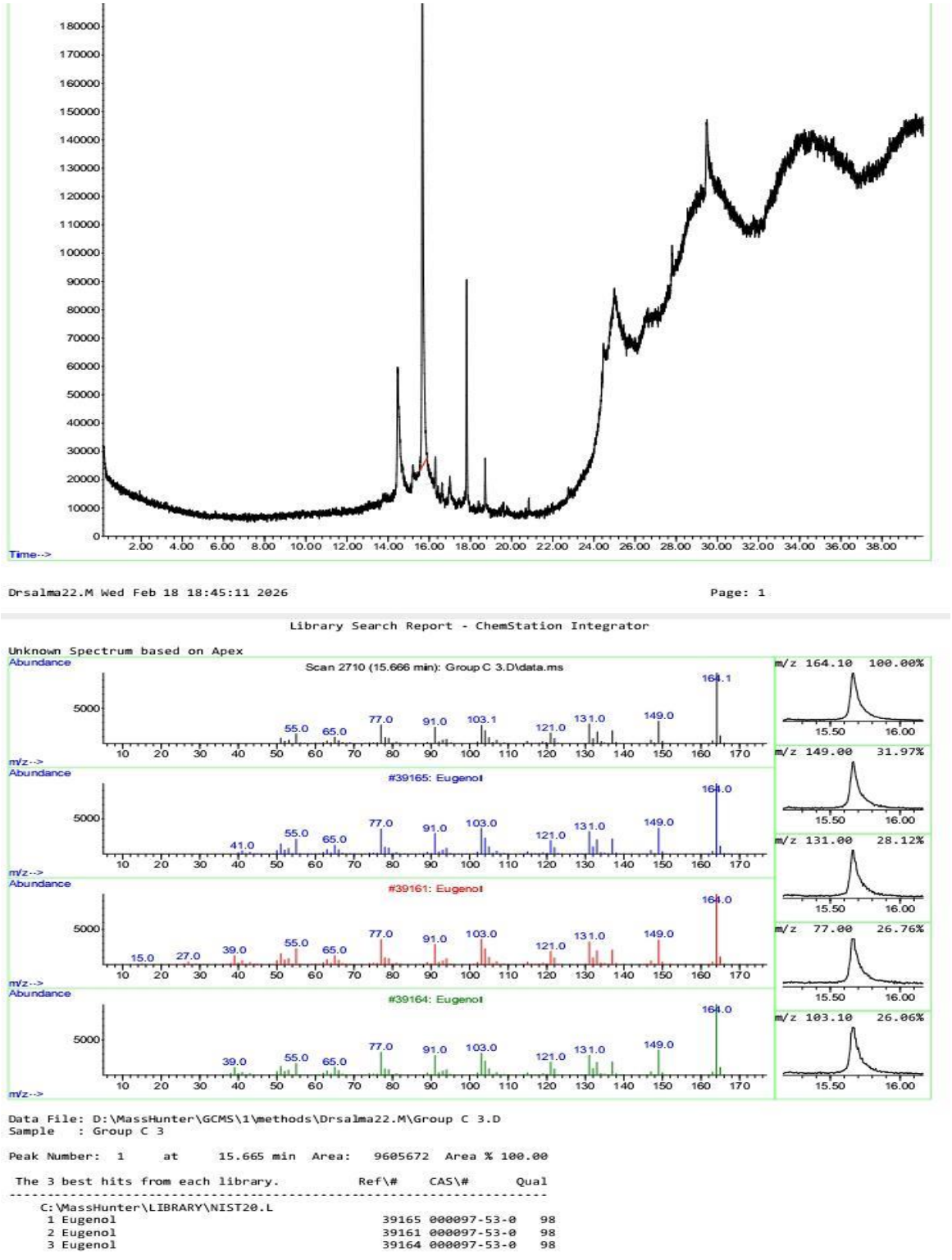


Figure 1. Overall metabolic profiling of serum samples from healthy controls, rural asthma patients and urban asthma patients, showing a progressive increase in metabolic complexity with increasing environmental exposure.

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3.2 Group-wise chromatographic patterns

3.2.1 Healthy control group

The chromatograms of the healthy control group showed a stable baseline with a limited number of peaks across a retention-time range of 0–40 minutes, indicating a relatively normal metabolic profile compared with the diseased samples. Distinct peaks were observed at retention times of approximately 10.5, 12.0, 14.6, 16.2 and 18.5 minutes (Figure 2). The peak at approximately 14.6 minutes exhibited the highest abundance, suggesting a dominant metabolite in healthy serum. The corresponding peak-value distribution is presented in Figure 3. Compared with the chromatograms obtained from asthma patients exposed to smog, the control chromatogram showed fewer peaks and lower overall intensity, indicating reduced metabolic disturbance. The detected peaks were subsequently identified by comparison with the NIST mass spectral library using Agilent MassHunter (Bessonneau et al., 2014; Fiehn, 2019).

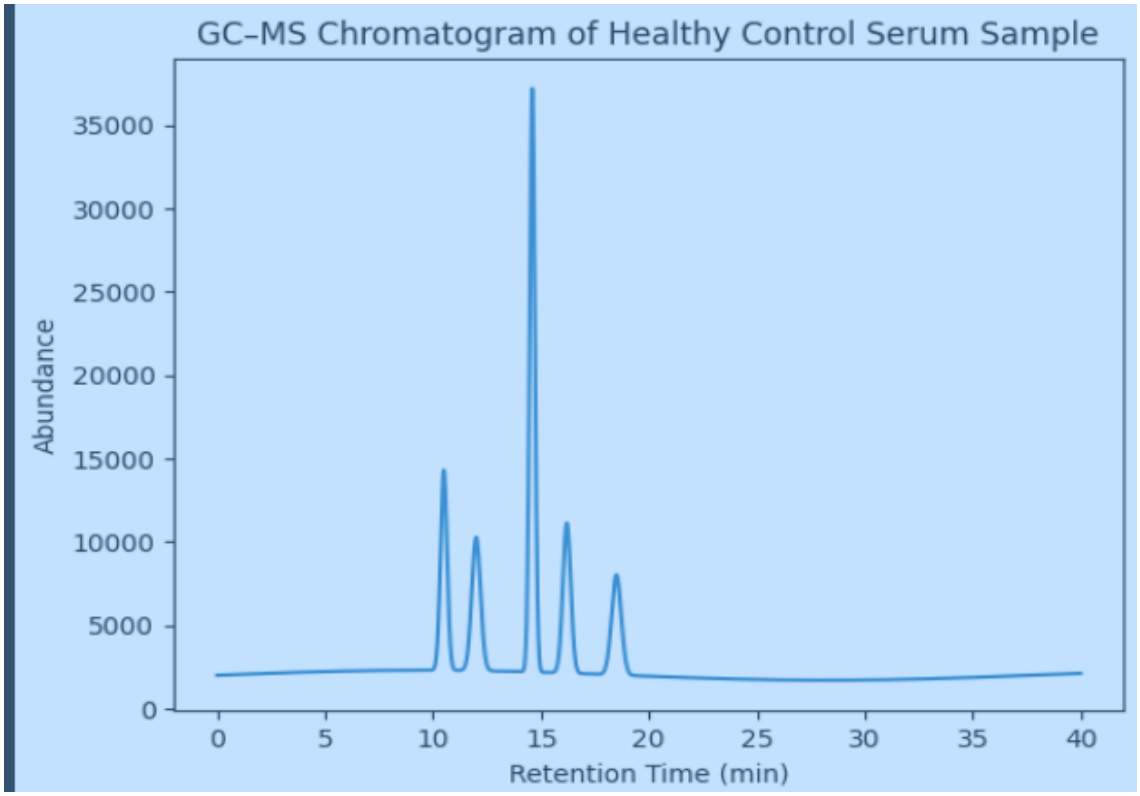
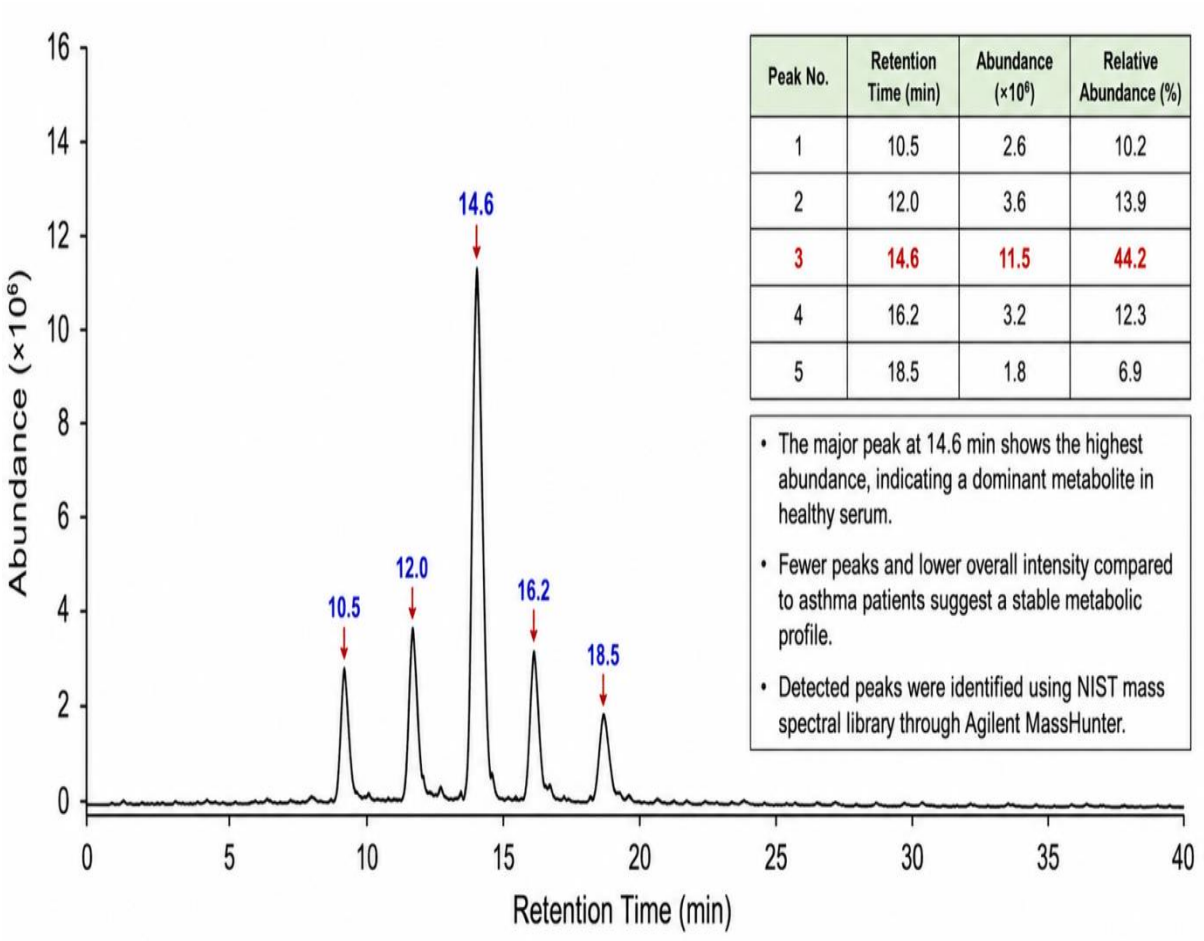


Figure 2. GC–MS chromatogram of serum from the healthy control group, showing a stable baseline and a limited number of peaks over the 0–40 minute retention-time window, with the dominant peak at approximately 14.6 minutes.

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Peak No.	Retention Time (min)	Abundance (×10⁶)	Relative Abundance (%)
1	10.5	2.6	10.2
2	12.0	3.6	13.9
3	14.6	11.5	44.2
4	16.2	3.2	12.3
5	18.5	1.8	6.9

- The major peak at 14.6 min shows the highest abundance, indicating a dominant metabolite in healthy serum.
- Fewer peaks and lower overall intensity compared to asthma patients suggest a stable metabolic profile.
- Detected peaks were identified using NIST mass spectral library through Agilent MassHunter.

Figure 3. Peak-value distribution of the metabolites detected in healthy control serum, showing low to moderate abundance across the identified retention times.

3.2.2 Asthma patients from rural areas

The serum of rural asthma patients showed a moderate number of peaks distributed over a retention-time range of approximately 0–40 minutes, with clear peaks in the vicinity of 9.8, 11.2, 13.0, 14.6, 16.5, 18.0 and 21.5 minutes and higher signal intensities compared with the controls (Figure 4). As in the control group, the peak at approximately 14.6 minutes exhibited the highest abundance, indicating a dominant metabolite within the serum of this group. The corresponding peak values and the graphical representation of relative abundance are shown in Figure 5 and Figure 6, respectively. These changes reflect alterations in pathways associated with inflammation, oxidative stress and immune response, which may be influenced by agricultural activities, exposure to biomass-fuel smoke and naturally occurring allergens commonly present in rural settings. Nevertheless, the number and complexity of the peaks remained moderate when compared with the urban asthma samples (National Institute of Standards and Technology, 2020; WHO, 2021).

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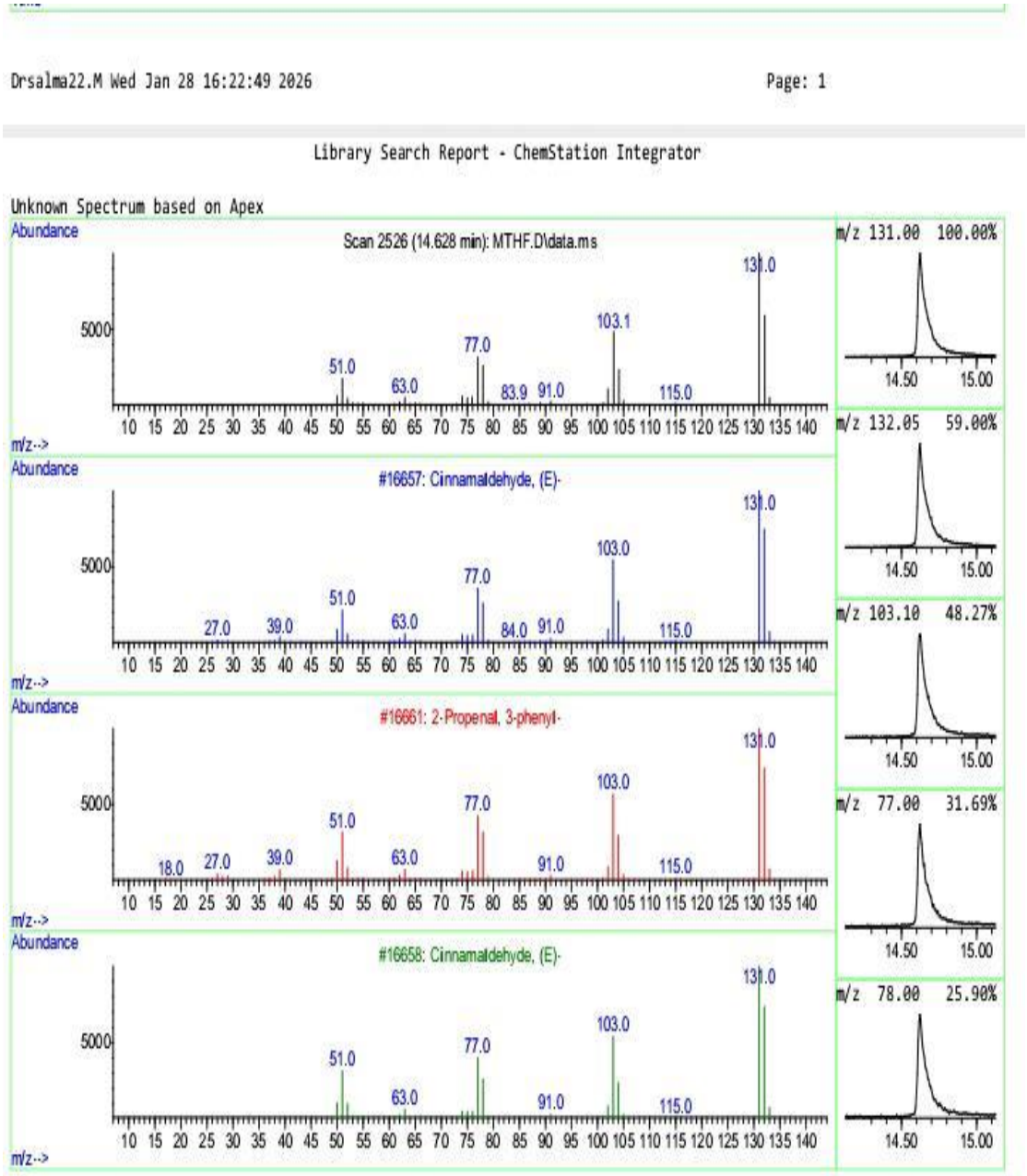
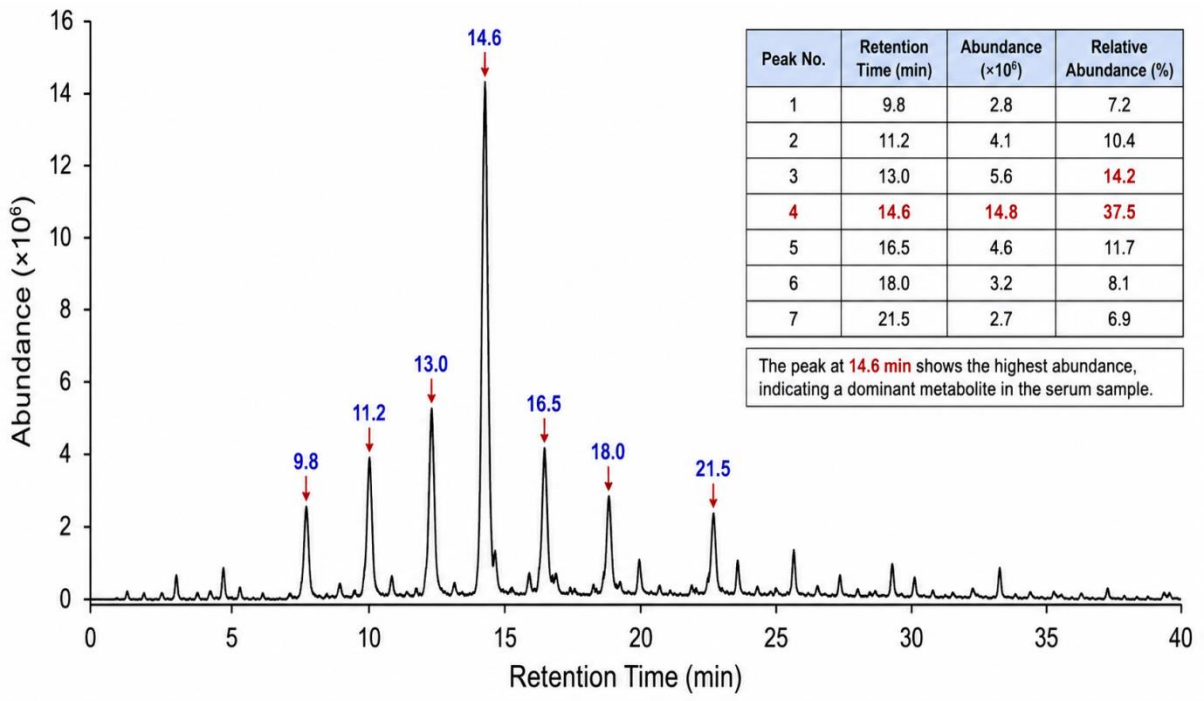


Figure 4. GC–MS chromatogram of serum from asthma patients residing in rural areas, showing a moderate number of peaks and higher signal intensities than the healthy control group.

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Peak No.	Retention Time (min)	Abundance (×10⁶)	Relative Abundance (%)
1	9.8	2.8	7.2
2	11.2	4.1	10.4
3	13.0	5.6	14.2
4	14.6	14.8	37.5
5	16.5	4.6	11.7
6	18.0	3.2	8.1
7	21.5	2.7	6.9

The peak at 14.6 min shows the highest abundance, indicating a dominant metabolite in the serum sample.

Figure 5. Peak values of the metabolites detected in the serum of rural asthma patients.

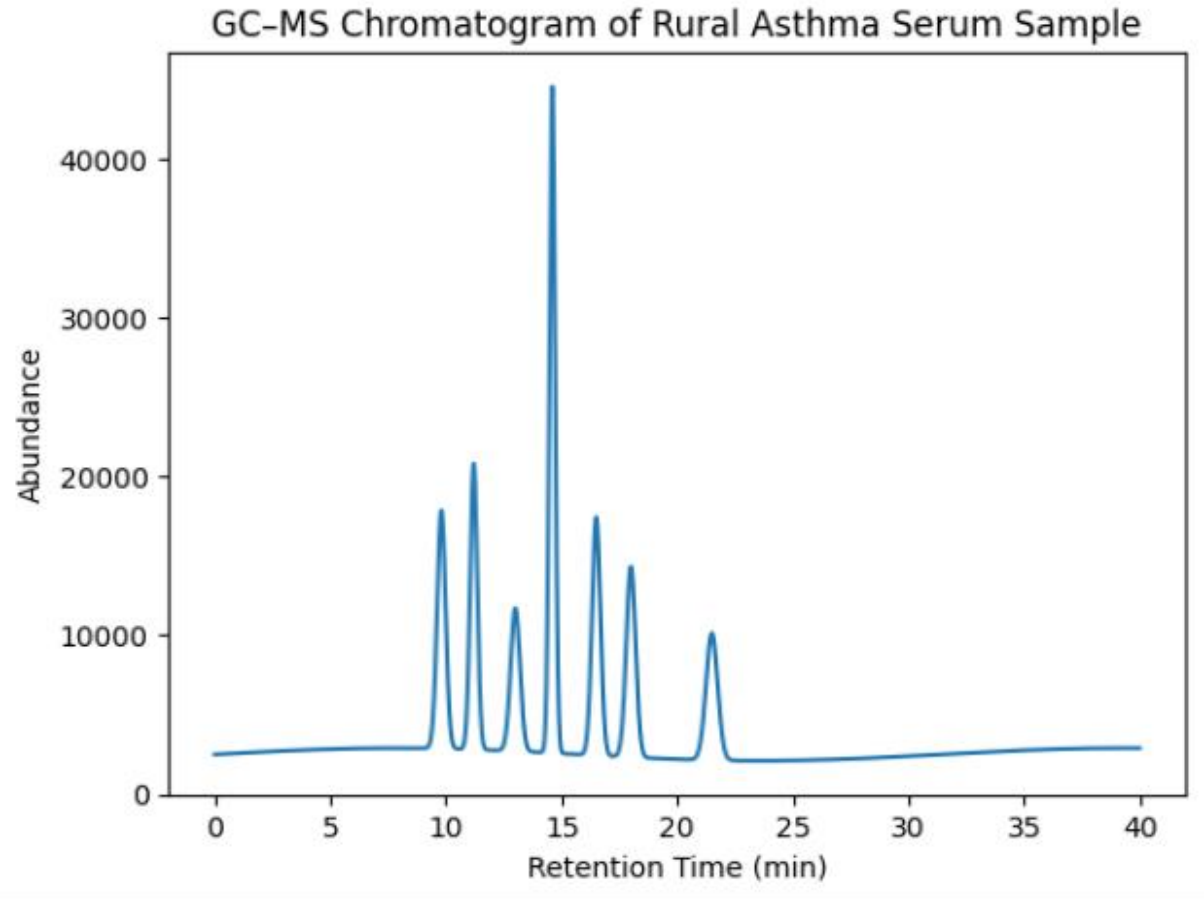


Figure 6. Graphical representation of relative metabolite abundance in the serum of rural asthma patients.

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3.2.3 Asthma patients from urban areas

Consistent with the complex metabolic effects of the PM2.5, NOx, SO2, O3 and volatile organic compounds that make up urban smog, urban asthma patients exhibited the most complicated profile, with numerous intense peaks and the highest abundance values (Figure 7). Multiple prominent peaks were detected at retention times of approximately 8.9, 10.5, 12.1, 14.6, 15.8, 17.3, 19.0, 23.0 and 27.5 minutes. The most intense signal was again observed at approximately 14.6 minutes (Figure 8), indicating a highly abundant major metabolite in the serum of urban asthma patients and suggesting substantial metabolic activity and possible accumulation of compounds related to environmental stress. The greater peak density and abundance in the urban group, relative to both the rural asthma group and the healthy controls, indicate that chronic exposure to urban smog plays a critical role in altering serum metabolite composition (Gautam et al., 2022; Kelly et al., 2017). The main qualitative differences between the three groups are summarized in Table 1.

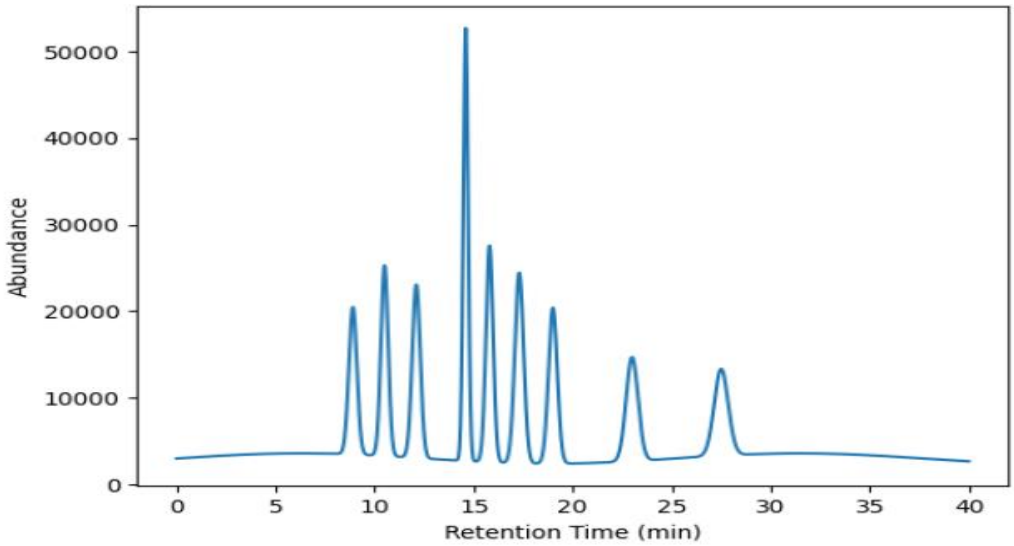
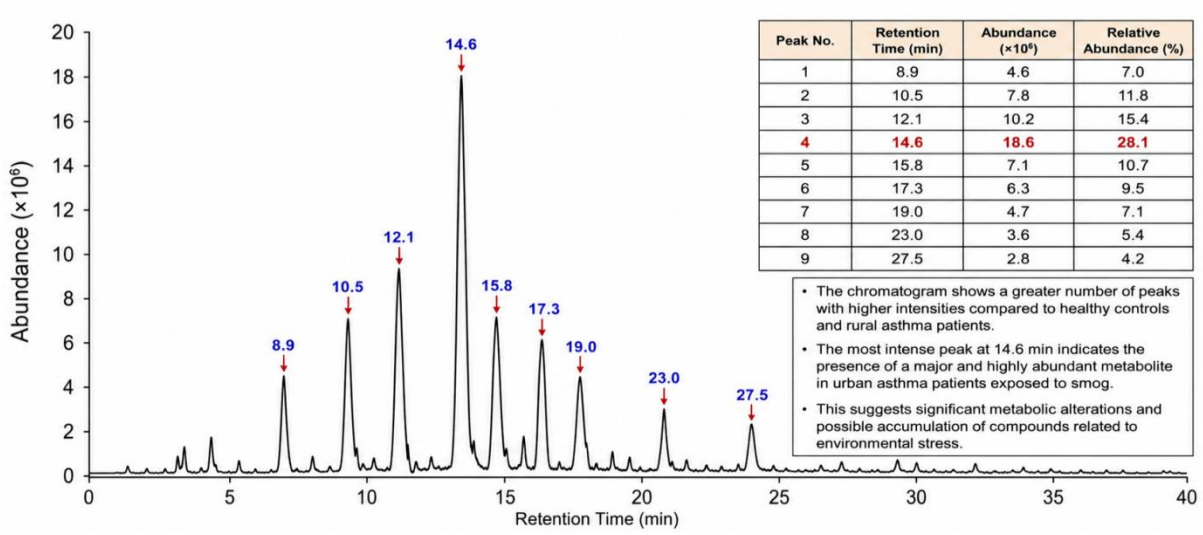


Figure 7. GC–MS chromatogram of serum from asthma patients residing in urban smog-exposed areas, showing the highest number of peaks and the greatest signal intensities among the three study groups.



Peak No.	Retention Time (min)	Abundance (×10⁶)	Relative Abundance (%)
1	8.9	4.6	7.0
2	10.5	7.8	11.8
3	12.1	10.2	15.4
4	14.6	18.6	28.1
5	15.8	7.1	10.7
6	17.3	6.3	9.5
7	19.0	4.7	7.1
8	23.0	3.6	5.4
9	27.5	2.8	4.2

Figure 8. Expanded view of the intense chromatographic peak detected at approximately 14.6 minutes in the serum of urban asthma patients, representing the most abundant metabolite in this group.

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Table 1. Qualitative comparison of GC–MS chromatographic profiles among the three study groups.

Feature	Healthy control	Rural asthma	Urban asthma
Number of peaks	Few	Moderate	Highest
Peak intensity	Low–moderate	Moderate	Very high
Metabolic complexity	Simple profile	Slightly altered	Highly altered
Environmental influence	No pollution exposure	Mild environmental factors	High smog / pollutant exposure
Biological interpretation	Normal metabolism	Disease-related change	Severe metabolic disturbance

3.3 Quantitative comparison of serum metabolites

One-way ANOVA revealed statistically significant differences in serum metabolite concentrations between the three groups (Table 2). Lactic acid increased progressively from healthy controls (1.76 ± 0.28 µmol/L) through rural asthma patients (2.35 ± 0.40 µmol/L) to urban asthma patients (3.08 ± 0.52 µmol/L; F = 9.12, p = 0.0008). The long-chain fatty acids palmitic, oleic and stearic acid increased in a similar manner; palmitic acid, for example, rose from 0.89 ± 0.16 to 1.94 ± 0.31 µmol/L (F = 8.45, p = 0.001). Levels of glucose and amino acid derivatives were also significantly higher in asthma patients (glucose derivative 4.21 ± 0.73 vs. 3.46 ± 0.61 µmol/L, F = 4.96, p = 0.013; amino acid derivative 2.29 ± 0.41 vs. 1.39 ± 0.27 µmol/L, F = 7.44, p = 0.003). In contrast, citric acid declined from 2.18 ± 0.36 µmol/L in controls to 1.48 ± 0.26 µmol/L in urban patients (F = 5.72, p = 0.008). All F-values ranged between 4.96 and 9.12 and all p-values were well below 0.05. The group-wise comparison of the key serum metabolites is illustrated in Figure 9.

Table 2. Statistical comparison of serum metabolites among study groups (mean ± SD; one-way ANOVA).

Serum metabolite	Healthy control (µmol/L)	Asthma – rural (µmol/L)	Asthma – urban (µmol/L)	F-value	p-value
Lactic acid	1.76 ± 0.28	2.35 ± 0.40	3.08 ± 0.52	9.12	0.0008
Palmitic acid	0.89 ± 0.16	1.27 ± 0.24	1.94 ± 0.31	8.45	0.001
Oleic acid	0.72 ± 0.19	1.18 ± 0.27	1.59 ± 0.33	7.36	0.003
Citric acid	2.18 ± 0.36	1.91 ± 0.34	1.48 ± 0.26	5.72	0.008
Glucose derivative	3.46 ± 0.61	3.79 ± 0.67	4.21 ± 0.73	4.96	0.013
Stearic acid	0.63 ± 0.12	0.88 ± 0.18	1.17 ± 0.23	6.88	0.004
Amino acid derivative	1.39 ± 0.27	1.86 ± 0.33	2.29 ± 0.41	7.44	0.003

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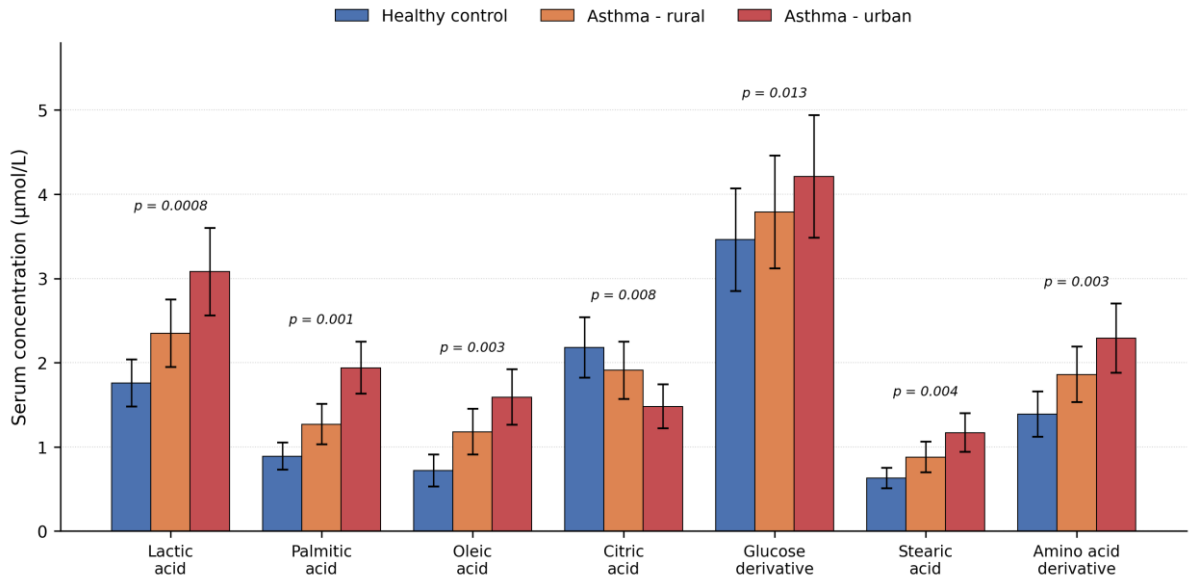


Figure 9. Comparison of key serum metabolite levels among healthy controls, rural asthma patients and urban asthma patients. Bars represent mean ± SD; p-values are derived from one-way ANOVA.

3.4 Cluster analysis

Samples and metabolites were clustered according to the similarity of their chemical profiles. Serum samples from asthma patients showed a clear separation from those of healthy controls, indicating that the overall metabolic composition of the two groups differs. Metabolites belonging to related biochemical pathways were grouped together: fatty acids formed a cluster related to lipid metabolism, while organic acids formed a cluster related to energy production. Consistent with the chromatographic and statistical analyses (Comhair et al., 2015; Kanehisa & Goto, 2000), these patterns suggest that smog exposure affects multiple and interconnected metabolic systems rather than isolated pathways.

4. Discussion

The present study revealed that exposure to smog is correlated with distinct serum metabolic changes in subjects with asthma from rural and urban areas of Faisalabad. GC–MS showed significant differences between the healthy controls and the asthma patients, and the extent of the disturbance observed in urban populations, who are exposed to higher levels of vehicular exhaust and particulate matter (Figures 7 and 8), suggests that chronic exposure to polluted air induces systemic biochemical changes that extend beyond the immediate airway inflammation seen in asthma (Kelly et al., 2017; Gautam et al., 2022).

An important finding was the higher abundance of metabolites related to oxidative stress and inflammation. Higher levels of organic acids, fatty acids and glucose derivatives are consistent with overproduction of reactive oxygen species and subsequent oxidative damage to cellular components, as reported previously for chronic exposure to PM2.5 and NO2 (Li et al., 2008; Otenbaker & Zuo, 2013). These oxidative injuries trigger inflammatory signalling and may contribute to airway hyper-responsiveness, mucus hypersecretion and progressive remodelling.

The increase in lactic acid and glucose derivatives together with the decrease in citric acid (Figure 9) indicates a change in energy metabolism. The decline in citric acid, a major intermediate of the tricarboxylic acid (TCA) cycle, may reflect reduced mitochondrial function and a metabolic switch to anaerobic glycolysis under inflammatory or hypoxic conditions; the rise in lactate suggests increased anaerobic metabolism, possibly as a compensatory mechanism for impaired oxygen utilization in asthmatic lungs (Agrawal et al., 2013; Lindon & Nicholson, 2012). The progressive elevation of palmitic, oleic and stearic acid suggests altered lipid metabolism with increased lipid peroxidation, while the

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increase in amino acid derivatives suggests an adaptive response to oxidative stress, in particular an increased requirement for antioxidant precursors such as glutathione (Rastogi et al., 2015; Pite et al., 2018).

Exposure intensity differed between rural and urban patients, which further demonstrates that the degree of exposure matters. Urban patients showed more numerous and more intense chromatographic peaks and higher metabolite abundances (Figure 7) than rural patients (Figure 4), indicating a greater biochemical perturbation caused by industrial emissions, vehicular exhaust and construction-related particulates. Despite this, the rural patients also showed evident metabolic changes compared with controls (Figures 2 and 4), likely due to exposure to biomass-fuel smoke and seasonal crop-residue burning prevalent in rural Punjab (Dikshit & Sharma, 2016; Vrijheid, 2014). Cluster analysis further showed that pollution-induced metabolic changes were coordinated across energy, lipid and inflammatory pathways (Reinke et al., 2017).

From a translational point of view, several of the metabolites identified here that relate to oxidative stress, lipid peroxidation and altered energy metabolism are promising candidates as serum markers of pollution-induced asthma. Such biomarkers could be useful for early detection before the onset of serious clinical symptoms, for measuring disease severity and for identifying patients at increased risk of pollution-related exacerbations, thereby embedding metabolomics further into precision respiratory medicine (Chiu & Huang, 2018; Wishart et al., 2013). The study is limited by the use of group-level environmental classification instead of quantification of individual exposure, and by the scope of the sample; future studies with individual exposure assessment and broader pathway-based analysis would extend and reinforce the results obtained here.

5. Conclusion

In this GC–MS-based metabolomic study, exposure to smog was found to disturb metabolic homeostasis in the serum of asthma patients, affecting several metabolic pathways including oxidative stress, lipid metabolism and energy production. Asthma patients living in urban areas showed the most pronounced changes, with increased levels of lactic acid, long-chain fatty acids, glucose derivatives and amino acid derivatives, and decreased levels of citric acid, compared with healthy controls. Asthma patients living in rural areas also showed clear pollution-related changes relative to healthy controls. A clear distinction between healthy and diseased metabolic profiles was established using cluster analysis. The results suggest that environmental pollutants act systemically, beyond the respiratory tract, and reveal the value of serum metabolomics for biomarker discovery and disease monitoring. They also highlight the importance of implementing effective environmental management measures to lower the health impact of air pollution on sensitive groups.

Conflict of Interest

The authors have no conflict of interest

Funding Source

There is no funding source for the current research

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