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Metabolites in Modern Medicine: Decoding the Future of Health and Diseases

B. Harshitha[1], Ashwini V.[2], Fazeela Mahaboob Begum S.M.[3,*]

Abstract

The end products of many metabolic processes in cells are called metabolites. Each reaction contributes a specific metabolite. Metabolites act as fingerprints of on-going biological processes. Constant changes in cellular composition due to both environmental and internal factors. By analysing the types and presence of metabolites, scientists can effectively reconstruct the inner workings of a cell or organism. In the past, analysing metabolites was a slow and tedious process, often limited to measuring a small number of known metabolites. As technology advances, the development of new analytical tools has made metabolic profiling convenient by screening thousands of metabolites simultaneously. By analysing changes in metabolite profiles, we can identify the effects of environmental contaminants on organisms. As the downstream products of gene expression and environmental interactions, metabolites serve as valuable biomarkers for various diseases. With their ability to predict treatment response, diagnose diseases earlier, and improve patient outcomes, metabolite biomarkers hold great promise to revolutionize the healthcare profession. By identifying unique metabolic fingerprints researchers can stratify patients into subgroups with distinct disease trajectories and treatment responses. Metabolomics is being used to develop personalized therapies that will improve patient outcomes and reduce side effects. Advances in technology of metabolomics paves a way for its integration into the clinical practices. This promises a future where diseases can be prevented, diagnosed, and treated, leading to improved health and longevity. This review highlights the metabolome's significance as a tool for understanding cellular function and disease. It also explores the application of metabolomics in various fields of biology and medicine.

Keywords: Metabolites, metabolic profile, biomarkers, cellular function, disease, environmental contaminants

INTRODUCTION

Metabolites, the intermediate products are produced by enzyme catalysed reactions in cells during metabolism. Plants, animals, and microbes produce the metabolites. Metabolites are the final product of any biochemical reactions taking place within a cell. Since metabolites are the product of any cellular activity, changes in metabolic profile reflect in phenotypic variations. The metabolome represents the entire collection of low-molecular-weight substances found within a biological system. Metabolomics is an emerging field where analytical technologies are used to discover metabolite profiling in a target organism. This high-throughput method enables researchers to analyze and understand the variances in total metabolite profiles at once. Recently, great progress has been made in this area. Technological advances in mass spectroscopy (MS) and

***Author for Correspondence**
Fazeela Mahaboob Begum S.M.
E-mail: fazeelabegum@crescent.education

[1–2]Students, School of Life Sciences, BS Abdur Rahman Crescent Institute of Science and Technology, Chennai, Tamil Nadu, India
[3]Assistant Professor, School of Life Sciences, BS Abdur Rahman Crescent Institute of Science and Technology, Chennai, Tamil Nadu, India

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bioinformatics have revolutionized the analysis and interpretation of large amounts of data from metabolomics studies [1, 2]. Figure 1 is central dogma of biology is depicted.

The basic step in any metabolomic experiment is to quantify the number of metabolites. In most cases, a specific set of metabolites are analyzed through a targeted approach. In other cases, huge quantities of metabolites are analyzed using a global approach. There are several approaches to metabolomics, and the chosen approach depends on the specific goals of the research. The leading methodologies used in metabolomics are (i) targeted analysis (ii) untargeted analysis [3, 4]. In Figure 2, workflow of metabolomics is depicted.

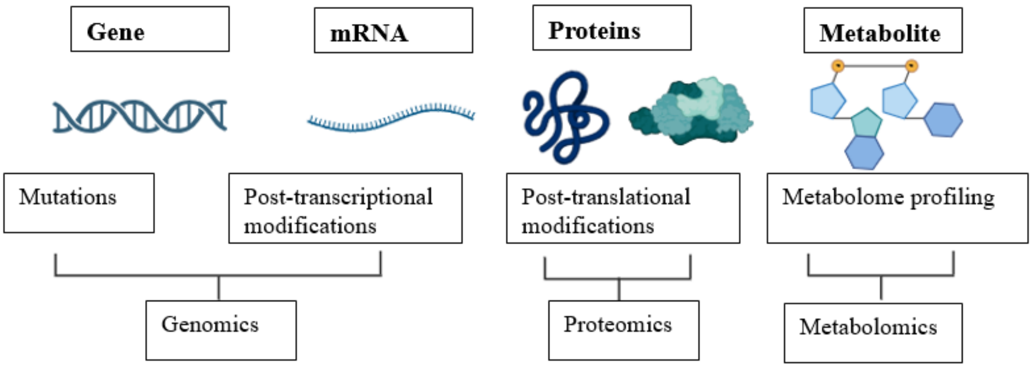

Figure 1. Central dogma of biology.

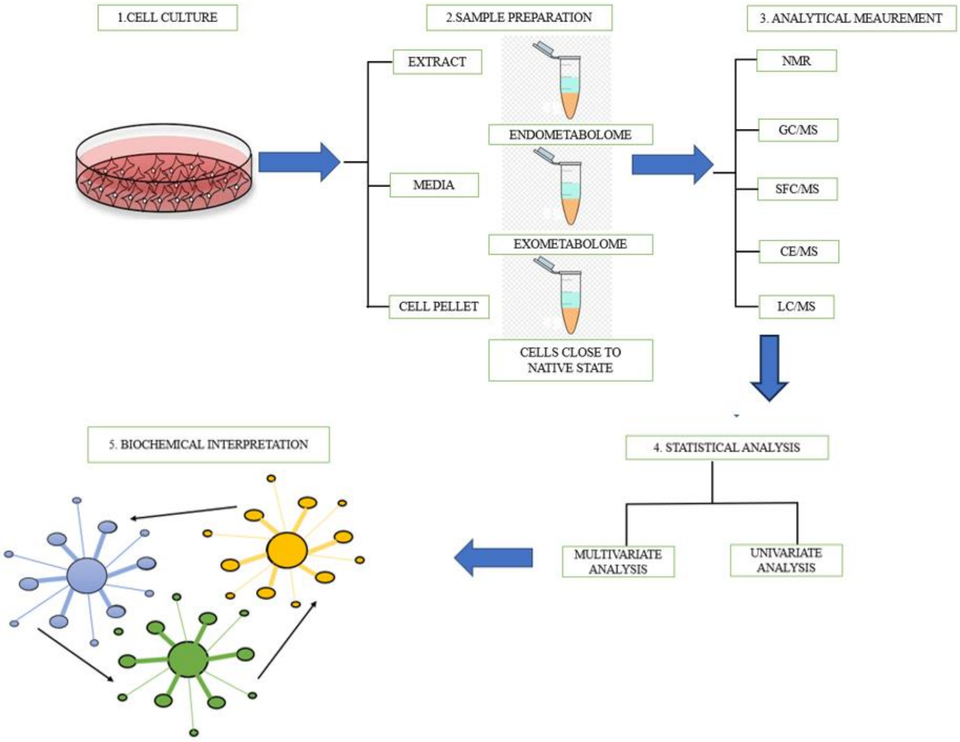

Figure 2. Workflow of metabolomics.

The targeted metabolomics focuses on a pre-defined list of well-characterized metabolites, based on the researcher's specific interest. As the targeted approach deals with only a specific set of metabolites, it offers higher precision and sensitivity in quantifying the metabolites. Targeted metabolomics has many advantages and serves as a powerful tool for researchers in pharmacokinetic studies by providing an in-depth investigation of drug metabolism. Low-abundance metabolites can be detected using targeted approach. Untargeted metabolomics measures all the metabolites present in the biological sample simultaneously. LC/MS is a powerful technique for untargeted metabolomics as it can measure a wide range of metabolites in a small sample volume. The untargeted approach produces a massive dataset when compared to targeted analysis. Precise quantification of the specific metabolite is not possible, posing to a major disadvantage [5, 6].

Metabolome has evolved as a powerful tool in disease diagnosis and has shown remarkable results in biomarker discovery. The goal of metabolomics is to comprehensively analyze all metabolites within a biological sample in a single experiment, a challenge scientists are actively addressing [7, 8].

TECHNOLOGICAL ADVANCEMENTS IN METABOLOMICS

Currently, no technology is available to analyze all the metabolites simultaneously as these metabolites vary greatly. So, it is needed to limit down the number of metabolite targets to obtain the metabolome data using a single or combination of instruments. Metabolomic techniques offer high-sensitivity analysis of biological specimens [9, 10]. Important methods for the analysis and characterisation of metabolites include nuclear magnetic resonance (NMR), gas chromatography-mass spectrometry (GC-MS), and liquid chromatography-mass spectrometry (LC-MS). Each technique provides different advantages, including specificity, sensitivity, and characterisation. MS is the higher standard for metabolite identification, providing exceptional sensitivity and specificity, enabling the detection of trace metabolites in biological fluids, and facilitating the characterisation and quantification of unknown compounds in conjunction with bioinformatics. Additionally, MS is integrated with NMR to provide efficient results using various software [11].

The following metabolomic tools are commonly employed in the analysis of samples.

NMR

NMR spectroscopy has emerged as the predominant analytical method in metabolomics research within the last 10 years. According to this method, metabolites are subjected to magnetic fields where specific resonance absorption rates of the metabolites are detected. NMR is based on rotations of atomic nuclei. The two key advantages of NMR that make it a valuable analytical measurement tool are non-invasiveness and there is no need for separation. In the next step, samples will be analyzed by LC-MS and GC-MS [12]. Sample preparation in NMR is relatively simple and easy when compared to other techniques. NMR is used to analyze biofluids and solids/ semi-solid samples. The greatest advantage of NMR is its ability to identify the structure of novel unknown samples. NMR spectroscopy, being a powerful tool for metabolomics, has a major drawback of being low sensitivity. It requires a relatively large amount of sample compared to other techniques to achieve accurate identification of metabolites [13–15].

GC/MS

GC utilizes the variance in physical and chemical characteristics to separate the components of a mixture. Through mass-to-charge (m/z) ratio analysis, MS enables the identification of specific molecules. This combination led to the evolution of the GC/MS technique. The key advantages that make GC/MS a popular and powerful tool in metabolomics are high peak capacity, retention time, and readily available compound libraries. Derivatisation is a crucial step in GC/MS analysis for non-volatile compounds. Only volatile samples can be analyzed in GC/MS. This is a challenge for non-volatile compounds that don’t readily get converted to the gas phase at high temperatures used in GC. This can be overcome by derivatisation. Derivatisation is a process of chemically modifying samples to make them into volatile and thermally stable compounds. Each compound generates a unique mass spectrum in GC/MS due to the fragmentation patterns created by electron ionisation (EI). This fingerprint serves as a unique identifier for the compound. EI is a consistent method of producing reproducible fragmentation patterns for a given compound. The National Institute of Standards and

Technology (NIST) maintains a massive library of mass spectra for a vast number of known compounds. By comparing the mass spectrum of an unknown compound with the NIST library, researchers can identify the compound. The more advanced version of GC/MS, the two-dimensional GC/MS that provides more upgraded results on peak values, sensitivity, and resolution [16–18].

LC/MS

LC utilizes the differences in chemical properties to separate the components of a mixture. MS identifies and characterizes the individual components separated by LC. LC/MS has higher sensitivity, it can detect a wide range of metabolites, even if present in low quantities, which is crucial for metabolite profiling. Electrospray Ionisation (ESI) is a critical component in LC/MS, especially for analysanalysing large and fragile metabolites [19]. The major advantage of the ESI technique is its soft ionisation principle. It doesn't cause any breakage in the fragile metabolite molecules during the ionisation process. This is crucial for accurately determining their molecular weight and structure. Ultra-High-Performance Liquid Chromatography (UHPLC) utilizes smaller particles in the column, allowing for higher pressure and faster separation times compared to traditional High-Performance Liquid Chromatography (HPLC). Also, there is no need for derivatisation in HPLC analysis [20, 21].

SUPERCRITICAL FLUID CHROMATOGRAPHY/MS

Recent studies have shown that SFC/MS is a better alternative for metabolomic analysis. Unlike traditional LC analysis, SFC uses supercritical fluid as a mobile phase. SFC has characteristics of both GC and HPLC and was developed especially to analyze lipid metabolites [22]. SFC surpasses HPLC in separation efficiency due to the superior diffusion rate of supercritical fluids. Carbon dioxide is most widely used supercritical fluid, making SFC an effective method to analyze hydrophobic metabolites. SFC is predominantly used for non-polar metabolite analysis because of carbon dioxide's non-polar nature. By adding a polar solvent to the CO_2 mobile phase, SFC can be altered to analyze polar metabolites. Some key advantages of SFC due to the supercritical fluid used in the mobile phase are high-solvating power, high-flow rates with consistent resolution, and coupling of columns. GC and HPLC may have some limitations, SFC is considered advantageous over these traditional techniques. Thus, SFC is used for metabolites that are thermally degradable and those having high-boiling points. SFC's combination of high resolution and high throughput make it an ideal technique for comprehensive metabolite profiling [23, 24].

CAPILLARY ELECTROPHORESIS/MS

CE/MS was developed to detect amino acids without the need for derivatization. CE utilizes a narrow capillary filled with a buffer solution. This separation process differentiates analytes (metabolites) based on their size, charge, and how they respond to the buffer environment. After separation in the capillary, the metabolites are efficiently transferred to the MS for sensitive detection and identification based on their mass-to-charge ratio. Metabolites carrying a negative charge are called anionic metabolites and those carrying a positive charge are called cationic metabolites [25, 26]. In CE, Electroosmotic flow (EOF) is a bulk flow of the solvent that moves from the positive electrode (anode) towards the negative electrode (cathode) due to the interaction between the charged capillary wall and the mobile phase. EOF can be manipulated by controlling the buffer pH and capillary wall properties. This controlled EOF is crucial for efficiently analysing charged metabolites, including anions (negatively charged) that would otherwise migrate against the flow. Based on separation capacity, CE/MS is considered mighty over HPLC/MS. Due to the smaller volume of sample in the capillary tube, the sensitivity of this technique is very low. Sample preparation in CEMS is comparatively more complex [27].

The past decade has seen a rapid rise in metabolomics research, through advancements in analytical tools. These tools allow scientists to measure a vast array of metabolites in biological samples, by providing a deeper understanding of the connection between biochemical processes and changes in the observable traits.

METABOLITES AS BIOMARKERS

Biomarkers are molecules in biological fluids that can be analyzed and measured to detect disease. These molecules are used to indicate how the body's metabolism changes during treatment. Studying the metabolic profiles of diseased cells or tissues can help to identify biomarkers for diagnosis and track treatment response. However, existing biomarkers may not be effective for diagnosing diseases due to their lack of specificity and sensitivity. This can be attributed to the complexity of biological systems, individual differences, and environmental factors. This has paved the way for the search for new biomarkers with high specificity and multi-omics integration, such as metabolites. These metabolites include amino acids, carbohydrates, and nucleotides, and they serve as promising biomarkers for the early detection of various complex diseases. These small molecules have garnered more attention than any other approaches, such as genomics, proteomics, and transcriptomics because metabolomics represents an interconnection of these omics' approaches [28, 29].

Metabolites can be categorized as primary metabolites (endogenous), directly linked to growth and development, and secondary metabolites, which do not contribute to growth and development. The latter, also referred to as exogenous metabolites or exposomes. Endogenous metabolites, which are highly conserved and present in all vertebrates from low-grade species to high-grade organisms (including humans), are important biomarkers [30]. Despite their similarity across species, differences exist in physiological characteristics (metabolic rate and organ function) and specific concentrations in cells. There is a hidden relationship between genes and metabolites that leads to various metabolic changes. A single base change in a gene results in a 10,000-fold change in endogenous metabolites. This confirms that metabolites are the important and final downstream molecules of genetic change. This process is followed by transcriptome generation, which leads to the production of proteins and enzymes. These changes produce unique metabolites at different stages of differentiation [31, 32]. In Figure 3, systemic illustration of how genes, proteins, and metabolites are interlinked with each other is depicted.

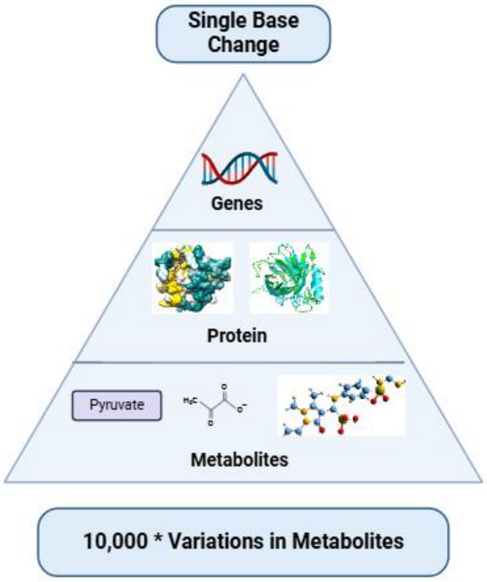

Figure 3. Systemic illustration of how genes, proteins, and metabolites are interlinked with each other.

It is crucial to analytically identify metabolites for their chemical nature and biological activity, as this knowledge can be used for accurate diagnosis and treatment. Small metabolites have unique features for treating specific conditions and are mostly found in blood and urine. Ongoing research aims to better understand the mechanism of each metabolite for application in various health areas [33]. In Figure 4, workflow of Metabolomics Experiment is depicted.

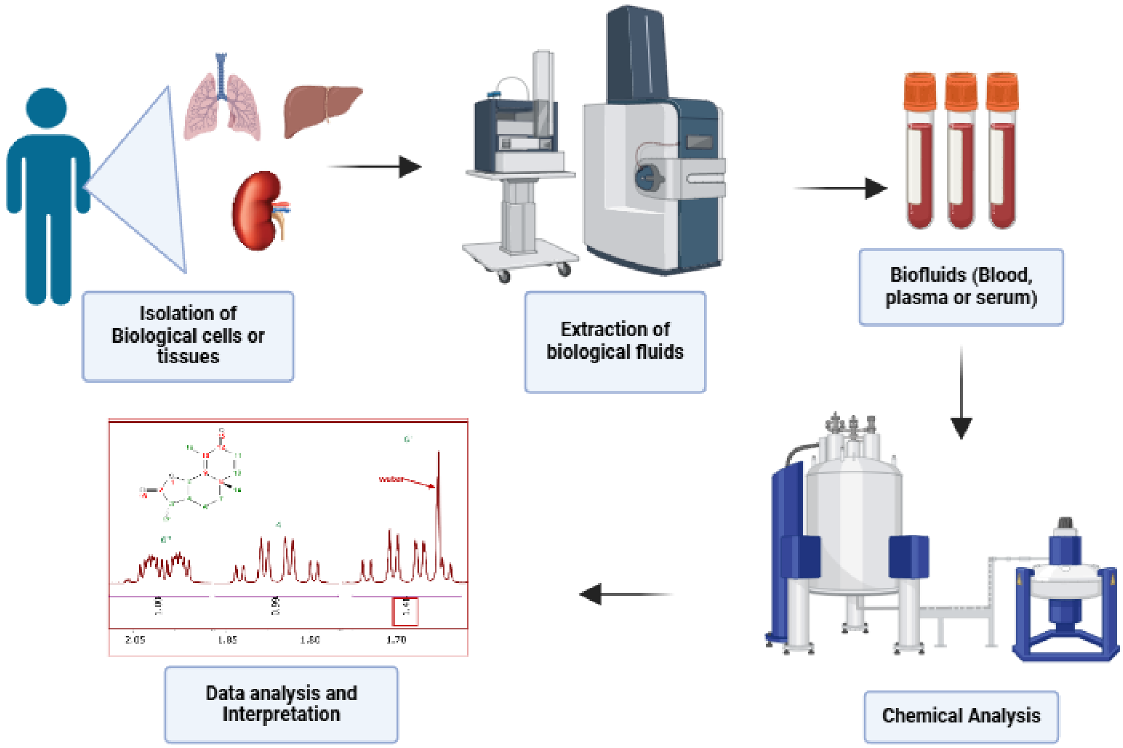

Figure 4. Workflow of metabolomics experiment.

METABOLITES IN PERSONALIZED MEDICINE

Personalized medication offers tailored healthcare support to patients by considering their genetic variations, disease severity, and related metabolism. This approach involves analyzing genetic, lifestyle, and environmental factors to provide individualized treatment. One important method is the use of biomarkers for predicting and treating diseases, offering benefits such as early disease detection, selecting therapies based on specific metabolic pathways and factors, ensuring accurate diagnosis, and mitigating risks associated with the condition [34, 35].

Through metabolomics, researchers have detected changes in intrinsic metabolites attributed to genetic and environmental influences. High-throughput analytical technology allows for the study of metabolites in various areas such as biomarker discovery, disease and drug activity research, metabolic variations, and drug toxicity [36]. Pharmaco-metabolomics is an emerging field that involves the study of a specific drug at a specific dosage for specific conditions and the metabolic response to the drug [37]. Based on the metabolic profile of the illness, a specific drug can be administered to target a particular downstream molecule for a specific metabolic response.

Based on a study by Nishiumi et al. 2012, a new screening method was investigated for the detection of colorectal cancer using GC/MS analysis. The study evaluated three groups: individuals with colorectal cancer, a prediction model with high AUC and sensitivity, and a validation set with high sensitivity for early detection. Metabolic variances were analyzed in intra-day (serum collected at different times of the day) and inter-day (serum collected continuously over three days at once) settings. The research proved that age and daily activity significantly influenced the levels of metabolites in the serum. For instance, tryptophan levels tended to increase in colorectal cancer, showing more significant variance than other metabolites. Additionally, its levels decreased at different times of the day, possibly due to diet or daily activity [38]. Therefore, it is important to thoroughly test all factors that may elucidate small variances in individuals to provide accurate medication and improve the efficiency of diagnosis and prognosis. However, there are still some drawbacks, such as peaks in analytical methods being the same for more than one metabolite, which requires further tests to identify potential metabolites [39]. In Figure 5, precision medicine approach with metabolites is depicted.

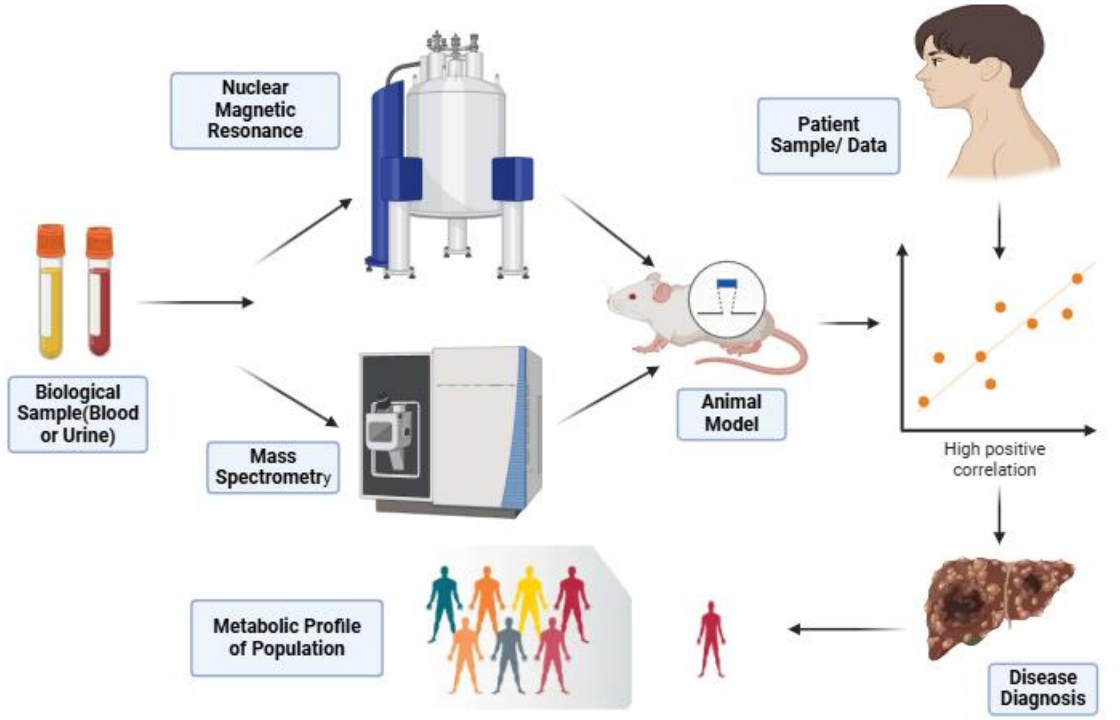

Figure 5. Precision medicine approach with metabolites.

Validation of metabolites for personalized medicine is challenging due to biological variability across populations and a lack of standardized protocols. Metabolomics alone is insufficient for producing metabolites – an integration of all omics studies is required to ensure stability and efficacy. To overcome these challenges, various standardized protocols for sample collection, preparation, storage, and processing must be implemented to improve productivity. Additionally, more sensitive and specific analytical methods need to be employed by combining two analytical strategies to enhance the detection and quantification of metabolites. Implementing these strategies can contribute to the advancement of personalized medicine by providing individualized treatment in healthcare [40, 41].

ENVIRONMENTAL AND LIFESTYLE INFLUENCES ON METABOLOME

Environmental metabolomics aims to understand how an organism’s metabolome changes in response to different environmental factors. Humans are exposed to a variety of environmental contaminants on a regular basis. Frequent exposure to these contaminants may alter the human metabolome. Pollutants, chemicals, and heavy metals can disrupt metabolic pathways by interfering with enzyme function or cellular processes. Also, the type and amount of food we consume significantly influence metabolic pathways. Disrupted sleep can negatively impact hormones that regulate metabolism (1) The research observed disruptions in pathways related to cholesterol, steroid metabolism, and bile acid biosynthesis. This is significant because these pathways are all influenced by the Aryl Hydrocarbon Receptor (AhR) [42]. Most metabolomic studies on persistent oxygen pollutants (POPs) have focused on dioxins and organochlorine pesticides like DDE, HCB, and HCH. This is likely because these POPs are widespread environmental contaminants with well-established health concerns [43].

Plasma metabolome gives us a detailed understanding of the metabolic activities of our body. By analysing the levels of different metabolites in the blood plasma, doctors may be able to identify disruptions in metabolic pathways that point toward specific diseases. The plasma metabolome is quite sensitive to various lifestyle and environmental factors and may vary accordingly. Temporal changes in metabolite levels can be indicative of developing health issues [44, 45].

Plants have evolved sophisticated mechanisms to respond to different environmental challenges. The ability of plants to handle stress varies greatly, and this directly impacts the metabolic changes they undergo. When a particular stress occurs, the plant activates specific pathways to produce helpful secondary metabolites for that situation. Long days with more sunshine can trigger plants to produce more protective compounds like flavonoids and phenolic acids, helping them shield themselves from the increased light exposure. While long days may increase overall secondary metabolite production, the effect on total polyphenols with varying light intensity is very minimal. High light intensity might only lead to a slight increase compared to medium light. As temperatures rise, some plants may reduce their production of certain secondary metabolites. Plants under water scarcity might increase production of osmoprotectants, secondary metabolites that help them retain water and maintain cell structure. When being eaten, plants might produce more defensive secondary metabolites like tannins, which make leaves less palatable to insects [46, 47].

MICROBIOME AND METABOLOME INTERACTION

Trillions of microorganisms in the gut form a complex ecosystem that significantly influences nutrient uptake, metabolism, and immune function. An unhealthy gut microbiome, known as dysbiosis, can hinder the body’s ability to process and absorb nutrients. Dysbiosis leads to impaired metabolism and potential health problems. Gut microbes also produce various metabolites that influence host metabolism. Dysbiosis can alter this metabolite production, impacting energy balance and causing conditions like obesity and metabolic syndrome [48]. The gut microbiome plays a significant role in regulating host metabolism. Microbial metabolites can modulate the host’s immune system. Microbial metabolites can influence insulin sensitivity, energy expenditure, and bile acid metabolism, all of which contribute to maintaining a healthy metabolic state. The mammalian immune system has microbial sensors called pattern recognition receptors that recognize the presence and activity of gut microbes. Scientists have recently found specific molecules produced by gut bacteria, and how these molecules affect the immune system. This new knowledge has helped us understand how these bacteria establish themselves in the gut and how they communicate with immune cells to create a healthy balance [49].

The gut microbiome is a diverse group of microbes that break down complex food substances into simple molecules. During this process, microbes produce a variety of metabolites, like the Short-Chain Fatty Acids (SCFAs) like acetate, propionate, and butyrate. The types of metabolites generated are determined by the specific makeup of the gut microbiome. These microbial metabolites act as signalling molecules and bind to receptors in the gut and triggers various responses in the host organism. The host also has a pivotal role in modulating the gut microbiota. The type of food the host consumes also impacts the composition of the gut microbes. Metabolites can have a selective effect on which microbes thrive. Some metabolites might favor the growth of beneficial bacteria while inhibiting harmful ones, thereby maintaining a healthy and balanced gut microbiome [50–52].

This interdependence between the microbiome and metabolites is crucial for maintaining good health. A balanced microbiome produces beneficial metabolites that promote gut health, regulate metabolism, and influence the immune system. On the other hand, an imbalanced microbiome might generate metabolites that contribute to inflammation, digestive issues, and even chronic diseases.

DISEASE DIAGNOSIS AND TREATMENT

Metabolomics is extensively used as a potential tool for understanding disease mechanisms, diagnosing diseases using various analytical instruments, and monitoring diseases. Metabolites, as biomarkers, are key not only in predicting diseases but also in understanding the pathophysiology of the condition, which in turn helps in providing specific targeted therapies for the active molecules in the disease condition [53, 54]. This can be achieved by comparing two groups of studies: one with healthy individuals as a control group and the other comprising targeted diseased persons as the test group. Biomarkers are selected based on early understanding of their metabolic pathways. By comparing the same marker in both groups, observed variations can serve as potential findings in treating the disease and understanding the severity of the condition [55, 56].

Cancer is a significant contributor to global mortality rates. The mortality rates continue to rise due to factors such as genetic mutations, environmental impact, and lifestyle influences. This concerning situation has prompted scientists to search for cancer biomarkers to target the metabolic mechanism. Metabolomics provides insight into all the metabolites involved in the physiological and pathological state of organisms, making it a powerful tool for identifying biomarkers and understanding cancer metabolism [57, 58]. Cancer is characterized by significant disruptions in cellular metabolism. The metabolic reprogramming of cancer cells leads to uncontrolled growth by altering the metabolites. These altered metabolites are called aberrant metabolites and they play a key role in targeting the tumour microenvironment. The identification of oncometabolites is a key finding in cancer pathophysiology by metabolomics. Oncometabolites are endogenous metabolites that help in the survival and proliferation of tumours. Another important finding includes the cell-based metabolism and the Warburg effect (aerobic glycolysis) [59, 60].

MS and NMR-based imaging are employed to detect and identify oncometabolites. These oncometabolites include 2-hydroxyglutarate, fumarate, succinate, and sarcosine, which originate from specific cancers due to somatic mutations in respective genes. Tumours are involved in almost all metabolic pathways, including glucose metabolism, lipid metabolism, amino acid metabolism, and nucleotide metabolism [59].

In glucose metabolism, pyruvate, as an intermediate junction between oxidative phosphorylation and the glycolysis pathway, has been identified as a potential target because it enhances glycolysis, thereby promoting tumourigenesis. Further studies have also characterized lactic acid as being involved in fostering tumor metastasis by altering gene expression. Lipids are responsible for signal transduction, maintaining membrane integrity, and ATP metabolism. Excessive levels of cancer can be predominantly linked to numerous cancer types, which is called ‘lipotoxicity’ [61, 62]. Both saturated and unsaturated free fatty acids have been discovered to have the potential to be used as biomarkers for the clinical diagnosis of tumours due to their involvement in the AKT pathway. Markers include arachidonic acids, linoleic acids, and oxylipins. The main hallmark of cancer cells is their capability to proliferate at high rates, which is achieved by the synthesis of biological macromolecule nucleotides [63]. Thus, it also acts as an important biomarker, as in the process of tumour formation, an imbalance is created in purine metabolism, and the enzymes related to it are overexpressed, providing adequate energy to the cells for growth, tumour formation, and expansion.

Cancer is not just one area where metabolites show potential. They can also be used to diagnose and treat inherited metabolic disorders by analysing specific metabolites and their regulation. By analysing metabolic profiles, it is possible to identify early signs of neurodegenerative conditions like Alzheimer’s and Parkinson’s. Metabolites can also play a crucial role in treating cardiovascular diseases, diabetes, and various infectious diseases.

CHALLENGES AND FUTURE SCOPE

There is a growing trend towards integrating various analytical methods. This will allow researchers to strengthen the fundamentals of each technique for untargeted and targeted analysis. By combining data from multiple platforms, researchers can resolve a wider range of metabolites, leading to a more detailed picture of the metabolic profile. Improvements in CE-MS interface optimisation could enhance the efficiency of coupling these techniques and improve data quality. Advancements in

GC require a reduction in the steps involved in the derivatisation process. Improvements in metabolite databases, would provide researchers with a more comprehensive and accurate reference for metabolite identification [64, 65].

With so many potential biomarkers, it becomes difficult to analyze and interpret the data effectively. Statistical techniques and advanced computational tools are needed to identify the most significant metabolites and create robust biomarker panels. Also, these broader categories of metabolites make it difficult to identify the potential biomarkers. Various factors like diet, lifestyle, environmental exposure, and medications can cause changes in the (2–6)metabolic profile. This makes it challenging to distinguish disease-specific metabolite changes from these background effects [66, 67].

Researchers are exploring the diverse and multifaceted group of chemicals produced by gut bacteria. By identifying and characterising these metabolites, we can gain a deeper understanding of their specific roles in host physiology. This helps in developing novel therapeutic strategies to treat various diseases associated with gut dysbiosis. The crosstalk between the host and its microbiome mediated by metabolites is a rapidly evolving area of research with immense potential for improving human health.

CONCLUSION

By identifying characteristic changes in metabolite levels associated with specific diseases, metabolomics can offer more precise diagnoses compared to traditional methods. Tracking changes in the metabolome profile can provide deeper view into disease progression and help determine the effectiveness of treatment strategies. Metabolomics can help medical practitioners predict how a patient might react to a particular treatment, allowing for personalized medicine approaches.

Factors such as diet, lifestyle, and medication use can alter metabolite concentrations. Understanding this microbiome-metabolite interaction helps us develop more advanced medications in the future.

Metabolomics is a relatively new field with significant growth potential in healthcare. To fully understand the role of metabolites in complex diseases, researchers are continually advancing research and technology. While challenges persist in this field, the integration of high-throughput analytical technologies holds the potential to unlock a comprehensive understanding of the biomarker–disease metabolism relationship.

REFERENCES

1. Putri SP, Yamamoto S, Tsugawa H, Fukusaki E. Current metabolomics: Technological advances. J Biosci Bioeng. 2013;116(1):9–16.
2. Patti GJ, Yanes O, Siuzdak G. Metabolomics: the apogee of the omics trilogy. Nat Rev Mol Cell Biol. 2012;13(4):263–9.
3. Liu X, Locasale JW. Metabolomics: A Primer. Trends Biochem Sci. 2017;42(4):274–84.
4. Pang H, Hu Z. Metabolomics in drug research and development: The recent advances in technologies and applications. Acta Pharm Sin B. 2023;13(7):3238–51.
5. Gonzalez-Covarrubias V, Martínez-Martínez E, del Bosque-Plata L. The potential of metabolomics in biomedical applications. Metabolites. 2022;12(2):194.
6. Nalbantoglu S. Metabolomics: basic principles and strategies. Mol Med. 2019;10(1).
7. Agin A, Heintz D, Ruhland E, de La Barca JC, Zumsteg J, Moal V, et al. Metabolomics–an overview. From basic principles to potential biomarkers (part 1). Med Nucl. 2016;40(1):4–10.
8. Hollywood K, Brison DR, Goodacre R. Metabolomics: current technologies and future trends. Proteomics. 2006;6(17):4716–23.
9. Ryan D, Robards K. Metabolomics: The greatest omics of them all? Anal Chem. 2006;78(23):7954–8.

10. Segers K, Declerck S, Mangelings D, Heyden YV, Eeckhaut AV. Analytical techniques for metabolomic studies: A review. Bioanalysis. 2019;11(24):2297–318.
11. Dunn WB, Bailey NJ, Johnson HE. Measuring the metabolome: current analytical technologies. Analyst. 2005;130(5):606–25.
12. Reo NV. NMR-based metabolomics. Drug Chem Toxicol. 2002;25(4):375–82.
13. Nagana Gowda GA, Raftery D. Recent advances in NMR-based metabolomics. Anal Chem. 2017;89(1):490–510.
14. Markley JL, Brüschweiler R, Edison AS, Eghbalnia HR, Powers R, Raftery D, et al. The future of NMR-based metabolomics. Curr Opin Biotechnol. 2017;43:34–40.
15. Emwas AHM, Salek RM, Griffin JL, Merzaban J. NMR-based metabolomics in human disease diagnosis: applications, limitations, and recommendations. Metabolomics. 2013;9(5):1048–72.
16. Vinaixa M, Schymanski EL, Neumann S, Navarro M, Salek RM, Yanes O. Mass spectral databases for LC/MS-and GC/MS-based metabolomics: State of the field and future prospects. TrAC Trends Anal Chem. 2016;78:23–35.
17. Fancy SA, Rumpel K. GC-MS-based metabolomics. Biomark Methods Drug Discov Dev. 2008;317–40.
18. Beale DJ, Pinu FR, Kouremenos KA, Poojary MM, Narayana VK, Boughton BA, et al. Review of recent developments in GC–MS approaches to metabolomics-based research. Metabolomics. 2018;14(12):1–31.
19. Zhou B, Xiao JF, Tuli L, Ressom HW. LC-MS-based metabolomics. Mol BioSyst. 2012;8(2):470–81.
20. Fang ZZ, Gonzalez FJ. LC–MS-based metabolomics: an update. Arch Toxicol. 2014;88(9):1491–502.
21. Lu W, Bennett BD, Rabinowitz JD. Analytical strategies for LC–MS-based targeted metabolomics. J Chromatogr B. 2008;871(2):236–42.
22. van de Velde B, Guillarme D, Kohler I. Supercritical fluid chromatography–Mass spectrometry in metabolomics: past, present, and future perspectives. J Chromatogr B. 2020;1161:122444.
23. Shulaev V, Isaac G. Supercritical fluid chromatography coupled to mass spectrometry–A metabolomics perspective. J Chromatogr B. 2018;1092:499–505.
24. Chen L, Dean B, Liang X. A technical overview of supercritical fluid chromatography-mass spectrometry (SFC-MS) and its recent applications in pharmaceutical research and development. Drug Discov Today Technol. 2021;40:69–75.
25. Ramautar R, Somsen GW, de Jong GJ. CE–MS in metabolomics. Electrophoresis. 2009;30(1):276–91.
26. Çelebier M, Nenni M. Recent developments in CE-MS based metabolomics. Curr Anal Chem. 2021;17(9):1229–42.
27. Soga T. Advances in capillary electrophoresis mass spectrometry for metabolomics. TrAC Trends Anal Chem. 2023;158:116883.
28. Qiu S, Cai Y, Yao H, Lin C, Xie Y, Tang S, et al. Small molecule metabolites: discovery of biomarkers and therapeutic targets. Signal Transduct Target Ther. 2023;8(1):132.
29. Wishart DS. Metabolomics for investigating physiological and pathophysiological processes. Physiol Rev. 2019;99(4):1819–75.
30. Li ZB, Liu J, Zhang SQ, Yu Y, Liang HF, Lu QQ, et al. Novel potential metabolic biomarker panel for early detection of severe COVID-19 using full-spectrum metabolome and whole-transcriptome analyses. Signal Transduct Target Ther. 2022;7(1):129.
31. Perazzoli G, García-Valdeavero OM, Peña M, Prados J, Melguizo C, Jiménez-Luna C. Evaluating metabolite-based biomarkers for early diagnosis of pancreatic cancer: a systematic review. Metabolites. 2023;13(7):872.
32. Holmes E, Wilson ID, Nicholson JK. Metabolic phenotyping in health and disease. Cell. 2008;134(5):714–7.
33. Metwaly A, Reitmeier S, Haller D. Microbiome risk profiles as biomarkers for inflammatory and metabolic disorders. Nat Rev Gastroenterol Hepatol. 2022;19(6):383–97.

34. Wishart DS. Emerging applications of metabolomics in drug discovery and precision medicine. Nat Rev Drug Discov. 2016;15(7):473–84.
35. Jacob M, Lopata AL, Dasouki M, Abdel Rahman AM. Metabolomics toward personalized medicine. Mass Spectrom Rev. 2019;38(3):221–38.
36. Amaro F, Carvalho M, Bastos MDL, Guedes de Pinho P, Pinto J. Pharmacometabolomics applied to personalized medicine in urological cancers. Pharmaceuticals. 2022;15(3):295.
37. Baraldi E, Carraro S, Giordano G, Reniero F, Perilongo G, Zacchello F. Metabolomics: moving towards personalized medicine. Ital J Pediatr. 2009;35(1):1–4.
38. Nishiumi S, Kobayashi T, Ikeda A, Yoshie T, Kibi M, Izumi Y, et al. A novel serum metabolomics-based diagnostic approach for colorectal cancer. PLoS One. 2012;7(7):e40459.
39. Beger RD, Dunn W, Schmidt MA, Gross SS, Kirwan JA, Cascante M, et al. Metabolomics enables precision medicine: “a white paper, community perspective”. Metabolomics. 2016;12(10):1–15.
40. Rahman M, editor. Metabolomics: A Path Towards Personalized Medicine. Academic Press; 2023.
41. Koen N, Du Preez I, Loots DT. Metabolomics and Personalized Medicine. In: Personalized Medicine. Academic Press; 2016. p. 53–78.
42. Thorburn AN, Macia L, Mackay CR. Diet, Metabolites, and “Western-Lifestyle” Inflammatory Diseases. Immunity. 2014;40(6):833–42.
43. Bonvallot N, David A, Chalmel F, Chevrier C, Cordier S, Cravedi JP, et al. Metabolomics as a powerful tool to decipher the biological effects of environmental contaminants in humans. Curr Opin Toxicol. 2018;8:48–56.
44. Chen L, Zhernakova DV, Kurilshikov A, Andreu-Sánchez S, Wang D, Augustijn HE, et al. Influence of the microbiome, diet and genetics on inter-individual variation in the human plasma metabolome. Nat Med. 2022;28(11):233
45. Bundy JG, Davey MP, Viant MR. Environmental metabolomics: a critical review and future perspectives. Metabolomics. 2009;5:3–21.
46. Spratlin JL, Serkova NJ, Eckhardt SG. Clinical applications of metabolomics in oncology: a review. Clin Cancer Res. 2009;15(2):431–40.
47. Qaderi MM, Martel AB, Strugnell CA. Environmental factors regulate plant secondary metabolites. Plants. 2023;12(3):447.
48. Kim CH. Immune regulation by microbiome metabolites. Immunology. 2018;154:220–9.
49. Levy M, Blacher E, Elinav E. Microbiome, metabolites and host immunity. Curr Opin Microbiol. 2017;35:8–15.
50. Shtossel O, Koren O, Shai I, Rinott E, Louzoun Y. Gut microbiome-metabolome interactions predict host condition. Microbiome. 2024;12(1):24.
51. Wu J, Wang K, Wang X, Pang Y, Jiang C. The role of the gut microbiome and its metabolites in metabolic diseases. Protein Cell. 2021;12:360–73.
52. La Barbera L, Rizzo C, Grasso G, Macaluso F, Camarda F, Ciccia F, Guggino G. The cross-talk between microbiome and metabolome in rheumatoid arthritis. BioChem. 2023;3(1):47–60.
53. Nicholson JK, Connelly J, Lindon JC, Holmes E. Metabolomics: a platform for studying drug toxicity and gene function. Nat Rev Drug Discov. 2002;1(2):153–61.
54. Peregrín-Alvarez JM, Sanford C, Parkinson J. The conservation and evolutionary modularity of metabolism. Genome Biol. 2009;10:1–17.
55. Suhre K, editor. Genetics meets metabolomics: from experiment to systems biology. Springer Science & Business Media; 2012.
56. Smoleńska Ż, Zdrojewski Z. Metabolomics and its potential in diagnosis, prognosis and treatment of rheumatic diseases. Reumatologia. 2015;53(3):152–6.
57. Zhang A, Sun H, Wang X. Serum metabolomics as a novel diagnostic approach for disease: a systematic review. Anal Bioanal Chem. 2012;404:1239–45.
58. Sreekumar A, Poisson LM, Rajendiran TM, Khan AP, Cao Q, Yu J, et al. Metabolomic profiles delineate potential role for sarcosine in prostate cancer progression. Nature. 2009;457(7231):910–4.

59. Yang M, Soga T, Pollard PJ. Oncometabolites: linking altered metabolism with cancer. J Clin Invest. 2013;123(9):3652–8.
60. Zhu S, Guo Y, Zhang X, Liu H, Yin M, Chen X, et al. Pyruvate kinase M2 (PKM2) in cancer and cancer therapeutics. Cancer Lett. 2021;503:240–8.
61. Yoon H, Shaw JL, Haigis MC, Greka A. Lipid metabolism in sickness and in health: Emerging regulators of lipotoxicity. Mol Cell. 2021;81(18):3708–30.
62. Liu J, Mazzone PJ, Cata JP, Kurz A, Bauer M, Mascha EJ, Sessler DI. Serum free fatty acid biomarkers of lung cancer. Chest. 2014;146(3):670–9.
63. Lane AN, Fan TW. Regulation of mammalian nucleotide metabolism and biosynthesis. Nucleic Acids Res. 2015;43(4):2466–85.
64. Di Minno A, Gelzo M, Caterino M, Costanzo M, Ruoppolo M, Castaldo G. Challenges in metabolomics-based tests, biomarkers revealed by metabolomic analysis, and the promise of the application of metabolomics in precision medicine. Int J Mol Sci. 2022;23(9):5213.
65. Misheva M, Ilott NE, McCullagh JS. Recent advances and future directions in microbiome metabolomics. Curr Opin Endocr Metab Res. 2021;20:100283.
66. Domenick TM, Gill EL, Vedam-Mai V, Yost RA. Mass spectrometry-based cellular metabolomics: current approaches, applications, and future directions. Anal Chem. 2020;93(1):546–66.
67. Soni V, Bartelo N, Schweickart A, Chawla Y, Dutta A, Jain S. Future perspectives of metabolomics: gaps, planning, and recommendations. In: Metabolomics: Recent Advances and Future Applications. Cham: Springer International Publishing; 2023. pp. 479–512.