Advances in Bioresearch
Adv. Biores., Vol 15 (3) May 2024: 402-409

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.15.3.402409

Advances in Bioresearch

REVIEW ARTICLE

Metabolomics- An Overview on Applications of Metabolomics

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ABSTRACT
The study of a small set of compounds known as metabolites—which include lipids, small peptides, amino acids, vitamins, organic acids, sugar, steroids, and fatty acids—is known as metabolomics, one of the emerging "omics" topics. Disease results from any abnormality in the functioning of metabolites. Metabolomics can identify biomarkers that can be used to track the effectiveness of treatments or diagnose illnesses. With the aid of numerous analytical techniques like mass spectroscopy, nuclear magnetic resonance, and high-performance liquid chromatography, metabolite analysis is carried out in cancer, diabetes, ophthalmology, clinical pharmacology, food safety and toxicity, drug discovery, respiratory diseases, neonatology, personalized medicines, plant biology, agriculture, etc. There are many applications for metabolomics in these fields. Combinations of analytical techniques, such as LC-MS and GC-MS, are sometimes employed when a single technique is insufficient to yield a precise result. This review article provides overview of history of metabolomics and current applications of metabolomics.
Keywords:*Metabolites, GC-MS, metabolic profile, diagnosis, biomarker.*

Received 26.01.2024 Revised 01.02.2024 Accepted 21.05.2024

How to cite this article:
Yogeshwari Ambekar, Hemant Chikhale, Saurabh Avhad, Sreya Kosanam, Laxmikant Borse. Metabolomics- An Overview on Applications of Metabolomics. Adv. Biores., Vol 15 (3) May 2024: 4028-409.

INTRODUCTION

The scientific investigation of the collection of metabolites found in a living thing, cell, or tissue is metabolomics [1]. The substrates, intermediates, and end products of metabolism are known as metabolites. The extensive study of tiny compounds, also referred to as metabolites, found in cells, biofluid, tissues, or organisms is known as metabolomics. It is the systematic study of small-molecule metabolite profiles, or the "unique chemical fingerprints that specific cellular processes leave behind." [2].

The study of the metabolome—a group of small-molecule chemical entities with molecular weights less than or equal to 1500 Daltons—is known as metabolomics. Stated differently, this is the study of complex biochemical pathways by products that arise from the metabolism of the genome, transcriptome, and proteome both inside and outside of cells [3]. The detection and quantification of metabolites and metabolite-related metabolic pathways are currently being done using a variety of cutting edge and inventive analytical techniques, such as mass spectrometry (MS), nuclear magnetic resonance (NMR), FT-

IR spectroscopy, Raman spectroscopy, and ion mobility systems (IMS), capillary electrophoresis (CE) systems, gas chromatography (GC), and liquid chromatography (LC) systems, which are often combined with each other [4, 5].

HISTORY

Roger Williams first proposed the idea in the late 1940s that people might have a "metabolic profile" that was reflected in the composition of their biological fluids. Six Horning et al. first coined the term "metabolic profile" in 1971 after proving that chemicals found in human urine and tissue samples could be measured using gas chromatography-mass spectrometry (GC-MS) [6, 7, 8]. Throughout the 1970s, the Horning group, in collaboration with Linus Pauling and Arthur B. Robinson, spearheaded the development of GC-MS techniques for tracking the metabolites found in urine. [9]. NMR spectroscopy, which was discovered in the 1940s, was also advancing quickly at the same time. Seeley et al. showed in 1974 how useful NMR is for identifying metabolites in biological samples that haven't been altered.10. This first study on muscle highlighted the value of NMR in that it was determined that 90% of cellular ATP is complexed with magnesium. As sensitivity has improved with the evolution of higher magnetic field strengths and magic angle spinning, NMR continues to be a leading analytical tool to investigate metabolism 7, 11]. Nicholson first demonstrated in 1984 that 1H NMR spectroscopy might be utilized to identify diabetes mellitus. He also was the first to apply pattern recognition techniques to NMR spectroscopic data [11-13]. Gary Siuzdak, then president of The Scripps Research Institute, and Benjamin Cravatt collaborated on liquid chromatography mass spectrometry metabolomics investigations [15][16] in 1994 and 1996 to analyse the cerebral spinal fluid of sleep-deprived rats. Oleamide is one particularly noteworthy chemical that was shown to have sleep-inducing qualities. One of the first studies of its kind to combine mass spectrometry and liquid chromatography in metabolomics is this one. [14, 15].

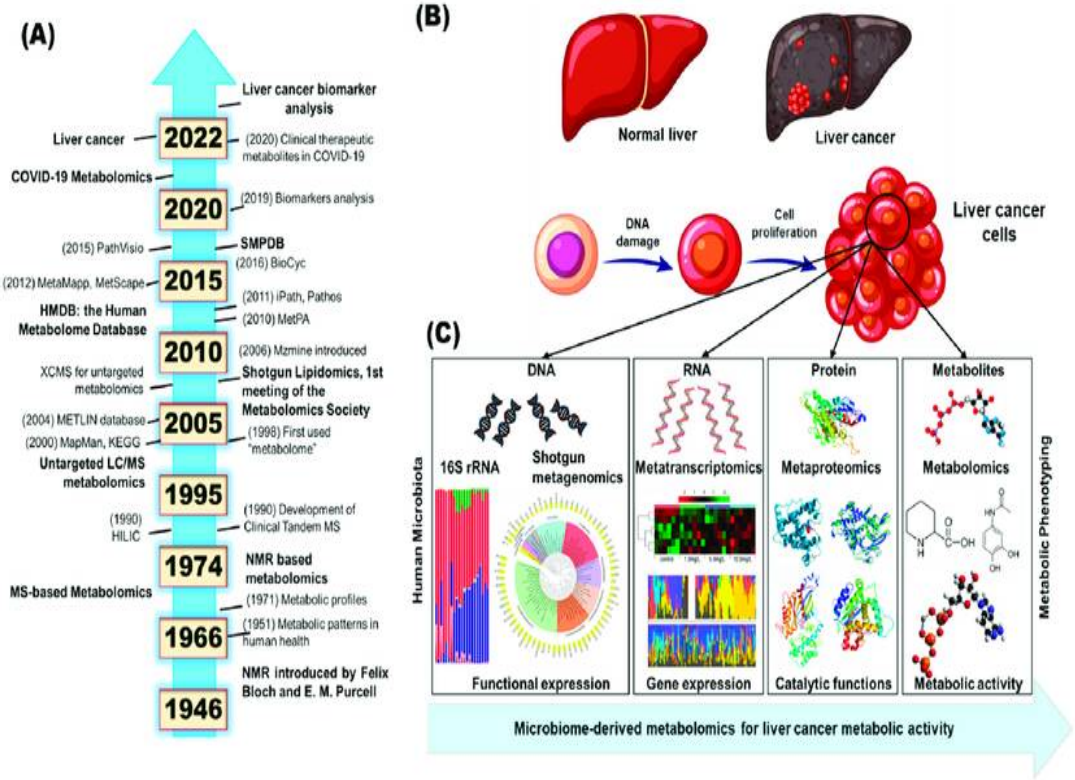

Figure 1. Long history of metabolomics.

In 2005, the first metabolomics tandem mass spectrometry database, METLIN,[17][18] for characterizing human metabolites was developed in the Siuzdak laboratory at The Scripps Research Institute.[16]

On 23 January 2007, the Human Metabolome Project, led by David S. Wishart, completed the first draft of the human metabolome, consisting of a database of approximately 2,500 metabolites, 1,200 drugs and 3,500 food components. [17-19]

APPLICATIONS

A potential systems biology method called metabolomics is making waves in a number of scientific areas, such as drug development, functional genomics, nutrition science, and illness detection. As shown in fig.

2&3, metabolism is becoming more and more popular in the pharmaceutical sector, following its quick development in academic and research institutions.
Currently used in a variety of fields, metabolomics:

Table 1. Applications of metabolomics in skin metabolomics.

Field	Disease	Treatment
A. Skin metabolomics	1. Psoriasis: Psoriasis appears to be associated with poor aminoacidic metabolism. [20 -21]. Psoriatic patients' cutaneous and plasmatic samples appear to have lower levels of asparagine, taurine, and glutamine than normal, although their skin appears to be less taurine-rich. [22] 2. Atopic Dermatitis (AD) and Other Inflammatory Dermatoses: A dysregulation of skin lipid metabolism in AD was validated by metabolomic study of atopic skin, indicating a relative deficiency of many ceramide subclasses. [27] 3. Remarkably, the tryptophan metabolic pathway appears to be important in Alzheimer's disease as well. [28] 4. There have also been reports of elevated levels of metabolites related to energy metabolism in the AD population, including lactic acid, free fatty acids, and carnitines. [29] 5. Melanoma: So far, the primary goal of metabolome analysis has been to find putative metabolic biomarkers for the diagnosis and prognosis of malignant cutaneous melanoma. [29, 31] 6. It has been discovered that melanoma cells exhibit modifications in the metabolism of alpha-Melanocyte-Stimulating Hormone (α-MSH). [32]	1. Steroid-sparing treatments for psoriasis have garnered attention recently, and a number of writers have used metabolomic analysis to show the effectiveness of several plant extracts (*Pithecellobium clypearia, Datura metel*, etc.). [23-26]. 2. Lastly, using a combination of transcriptomics, metabolomics, and genome- and phenome-wide association studies, Khosravi et al. identified 35 prospective medicines for melanoma treatment in 2019. [33]

B. Cancer metabolomics

Table 2. Application of metabolomics in cancer.

Cancer	Sample	Analytical platform	Metabolite biomarker	Reference
Colorectal	Serum	FTICR-MS NMR LC–MS/MS ESI-MS/MS GC–MS UPLC–MS Urine GC–MS Tissue CE-MS	Ultra-long-chain fatty acids 446, 448, 450 Lysine, alanine, aspartic acid, glycine, histidine, (iso)leucine, methionine, sarcosine, threonine, tyrosine, valine Pyruvate, lactate, tryptophan, tyrosine, uridine Citrate, Hippurate, p-cresol, 2-aminobutyrate, myristate, putrescine, kynurenate 22 markers including hydroxyproline, nucleotides, amino acids; metabolites from glycolysis, TCA cycle and pentose phosphate pathway	Ritchie et al. [34] Leichtle et al. [35] Qiu et al. [36] Cheng et al. [37] Hirayama et al. [38]
Pancreatic	Plasma Serum	GC–MS LC–MS NMR	N-methyl alanine, lysine, glutamine, phenylalanine, arachidonic acid, tauro(ursodeoxy)cholic acid, (deoxy)cholylglycine 3-Hydroxybutyrate, 3-hydroxyisovalerate, lactate,	Urayama et al. [39] OuYang et al. [40]

			trimethylamine-N-oxide, triglyceride, (iso)leucine, creatinine	
Gastric	Mucosa	GC–MS	18 markers including 5 distinguishing invasive from non-invasive tumours (cysteine, tyrosine, hypoxanthine, phenanthrenol, butanoic acid)	Wu et al. [41]
Breast	Serum Cultured cells	GC–MS ESI-MS	Free fatty acids, palmitic acid, stearic acid, linoleic acid Lysophospholipids, saturated fatty acids in phosphatidylinositol	Lv et al. [42] Luisa Doria et al. [43]
Prostate	Urine	CE-MS/MS	Sarcosine	Soliman et al. [44]
Lung	Serum	FTICR-MS	7 markers including fatty acid derivations, Lys phosphatidylcholine, sphingomyelin	Guo et al. [45]
Oral	Saliva	CE-MS	Taurine, piperidine	Sugimoto et al. [46]

C. RESPIRATORY METABOLOMICS

Table 3. Applications of metabolomics in respiratory disease.

SAMPLE	ANALYTICAL PLATFORM	METABOLITE BIOMARKER	REFERENCES
1. Urine	NMR	1-methylhistamine, 2-hydroxyisobutyrate, Acetone, Alanine, Creatine, Formate level increased in asthmatic patients. Glycolate, Hippurate. Methylamine, O-acetyl carnitine, Threonine level decreased in asthmatic patients.	47,48,49
2. Serum	NMR	3-hydroxybutyrate, Acetate, Alanine, Ascorbate, Glutamine, Pyruvate level increased in chronic obstructive pulmonary disorder patients. 3-hydroxyisobutyrate, Butyrate, Creatine, Glycerol, glycin, Isobutyrate, Methionine, Valine decreased in level in chronic obstructive pulmonary disorder patients.	50,51,52

D. Application of metabolomics in neonatology:

A person's health can also be affected by a number of perinatal and neonatal problems (premature birth, hypoxia, bronchopulmonary dysplasia, periventricular haemorrhage–intraventricular haemorrhage [IVH–PVH], etc.) throughout their lifetime. Utilizing comprehensive research instruments such as metabolomics on particular cohorts of preterm infants may be able to forecast the development of various adult conditions (such as metabolic syndrome and hypertension), allowing for the prompt administration of treatment, if required. Furthermore, metabolomic analysis could be used from birth to track the time evolution of the metabolic profile in very preterm new-borns or in neonates with specific disorders in order to enhance and personalize the therapeutic strategy and advance the definition of prognosis.[53] To lessen the consequences of diabetes and enhance quality of life, it is evident that novel approaches to diagnosis and glycaemic status evaluation are needed. Identifying and evaluating metabolic traits, alterations, and phenotypes in response to environmental, dietary, lifestyle, and pathophysiological conditions is known as metabolomics [54]. Insulin, glucose, pancreatic polypeptide, γ-glutamyl transferase, and testosterone are examples of metabolic biomarkers that are employed.[55], [56], [57], [58], [59].

E. biomarker discovery:

Biomarkers, or tiny molecules (metabolites), are used in metabolomics to differentiate between two groups of samples, usually a disease group and a control group. A metabolite that is consistently found in samples of disease but absent from healthy persons would be considered a biomarker. Seminal fluid, bile,

saliva, and urine samples all contain very informative chemicals that are easily analysed using metabolomics fingerprinting or profiling to find biomarkers.

Personalised Medicine and Nutrition:

Another important area where metabolomics has the potential to have a significant impact is personalized medicine and nutrition, since it is well known that one patient may not respond well to a particular treatment plan. In this instance, full measurement of an individual's metabolome or other omics will help with advanced screening of healthy patients or pre-determining reference intervals to diagnosis a clinical problem. 61, 60]. Nutrition is another field where metabolomics finds many uses. Understanding how the chronic or acute consumption of various foods impacts an organism's metabolism is the main topic of research in this field.[62]

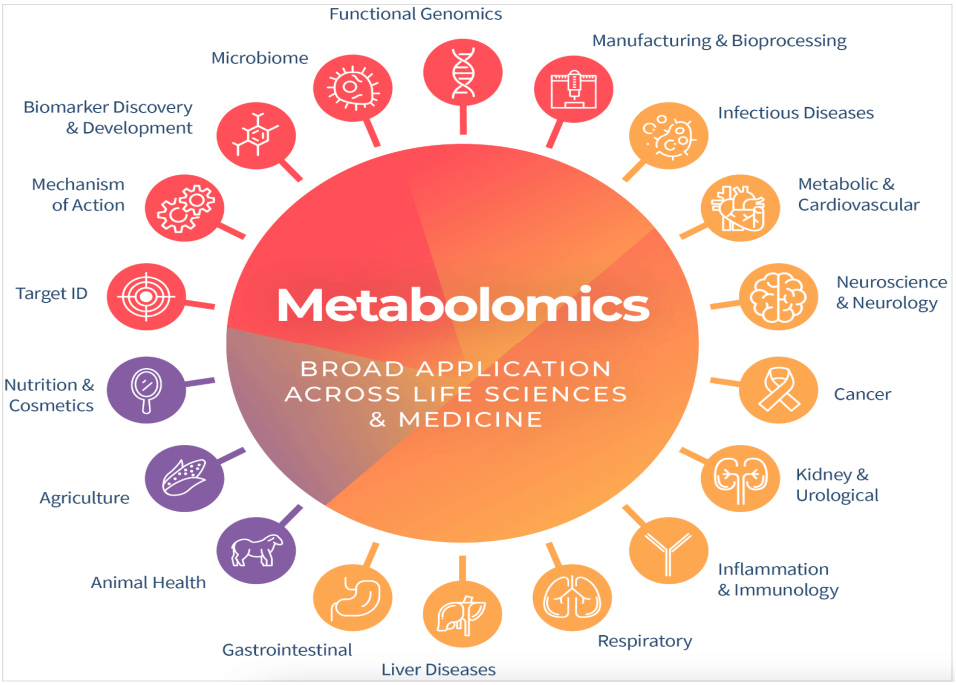

Figure 2. Applications of metabolomics

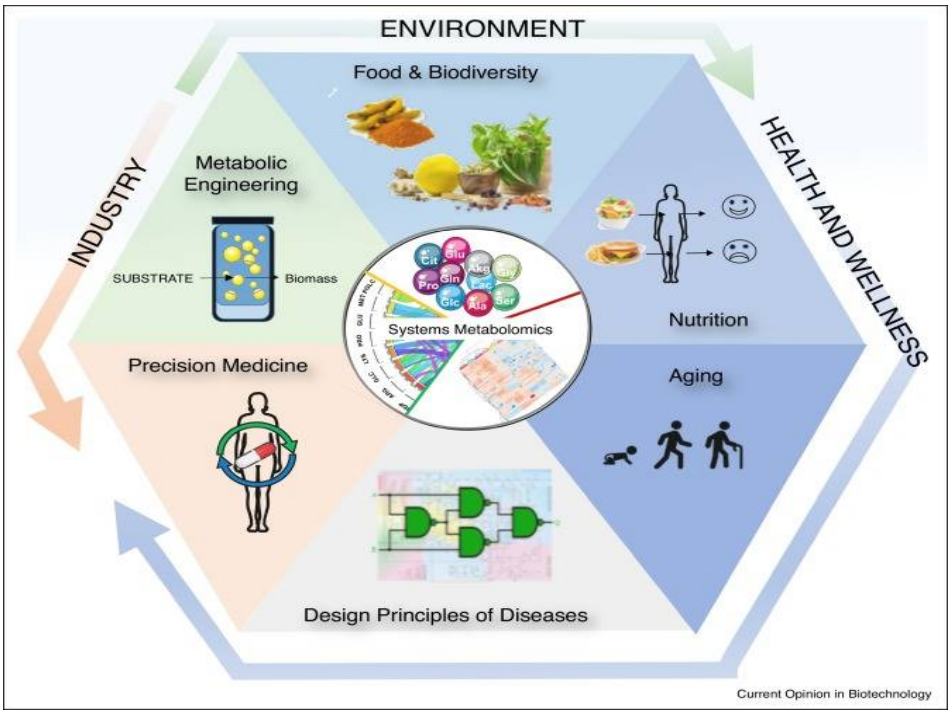

Figure 3. System metabolomics

FUTURE SCOPE

One of the newest omics technologies, metabolomics has been successfully used in numerous life sciences fields. The majority of quantitative approaches are targeted, nevertheless, thus more focus must be placed on developing untargeted quantitative metabolomics methods, as they will prove to be quite helpful in work pertaining to biomarker discovery. It would be beneficial to support further research on the production of smaller, more affordable, and more widely available instruments. The creation of user-friendly databases and software, as well as automated data processing, should be promoted. More open-source web-based data analysis platforms should be developed in particular. This will create opportunities for more translational metabolomics research and strengthen the interpretation of data.

CONCLUSION

With intriguing discoveries that connect biological systems and food analysis, metabolomics has made significant strides. By combining multiple analytical techniques, it can analyse over a thousand metabolites in a single run and has enormous promise for use in a wide range of life sciences disciplines. The pharmaceutical, preventative healthcare, and agricultural industries, among others, find metabolomics to be an appropriate tool because to its non-invasive nature and close association with the phenotype. Metabolomics has already made it possible to make well-informed decisions in two areas: drug safety screenings and biomarker development. In the future, we could be able to monitor our own metabolome's trends for tailored medications and better treatment plans thanks to the availability of personalized metabolomics. Individualized care is probably going to be more successful than the population-based medical approaches we currently use.

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