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Metabolomics in Human Health: A Narrative Review

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ABSTRACT
The metabolome provides a potent, thorough, and accurate image of the phenotype. Modern high-throughput methods have enabled the identification of important metabolic pathways that describe a variety of human characteristics like health, illness, and medication management, and even ageing. Similar to genomics, metabolomics has assisted in the study of various molecular pathways and contributed to the progression of biomarkers, emphasizing its use in the field of personalized medicine. This study concentrates on metabolomics and how it can help people live healthier lives, as well as its developments and implications for cancer, lifespan, the exposome, and pharmacometabolomics. The development and advancement of therapeutic approaches to treat human disease will be aided by determining distinct metabolomic profiles. Metabolomics will increasingly be used to monitor and diagnose ageing, illness, and medication development in the coming years. Acylcarnitines, branch-chain amino acids specific To track the emergence of metabolic illnesses like obesity and diabetes, phospholipids and genomes are already being employed in medication development in biomedical applications of metabolomics these can evaluate the severity of the condition and suggest a possible treatment. Future research should concentrate on evaluating the adaptability and therapeutic efficacy of indicators produced from metabolomics and how best to apply them in extensive clinical settings.

Keywords: Human health, Biomarkers, Drug development, Nutrigenomics, Metabolite

I. INTRODUCTION

Metabolomics is the systematic identification and analysis of the molecular metabolic by-products of a biological process (organ, biological fluid, cell, tissue or organism small). The most commonly used techniques for metabolome profiling are mass spectrometry and NMR spectroscopy [1].Similarly to how genomics studies DNA and genetic information within a cell and transcriptomics studies RNA and changes in mRNA expression, The field of metabolomics investigates the compounds and by-products of metabolism, which are influenced by both genetic and environmental influences. Because metabolites and their concentrations directly represent the associated metabolic activity and status of cells and tissues, unlike other "omics" metrics, metabolomics is a helpful technique. So, the molecular phenotype is best represented by metabolomics [2].The numerous distinct metabolites that are present in biological samples are counted and contrasted using analytical profiling techniques like metabolomics. Using a combination of high-throughput analytical chemistry and multivariate data processing, metabolomics opens a window into metabolic processes. Due to their frequent and close use of host metabolic processes, viruses are excellent study subjects for metabolic techniques [3].

In molecular and individualized medicine, metabolomics is the study of the metabolome found in cells, biofluids, tissues, or species. It is used in newborn screening, toxicology, clinical chemistry,

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pharmacology, and transplant monitoring. Under specific genetic, dietary, and environmental circumstances, it has been predicted that the metabolome of a biological system will contain 3000-20,000 global metabolite profiles. [4]. The metabolome is more physiologically and chemically complicated than the other "omes" since it is the ultimate downstream result and is directly impacted by changes and connections in gene expression, protein levels, and the environment. The molecular phenotype of health and disease is best modified and shown by metabolomics, which is the omics approach that most closely resembles the phenotypic among others. It is superior to other omics techniques and a great source for the creation of biomarkers [5].

Metabolomics approaches utilize "targeted-validation-tandem" and "untargeted-discovery-global," respectively, as their two primary analytic platforms, depending on the investigation's objectives. In order to thoroughly characterize the targets of biomarkers and carefully locate and measure the metabolites from biological samples, the study takes into consideration both the endometabolome and exometabolome[6].The metabolome can be fully scanned using untargeted discovery metabolomics, patterns may be identified, and "metabolic fingerprinting" can be used to classify phenotypes globally according to relationships across pathways.

An untargeted analysis is often validated by targeted metabolomics, which involves hypothesis testing. With the focused techniques (tandem-MS/MS), a known standard is used to quantitatively analyse certain small molecules/metabolites or alterations in a metabolic pathway. This process is often referred to as "metabolic profiling" or "biassed or targeted metabolomics" [7]. Hypothesis-testing procedures include target analysis and diagnostic analysis, whereas hypothesis-generating strategies for metabolomics include nontargeted profiling, fingerprinting, and footprinting [8].Since metabolites serve a broad variety of biochemical purposes, there is an increasing need to create a complete library of clinically trustworthy and useful metabolite profiles and to more accurately represent the entire human metabolome.This will encourage investigation into specific physiological processes and their roles in both health and disease, as well as the potential impact of pharmacogenomics and nutrition on genes and metabolic pathways that may be impacted by medication, food, or food intake on ageing and acute or chronic illnesses. It might be feasible to advance metabolomics research by combining and standardizing a number of methods.For example attempts are being made to fully define a certain phenotypic across time In order to determine the compounds and metabolic pathways that are related to particular diseases, their onset, and progression, [9].

The study of metabolomics is significantly hampered by the abundance of metabolites with high degrees of chemical complexity, includes a range of pKa and lipophilicity, different functional groups, physical and chemical characteristics, carbon length, and chiral molecules, among others. For instance, thousands of lipids from at least 15 different chemical families make up the lipidome, which accounts for around two-thirds of the plasma metabolome. Additionally, it may not always be clear how a specific metabolomic profile relates to the metabolism of a specific organ, tissue, dietary intake, microbiome activity, or interactions in between microbiome and the environment [10].In an effort to obtain an accurate biochemical assessment, analytical tests on metabolomic samples recently improved in terms of sensitivity and spectrum resolution. The two most used techniques for measuring metabolites, NMR spectroscopy and MS, have undergone the greatest technological development in recent years. [11].For example-

- Human diseases, assessment, classification of clinical conditions prevention, identification of biomarkers, and risk assessment
- Drug development, pharmacology, dosage assessment, and treatments
- The identification of biochemical pathways, Improve the efficiency of an enzyme's catalytic activity by relating changes in metabolite levels to it.
- Nutrigenomics, food safety, and technology
- Crop enhancement, transgenic research, plant breeding, and increased stress tolerance.
- Toxicology, pharmacological toxicity, and toxic evaluation.
- Biotechnology chemicals, microbial enhancement, fermentation,
- System biology, biological system dynamics, and metabolic network exploration[12].

The identification of pertinent human phenotypes that are described by a variety of metabolites in terms of health, sickness, medication monitoring, and even ageing has been made possible by modern high-throughput methods.

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Similar to genomics, metabolomics has assisted in the study of contributed to the creation of biomarkers through a variety of molecular processes, emphasizing its use in precision medicine [13].

Metabolomics in human health

The advancements in metabolomics and how it can be utilized to improve human health in liquid biopsies, cancer, the exposome, and pharmacometabolomics, as well as its trends and effects. The development and advancement of therapeutic approaches to treat human disease will be aided by the identification of distinctive metabolomics profiles. Metabolomics will increasingly be used to monitor and diagnose ageing, illness, and medication development in the coming years. Branch-chain amino acids can be used to monitor the development of metabolic disorders like diabetes and obesity, particular lipid, and genetic testing are already being used in biomedical applications of metabolomics. These can assess the severity of the condition and offer a potential treatment [14].Nutrigenomics is another way that metabolomics in use the domain of human health. The word nutrigenomics refers to the relationship between nutrition and genes and describes the alteration in the expression of genes results from exposure to various nutrients. The discovery of specific chemicals that might influence targeting genes are expressed when crucial for the prevention of illnesses like cancer. Additionally, this interaction could affect how metabolites are absorbed, digested, and eliminated. Consequently, the metabolomic technique could enable the discovery of foods that are bioprotective [15].

In Biomedical research

Following any disturbance, the metabolic profile serves as a direct indicator of phenotypic and biochemical activity. Depending on the biological system being examined, metabolites might include natural chemicals and medicines, as well as the by-products of their metabolism. Metabolomics can identify binding partners for molecules, provide relevant targets for drug development, and offer activity information on potential new medicines and drug scaffolds. Metabolomics can also be utilized to produce new medicines and find novel natural compounds. The development and testing of novel therapeutics can be improved by metabolomics, which can also shed light on the on- and off-target effects of medications [16].

Metabolomics can help with drug discovery and testing give information on the effects of medications both on and off-target, and offer useful markers for clinical trials and other uses.High throughput drug testing and discovery can be used with experimental and computational metabolomics to produce novel molecules and pharmacological leads for better, less toxic medicines. Metabolomics experimental and analytical technologies are rapidly evolving, offering more sensitive approaches, improved methods for assignment, and the identification of novel molecules. As both endeavour to extract molecular data from intricate metabolic mixtures, natural product discovery and metabolomics are closely connected. As a result, metabolomics techniques are directly applicable to natural product discovery. Molecular information can be added by metabolomics to high-throughput drug screening techniques [17].

Human Diseases and Metabolomics

Oncobiology

Oncobiology is one of the most significant fields where metabolomics has been used to analyse human illnesses. Due to their high rate of proliferation, quick translation and transcription rates, and higher energy needs, tumour cells differ from normal cells in their metabolic requirements and frequently lose a substantial amount of regulatory activities [18]. Therefore, using metabolomics to anticipate the emergence of tumour cells is one of the biggest difficulties in medicine. In preclinical studies, Potential metabolic biomarkers for cancer detection and/or evaluation of the effectiveness of anticancer therapy have been identified in preliminary studies. Then, in biofluids, these indicators are verified (blood, urine, prostatic secretions, etc.) [19].

In cancer immunotherapy, human metabolomics may offer us crucial chemicals for comprehending, forecasting, treating, and managing immune responses. Clinicians might use successful nutritional or therapeutic therapies and checkpoint inhibitors by predicting immune cell metabolism [20].Along with the numerous nutrient-sensing systems and metabolic switches, the connection between cancer cells and inflammatory cells divisions inside the tumour microenvironment, must be understood. With or without the use of checkpoint inhibitor therapy, these variables are crucial in regulating how the

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immune system reacts to malignancies [21].The nearby tumour microenvironment, where a variety of immune and metabolic factors are crucial in the cross-talk, regulation, and immune cells that are invaded are reprogrammed, has a significant impact on the growth of tumours [20].One of the most common cancers in humans is hepatocellular carcinoma, and its prevalence is rising (HCC). Using antibody microarrays, Liu et al. [22] described the detection of biomarkers for cytokines. They discovered multiple protein markers in individuals with liver cancer, containing a macrophage-derived chemokine and a protein that stimulates macrophages but did so in a different way. Additionally, several researches were carried out to determine the metabolite profiles of HCC patients. Patterson et al. [23].found a shift in lipoprotein metabolism in these people, as evidenced by an increase in bilirubin, glycodeoxycholate, and deoxycholate-3-sulfate. They accomplished this utilising TOF mass spectrometry and ultraperformance liquid chromatography-electrospray ionisation.Additionally, there was a correlation between the development of HCC and the decline in lysophosphocholine levels. Especially the amino acid family's polar molecules like proline, arginine, alanine, lysine, and aspartate, were among the other metabolites that were discovered to be changed in liver cancer [24]. In addition, additional malignancies such brain tumours, gliomas, and neuroepithelial tumours were discovered to have higher levels of several amino acids, including alanine [25]. Recently, it was explained that certain forms of breast tumours had changed levels of substances such glycine, taurine, myoinositol, phosphocholine, phosphocholine, and glycerophosphocholine. In this type of sickness, Other molecules, like the oestrogen receptors and the Human Epidermal Growth Factor Receptor 2 (Her2/neu) are frequently utilised as biomarkers for prognostic or predictive purposes [26].

In contrast, it was discovered that myo-inositol levels were elevated in prostate andmalignancies of the colon and ovaries [27–28].

It has also been shown that stable isotopes are used in cancer studies. Stable isotopes are safe substances like C-labelled metabolites that may be utilized to study the metabolic processes in healthy or excessively proliferating cells. By providing information on differences Such isotopes may be easily identified by NMR or MS and enable the creation of novel diagnostic techniques in the control of metabolic pathways among cancer and non-cancerous cells [29].

Cardio vascular disease

CVD refers to a group of diseases that affect the blood vessels or the heart. It is often linked to artery and organ damage, including kidney, heart, brain, and eye damage as well as hypertension, fatty acid buildup in the arteries, a higher risk of blood clots, and hypertension. An essential component of a medical preventive plan is predicting the risk of CVD. In a variety of cardiovascular disease conditions, metabolomics has assisted in defining alterations both in general metabolism and cardiac-specific metabolism. For instance, metabolomics and other omics, such as genomes, the molecular basis of the SCDA metabolites clusters in cardiac arrest and ischemic heart disease has been partially elucidated via transcriptomics and epigenetics. [30].Finally, the detection and prevention of coronary heart disease depended heavily on metabolomics. The diagnosis and treatment of the condition depend on the ability to recognise a myocardial ischemia event [29]. Currently, a variety of protein and enzyme biomarkers are utilized to identify people who are at risk for cardiac disorders. Various metabolite levels that could serve as indicators of myocardial ischemia changingwere reported by Sabatine et al. in 2005 [31].

Despite numerous attempts to find novel biochemical indications the metabolomic method is currently being investigated for the prevention of heart issues. Integrated techniques incorporating biomarkers from genomics, proteomics, and metabolomics are needed to fully understand changes to metabolic pathways, such as changes in metabolite levels and transcriptional regulation occurring in individuals at risk for heart disease. As a result, prospective biomarkers for heart disease prevention, diagnosis, and risk prediction will be more efficiently selected [32].Metabolomics was built on the basis of metabolic profiling. Early in the 1970s, Analyses of steroid, acid, and neutral and acidic urine drug metabolite samples were performed using GC-MS technology [33, 34].

Obesity

The World Health Organization estimates that 340 million children and 40% of adults worldwide are overweight or obese [35]. Obesity has a significant detrimental effect on health since it increases the chance of developing type 2 diabetes and the metabolic syndrome,

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cardiovascular disease, and cancer. Finding the metabolic adaptations connected to the many effects obese individuals and animal models present a significant problem [36]. Metabolomics has enabled the development Chemical metabolite patterns that differentiate obese people with impaired metabolism and those with normal metabolism. For instance, it has been discovered that obesity increases the blood's concentration of amino acids with branches (BCAAs), which is an indication of insulin resistance. It is possible to employ BCAA plasma concentration as an early signal in the case of BCAAs since it indicates a higher chance of developing the metabolic syndrome [37].

Diabetes

The majority of this study has combined gas- or liquid-phase chromatography with NMR or MS. The chemical alterations that can help in the early diagnosis of pre - diabetes, Type1Diabetes, and Type 2 diabetes have begun to be revealed by these investigations. For the purpose of creating strategies, methods, and therapies for T2D, it is essential to comprehend which metabolites can alter how food consumption impacts metabolites in the body and how diet influences metabolites in the body [38]. For instance, elevated levels of BCAAs and tyrosine and other aromatic amino acids like phenylalanine can forecast the onset of T2D and insulin resistance [39].

Dietary metabolites

However, metabolite profiling was employed to examine plant organisms in the early 1990s [40].

It is feasible to pinpoint the metabolic processes that produce significant dietary certain metabolites may be helpful in enhancing human health using metabolomics. There are numerous instances where altering specific metabolic pathways resulted in the creation of plants that are more nutritious. The situation with Golden Rice (GR), a variety of genetically modified rice that accumulates -carotene in the endosperm, is as follows [41]. This rice variety's creation made it possible to address vitamin A deficiency, a significant global nutritional issue. In the future, an overexpressed phytoene synthase gene increased the nutritional value of GR, resulting in the creation of the GR2 variety, This produces more carotenoids (-carotene accounts for 84% of the total) [42]. S-adenosylmethionine decarboxylase was successfully expressed in tomato by Mehta et al. (2002) using the induced E8 promoter. An increase in many polyamines is seen in the transgenic variant, such as spermidine and spermine, during fruit ripening, It lengthens vine life and enhances fruit juice and nutrient quality [43] by increasing the metabolite lycopene. Other examples involve altering plants to have more anthocyanin. The group of pigments known as flavonoids, which includes anthocyanins, is responsible for the colours and antioxidant qualities of plants. A number of human illnesses have also been connected to the prevention of these metabolites,However, plants do not naturally have enough of them to provide the most benefits. According to a recent study, an increase in anthocyanin production at levels comparable to those found in high anthocyanin-containing plants like blackberries and blueberries was caused by the expression of two transcription factors in tomatoes. [44].

Future aspects

To ensure the growth of metabolomics, the technology of metabolomics will be combined with other novel technologies. MS-based metabolomics will be more accurate, and various combined techniques, LC/MS, GC/MS, and other methods, will offer a solid scientific foundation for addressing the problem of studying metabolites and revealing metabolic pathways. In the field of metabolomics, extended mass spectrometry to have a prominent position as a crucial analytical instrument. The development of this field has helped identify numerous potential illness biomarkers and shed light on the aetiology of numerous diseases [45, 46**]**.Research for early disease diagnosis, medication prognosis and prediction, suitable treatment, and recurrence testing are only a few of the studies that have been evaluated. [47, 48] Given that biological mixtures are extremely complicated, LC, GC, or CE is used in the majority of MS analytical procedures. However, there are opportunities and difficulties associated with quickly expanding applications that use changing separation mechanisms and protocols. The ability to separate metabolites and increase the quantity of metabolites discovered has undoubtedly improved with the introduction of chromatographic techniques[49,50].Nevertheless, a significant obstacle is the difficulty to analyse and connect the findings the latter investigations, they are conducted on similar or identical samples collected by several research institutions. Most significant roadblock to the advancement in this area is this. Data variability can also be caused by other elements including sample preparation, sample matrix, and residual

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effects. It is crucial to go from determining relative metabolite concentrations to absolute concentration measurements that is more accurate and inspite of the analytical platform, approach, and procedure in order to address these difficulties. Although MS finds this strategy challenging, it is crucial.

II. DISCUSSION

Biomedical applications will result from the identification of metabolomic signatures for health and disease, making it easier to differentiate pathophysiological states, make diagnoses, provide individualized care, and create new drugs. The goal of human metabolomics research is to visualizeboth small and large molecules that affect both health and disease states in real time. Finding metabolomic signatures may help in disease prevention and improved medical care. The vast array of analytical instruments and samples used in metabolomics research are primarily depending on the physico - chemical properties of the target chemicals and biological matrices [51]. The goal of metabolomics analyses is to find, define, validate, and use molecular signatures to advance medicine. These investigations can be hypothesis-free or hypothesis-generating, targeted or untargeted.The microbiome, environmental influences, drug use, dietary changes, developmental stage, and advancement. The simultaneous and precise analytical measurement of the metabolome is considered to be difficult [52]. Immunotherapy for cancer using human metabolomics may offer us important molecules for comprehending, forecasting, managing, and regulating immune responses. Clinicians could use targeted checkpoint inhibitors and effective nutritional or pharmacological therapies by anticipating the metabolism of immune cells. Cancer biomarkers and tumor-genesis-promoting factors may be found using metabolomics. For instance, cancer metabolomics has identified an increase of the pentose phosphate pathway, Other biosynthetic and bioenergetics routes include mitochondrial biogenesis, lipid metabolism, glycolysis, glutaminolysis, and others [53].In T2D, genomics, metabolomics, and BCAA levels were identified by pathway analysis as potentially contributing to the development of diabetic mellitus. This is an example of excellent omics integration. The BCAA catabolism process that is rate-limited was first discovered by metabolomics to be the BCAA levels connected to BCKD complex route for alpha-keto acid dehydrogenase. The link between these three was then established by the discovery that the mitochondrial phosphatase gene PPM1K is involved in the synthesis of BCAAs [54]. Global standardized metabolomic studies are required, in addition to the improvement of analytical systems. Currently, metabolomics does not have established processes for reporting and confirming discoveries, as has previously occurred for clinical trials, drug development, genomics, and pharmacogenomics. As a result, there is currently no universal agreement on how to establish a metabolomic signature that is both legitimate and relevant in therapeutic settings. In order for metabolomics to be Schmith et al. stated that there is a need for the utilisation of standardised procedures, low-cost inexpensive devices, and user-friendly analytical platforms in order to address the growing need for diagnostic and prognostic testing. [55].Chronic illnesses and those brought on by an ageing population are the two health issues that are most common nowadays. T2D is one of them, along with cardiovascular and neurological conditions. Metabolomics may aid with personalized medication therapy, lifespan enhancement, and the treatment of various disorders. Studies should be consistent, with little change between people, because the metabolome is varied, complicated, and sensitive. Some distinct indicators of illness development and medication effectiveness have been offered by metabolomics. To advance human health, a list of beneficial and potential therapeutic applicable metabolomic signatures will be available soon. Through the development of increasingly specialized devices as well as computerized tools for statistical analysis and data interpretation, metabolomics provides the potential to increase our understanding of the molecular causes of illness. Additionally, the discovery of novel medications will be made possible by the discovery and characterization of novel biomarkers that will aid in the detection and treatment of a variety of disorders. However, the examination of additional biomarkers in most illnesses, such as protein indicators, as well as the assessment of the physiological condition is also necessary for diagnosis and therapy.

Metabolomics, in conjunction with genomic and proteomic investigations, has helped researchers in the field of plant biotechnology find new genes or genes with novel roles. Metabolomics has become more significant in this field for review of transgenic plants, enhancement of disease resistance, dietary value, and herbicide or salinity tolerance.The use of metabolomics to the study of plants becomes crucial in the pursuit of bettering

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human health. Through the alteration of plant metabolic pathways, novel medications that might be utilized to treat a variety of ailments may be created.

III. CONCLUSION

Metabolomics is still making significant contributions to biological researchsuch is the development of illness monitoring indicators, therapeutic effectiveness, and patient quality of life improvement. In many cases, Identification and analysis have benefited from analytical approaches, in certain cases they are employed in the clinic. Any metabolomic analysis platform's fundamental drawback is its inability to fully describe a phenotype. A more in-depth molecular knowledge metabolomics of human beings in health and disease will eventually be possible thanks to multi-omics techniques. For directing cutting-edge diagnosis and treatments, this is crucial. For metabolomics to develop into a technology with clinical usefulness and analytical validitythere is a pressing need for the creation of new or integrated analytical techniques, such as metabolite imaging, statistics, and computer algorithms.

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