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Omics-Based Approaches for Investigating the Mechanistic Action of Natural Products as Anti-Diabetic Agents: A Comprehensive Review

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With the rising prevalence of diabetes mellitus (DM), the search for novel antidiabetic agents has become increasingly urgent. In the past two decades, there has been a significant shift toward exploring natural products as viable alternatives to synthetic antidiabetic drugs, which often come with undesirable side effects. Researchers have employed various methodologies to uncover the antidiabetic potential of these natural products, focusing on their mechanisms of action and molecular targets involved in DM pathogenesis. Advancements in high-throughput technologies have propelled omics-based techniques such as genomics, transcriptomics, proteomics, metabolomics, and bioinformatics into the forefront of research. These tools are instrumental in detailing the molecular changes that occur in DM and in identifying novel targets for natural products. By utilising these omics technologies, a review on molecular perspective on DM development will explore how these insights can lead to innovative strategies for diabetes management. The ability to identify new molecular targets and pathways promises for more effective and novel antidiabetic agents, thus contributing significantly to the future of diabetes treatment.

Keywords: natural products; genomics; transcriptomics; proteomics; metabolomics

I. INTRODUCTION

Diabetes mellitus (DM) is a multifaceted metabolic disorder marked by chronic hyperglycaemia, resulting from either or both inadequate insulin secretion and insulin resistance. It manifests with symptoms including excessive thirst, urination, and hunger (Banday *et al.*, 2021). DM is a prevalent global health concern, associated with organ damage and increased mortality if untreated (Al-lawati, 2017). The International Diabetes Federation (IDF) projects a significant rise in the number of people affected by DM by 2045 (International Diabetes Federation, 2022). Current treatments for DM, such as meglitinides, biguanides, and thiazolidinediones, can lead to various side effects (Shrestha *et al.*, 2017). Consequently, there is growing interest in exploring natural antidiabetic agents as safer and more sustainable treatment alternatives for DM. Over 1000 natural plant products, including curcumin (Yang *et al.*, 2018), aloe vera (Riyanto & Wariyah, 2018) and ellagic acid (Shrestha *et al.*, 2017), have shown potential as antidiabetic agents. These active phytochemicals target multiple pathways, differing from synthetic drugs (Engwa *et al.*, 2020). However, understanding the mechanism of action and potential use as lead molecules for new drugs is crucial. Progress in omics technologies, such as genomics, transcriptomics, proteomics, and metabolomics has been employed to investigate plant

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metabolites and the molecular mechanisms of action (MOA) of antidiabetic compounds (Aborode *et al.*, 2022). Omics technologies, also known as high-dimensional biology, combine data from various platforms, detecting genes, proteins, mRNAs, and metabolites in untargeted and unbiased ways. Systems biology studies the interactions and integrations among biological processes. The omics technologies approach helps identify potential biomarkers in DM and molecular targets in antidiabetic agents from natural products (Narad & Kirthanashri, 2022). These technologies provide collective and high-throughput analyses, providing more robust data and new targets than conventional research techniques (Nalbantoglu, 2019). The omics technologies approach for identification of potential biomarkers in DM and molecular targets in antidiabetic agents from natural products are illustrated in Figure 1. This review discusses the methodologies used to unravel the MOA of natural products as antidiabetic agents.

II. PREVIOUS MOLECULAR TECHNIQUES AND APPROACHES TO ELUCIDATE THE MECHANISM OF ANTIDIABETIC AGENTS FROM NATURAL PRODUCTS

A. Polymerase Chain Reaction (PCR)

Reverse transcription polymerase chain reaction (RT-PCR) and real-time PCR (q-PCR) are crucial techniques for analysing the molecular mechanisms of natural products in antidiabetic studies. These methods amplify target genes in samples (Jalali *et al.*, 2017), extracting RNA from cells or tissues, and transcribed into complementary deoxyribonucleic acid (cDNA) (Nicola, 2011). It is then used as a template for RT-PCR and q-PCR reactions. Studies have shown that reversible transcription PCR can alleviate insulin resistance in type two diabetic rats, while q-PCR can increase pancreatic and duodenal homeo-box 1 (Pdx1) and insulin expression in pancreatic tissue. Novel oligosaccharide isolated from *Rosa canina* can also improve the regeneration and function of islet cells (Bahrami *et al.*, 2020). However, the hybridisation of primer molecules in q-PCR is a limitation, which can be optimised through multiplex PCR library preparation techniques. The development of more sophisticated techniques is needed to investigate more target proteins and related pathways in antidiabetic studies.

B. Immunohistochemistry (IHC)

Immunohistochemistry (IHC) is a crucial method in clinical diagnosis of anatomic pathology, detecting specific antigens and proteins in cells and tissues (Dong *et al.*, 2020). It has been applied in antidiabetic studies of natural products. Studies have shown that IHC staining can enhance the immunoreactivity of Glutathione peroxidase-1 (GPx-1) in diabetic rats treated with *Heracleum persicum* extract (HPE), increase insulin expression, and downregulate expression of TNF-α, NF-kβ, IKK-β, IL-1β, and caspase-9 in the pancreatic section of stingless bee honey-treated diabetic rats (Masaenah *et al.*, 2021). These studies helped us to comprehend on the therapeutic response of natural products in treated diabetic animals.

C. Enzyme-linked Immunosorbent Assay (ELISA)

ELISA is a laboratory technique used to study the antidiabetic action of natural products. It is a plate-based method that uses a highly chemical reaction to access and measure target antigens in samples (Waritani *et al.*, 2017). Studies have shown that resveratrol can decrease anti-inflammatory markers in type two diabetic Goto-Kakizaki rats, while black solo garlic suppresses IL-6, TNF-α, IL-1β, and IFN-γ formation in diabetic rats. ELISA is also an excellent method for quantifying insulin levels, as demonstrated in studies involving stingless bee honey (*Geniotrigona thoracica*) and *Zanthoxylum zanthoxyloides* alkaloid extract (Aziz *et al.*, 2017; Kyei-Barffour *et al.*, 2021). Both studies suggest that natural products improve insulin secretion in diabetic rats.

D. Western Blotting (WB)

Western blot is a method used to identify proteins in samples, which are separated by size and transferred to nitrocellulose or polyvinylidene difluoride membranes. The membrane is then incubated with primary and secondary antibodies to detect the target proteins (Bass *et al.*, 2017). Studies have shown that curcumin and its analogue A13 downregulate NF-Kβ p65, TNF-α, and COX-2 protein expression in diabetic rats, which can alleviate diabetic encephalopathy (Miao *et al.*, 2021). Another study found that alkaloid Fangchinoline reduced the expression of RAGE, TNF-α, IL-6, IL-1β, and VEGF retinal tissue in streptozotocin-induced diabetic retinopathy in rats (Wu *et al.*, 2019). Oxymatrine, a major

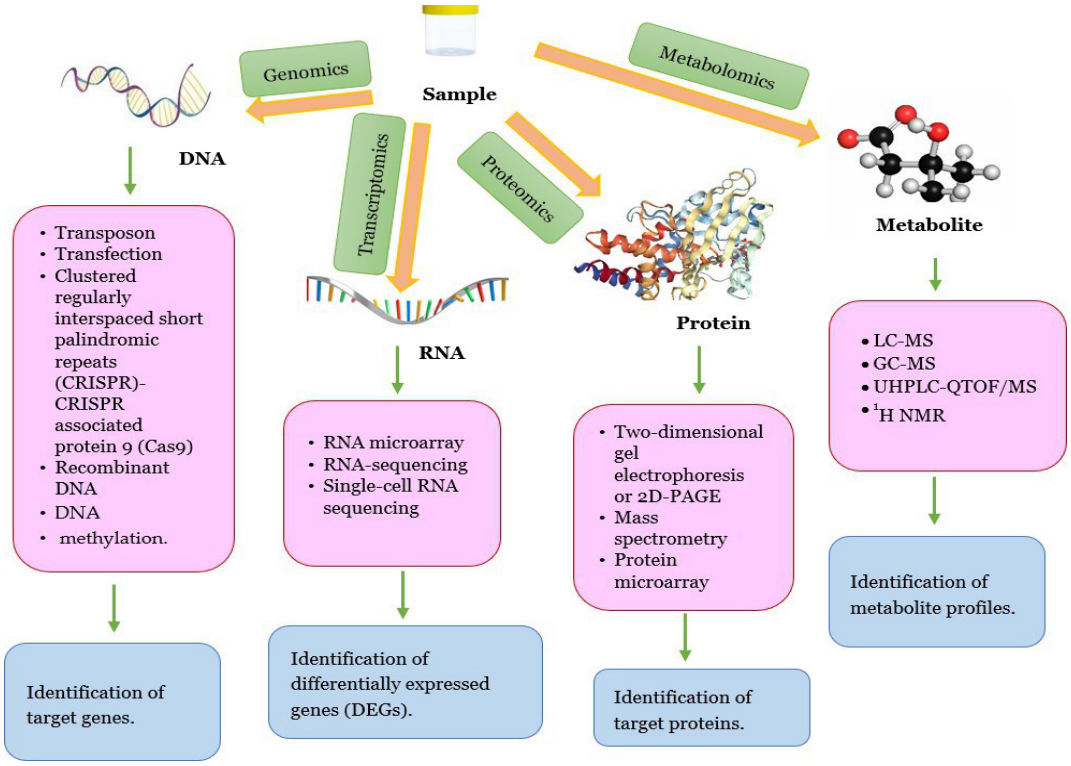

Figure 1. The omics technologies approach for identification of potential biomarkers in diabetes and molecular targets in antidiabetic agents from natural products

component extracted from *Sophora flavescens* Aiton, alleviated diabetes-associated cognitive decline, oxidative stress, and apoptosis by reducing the expression of NOX-2, NOX-4, and caspase-3 in brain tissue of diabetic rats. Traditional molecular techniques like PCR, IHC, WB, and ELISA are specific, simple, and reliable, but only a few targeted genes are analysed and identified (Huang *et al.*, 2020). Omics technologies, such as genomics and transcriptomics, facilitate global analysis of proteins and metabolomics, allowing for the discovery of many new and novel therapeutic biomarkers.

III. ADVANCEMENT OF OMICS APPROACHES FOR DM STUDY

A. Genomics

Recombinant DNA technology, also known as genetic engineering, is crucial in developing new therapeutics and vaccines for improving health conditions. This technique involves inserting DNA sequences from one organism to another to introduce new characteristics (Merchán *et al.*, 2020).

Genomics studies used in explaining antidiabetic action of natural products is exhibited in Table 1. Studies have shown that natural products, such as recombinant *Momordica charantia* (rMcnapin) and recombinant human erythropoietin (rhEPO), can be used to treat diabetes (Murugesan *et al.*, 2022). Recombinant human GLP-1 (rhGLP-1) inhibits NF-κB and MAPK phosphorylation in diabetic tubular and human proximal tubule cells, indicating renal protection (Dar, 2017). A novel oligosaccharide isolated from *Rosa canina* regulates DNA methylation, downregulating the expression of DNA methyltransferases in diabetic rats, which leads to hyperglycaemia and cardiomyopathy. These findings suggest that genetically engineered products from human cell lines and natural sources are therapeutic approaches for diabetes (Bahrami *et al.*, 2020). A miRNA microarray profiling study found that HuoXue JieDu Formula (HXJDF) rescued seven miRNA related to diabetic retinopathy progression, suggesting that HXJDF restored retinal thickness, improved haemodynamic parameters, decreased apoptosis, and retinal structure by inhibiting the STAT3 pathway and VEGF expression in diabetic rat retinas (Li *et al.*, 2021).

Table 1. Application of genomics in antidiabetic action of natural products

Natural product	Genomics	Sample	Animal species	Main Target	References
Oligosaccharide (*Rosa caninavia*)	DNA methylation	Pancreatic tissue Blood	male Wistar rats	*Dnmt1*, *Dnmt3α* and *Dnmt3β*	(Bahrami *et al.*, 2020)
HuoXue JieDu Formula (Euonymus alatus (Thunb.) Siebold, Panax notoginseng (Burkill) F.H. Chen, the roots of Anguina kirilowii (Maxim.) Kuntze, and Coptis omeiensis (C. Chen) C.Y.Cheng	microRNA microarray	Retina tissue	Male *Sprague -Dawley* rats	miR-423-5p (NF-κB signalling pathway) and miR-3099 (JAK-STAT signalling pathway)	(Li *et al.*, 2021)

Dnmt: DNA methyltransferases; miR-423-5p (microRNA-423-5p); NF-κB (Nuclear Factor kappa B); miR-3099 (microRNA-3099); JAK (Janus tyrosine Kinase)-STAT (Signal Transducer and Activator of Transcription)

RNA sequencing (RNA-seq) is a powerful technique used to investigate the whole transcriptomes of transcriptomes using the next-generation sequencing (NGS) method. It involves several steps such as RNA isolation, cDNA conversion, library construction, PCR amplification, and sequencing (Hrdlickova *et al.*, 2017). RNA-seq has been used in numerous studies to understand the molecular mechanisms of diabetes mellitus (DM) as exhibited in Table 2. Studies have shown that Zucker diabetic fatty rats treated with the combination of sitagliptin phosphate and fuzhu jiangtang granule regulated metabolic pathway, drug metabolism cytochrome P450, N-glycan biosynthesis, apoptosis, adipocytokine signalling pathway, T-cell receptor signalling pathway and RIG-I-like receptor genes (DEGs) associated with PI3K-Akt signalling pathway, cell adhesion molecule, and allograft rejection (Xing *et al.*, 2020).

The transcriptional changes induced by 200 mg/kg MCP in diabetic rats were also analysed using RNA-seq. *Momordica charantia* polysaccharide (MCP) exerted hypoglycaemic effect through transactivation of pathways, while the combination treatment of berberine and stachyose (BBR+STA) was found to attenuate glycometabolism (Bai *et al.*, 2018). Diosgenin, a common plant found in Dioscoreaceae and Leguminosae, could protect podocyte injury in the initial development of

Table 2. Application of transcriptomics in antidiabetic action of natural products

Natural product	Transcriptomics	Sample	Animal species	Main Target	References
Momordica charantia polysaccharide	RNA-seq	Liver tissue	Male *Sprague-Dawley* rats	Glucose and fat Metabolism	(Bai *et al.*, 2018)
Berberine and stachyose	RNA-seq and miRNA-seq	Colon tissue	Male ZDF-Leprfa/Crl rats	TGF-beta signalling pathway, Oxidative phosphorylation, and glycerolipid metabolism and ErbB signalling pathway miR-10a-5p, Egr1 and Hbeg	(Li *et al.*, 2021)
Diosgenin	mRNA-seq	Mice podocyte cell line of kidney	Diabetic *db/db* mice	Cholesterol metabolism, biosynthesis of unsaturated fatty acids	(Wang *et al.*, 2022)
Rhizoma Coptidis alkaloids	RNA-seq	Kidney tissue	*db/db* and *db/m* mice	AGEs-RAGE-TGFβ/Smad and PI3K-Akt pathways	(Xiao *et al.*, 2021)
Maple syrup extract	DNA microarray	Liver tissue	Male KK-Ay mice	Triglyceride and fatty acid degradation pathways and the ketone body metabolic Pathway	(Toyoda *et al.*, 2020)

RNA-seq (RNA sequencing); MicroRNA sequencing (miRNA-seq); Zucker diabetic fatty (ZDF), Epidermal growth factor receptor (ErbB), microRNA-10a-5p (miR-10a-5p); Egr1 (Early growth response factor 1), AGEs (advanced glycation end products); RAGE (Receptor for AGE); TGF-β (Transforming growth factor β); PI3K (Phosphatidylinositol-3-kinase); Akt (protein kinase B).

diabetic nephropathy by modulating Sirtuins (SIRT6) and PDK and ANGPTL4 (Wang *et al.*, 2022). Furthermore, tropical targets like insulin resistance, PI3K-Akt signalling pathway and advanced glycation end products (AGE-RAGE signalling pathway) are potential target pathways for *Rhizoma coptidis* alkaloids to improve diabetes (Wang *et al.*, 2022). Huanglian-Renshen-Decoction (HRD) treatment activating hormone downstream molecular signalling (Fan *et al.*, 2021). Another study found that 527 and 832 DEGs were upregulated and dysregulated in liver diabetic mice treated with maple syrup extract (MSE), suggesting that these pathways potentially mitigate the accumulation of triglyceride in the liver (Toyoda *et al.*, 2020). RNA-seq provides better quantification of gene expression than microarrays and other gene-probe-based methods, but they have limitations such as the availability of arrays for specific

target genes and technical issues like reproducibility (dos Santos *et al*., 2016).

C. Proteomics

Proteomics is a crucial approach for disease diagnosis, prognosis, and monitoring disease progression, as well as target molecule identification for drug discovery (Aslam *et al*., 2017). Mass spectrometry (MS)-based proteomics quantitates proteins from protein samples and is used in most proteomics studies. Two-dimensional gel electrophoresis (2DE) and sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) are the main techniques for protein separation in proteomic studies (Alsagaby, 2019). Coomassie dye is used for protein detection using fluorescent total-protein statins or silver (Buyukkoroglu *et al*., 2018). Recent advances in proteomics technology have led to platforms such as isobaric tags for relative and absolute quantification (iTRAQ), stable isotopic labelling by amino acids in cell culture (SILAC), isotope coded affinity tags (ICAT), activity-based probes (ABPs), and protein arrays (Amiri-Dashatana *et al*., 2018). Proteomic analysis of left kidney tissue in diabetic rats treated with aloe vera identified 11 proteins expression related to mitochondrial function, glycolysis/pentose pathway and only 6 of them namely 10 kDa heat shock protein, mitochondrial (Hspe), aldolase A (Aldoa), cAMP-dependent protein kinase catalytic subunit beta (Prkacb), transaldolase (Taldo), L-lactate dehydrogenase B chain (Ldhb) and Cytochrome P450 2C23 (Cyp2c23) showing interaction with each other. These findings suggest aloe vera as a potential therapeutic for DM-associated kidney damage through modulation of these proteins (Xiao *et al*., 2009).

Moreover, grape seed proanthocyanidin extracts (GSPE) also regulated the expression of 15 proteins in the aorta of diabetic rats notably catalase, lamin A, ATP synthase chain, apolipoprotein A-I (ApoA-I), lactadherin, adenylyl cyclase-associated protein 1 (CAP 1), proline arginine-rich end leucine-rich repeat protein precursor (PRELP), HSP27, Dermcidin, enoyl-CoA hydratase (ECH), protein-L-isoaspartate (D-aspartate) O-methyl-transferase 1 (PIMT1), glutamate dehydrogenase (GDH), leucine aminopeptidase 3 (LAP 3), LOC500183 protein, and fibrinogen ß chain, which identified by 3 different proteomic methods such as 2-D difference gel electrophoresis (2-D DIGE), flight mass spectrometry with LIFT technology (MALDI-TOF/ TOF MS) or liquid chromatography-electrospray ionisation mass spectrometry/mass spectrometry (LC-ESI-MS/MS), providing insight into the molecular mechanism of GSPE in treating vascular complications in diabetic patients (Beeton-Kempen, 2022).

However, the study of antidiabetic MOA using natural products has not adopted a proteomic approach in abundance and some of the studies are summarised in Table 3, possibly due to the cost of laboratory equipment and the need for bioinformatics skills.

D. Metabolomics

The characterisation of the metabolite group (metabolome) using Liquid Chromatography-Mass Spectrometry (LC-MS), Gas Chromatography-Mass Spectrometry (GC-MS) and High-Performance Liquid Chromatography (HPLC) is crucial for detecting clinically relevant metabolic markers. Non-targeted metabolomics scans small molecular ions to obtain the ion fragment mass spectrum for metabolite identification, while targeted metabolomics focuses on the precise determination of known metabolites to comprehend the metabolite changing process under the state of diseases (Yu *et al*., 2017).

Both nonpolar and polar metabolites extraction is optimised by two-phase extraction applications before chromatographic separation by metabolomic analytical tools. Ultra-high performance liquid chromatography (UPLC) improves the analysis sensitivity, speed, and resolution. Capillary electrophoresis coupled to mass spectrometry (CE-MS) is also a prospective metabolomic tool for metabolites associated with disease profiling due to high sensitivity, stable coupling of CE to MS instrument, and a restricted loading volume of CE capillaries (Boizard *et al*., 2016).

Various software is used for interpreting metabolomic data, including Human Metabolome database (HMDB), MetaboAnalyst, KEEG pathway database, Orthogonal partial least squares discriminant analysis (OPLS-DA), Principal component analysis (PCA), and SIMCA-P+ (Gong *et al*., 2022). Studies using the metabolomic approach to elucidate the metabolic mechanistic study of natural products are most abundant

Table 3. Application of proteomics in antidiabetic action of natural products

Natural product	Proteomics	Sample	Animal species	Main Target	References
Aloe vera	Quadrupole-orbitrap mass spectrometer coupled to liquid chromatography	Kidney tissue	Male *Wistar* rats	Transaldolase (Taldo), L-lactate dehydrogenase B chain (Ldhb), N(G), N(G)-dimethylarginine dimethylaminohydrolase 1 (Ddah1), Fructose-bisphosphate aldolase A (Aldoa), Arginase-2, mitochondrial (Arg2), cAMP-dependent protein kinase catalytic subunit beta (Prkacb), Inositol monophosphate (Impa1), Aromatic-L-amino-acid decarboxylase (Ddc), Cytochrome P450 2C23 (Cyp2c23), 10 kDa heat shock protein, mitochondrial (Hspe1) and Hp (Haptoglobin)	(dos Santos *et al*., 2021)
Grape seed proanthocyanidin extracts	2D DIGE, MALDI-TOF/TOF MS and LTQ-ESI-MS/MS	Aorta	Male *Wistar* rat	Oxidative stress, cell proliferation, inflammatory pathways and substance metabolism.	(Li *et al*., 2009)

2D DIGE (Two-dimensional gel electrophoresis), MALDI-TOF (Matrix-Assisted Laser Desorption/Ionization- Time of Flight); TOF-MS (Time of Flight-Mass Spectrometry); LTQ-ESI-MS/MS (Linear Ion Trap - Electrospray ionization- Mass Spectrometer/ Mass Spectrometer).

compared to other omics techniques. We highlighted some of them herein and more studies are exhibited in Table 4. A study found that *Scutellaria baicalensis Georgi* regulates glycerophospholipid metabolism, retinol metabolism, and arachidonic acid metabolism in rats after treatment for ten weeks (Men *et al*., 2021). The study identified biomarkers in Metlin and HMDB databases and investigated the antidiabetic effect of *Lycium barbarum* polysaccharides (LBP) in ameliorating T2DM in rats. LBP modulates various metabolisms in the liver and urine, while some metabolites are regulated by LBP in urine.

Most antidiabetic MOA studies of natural products use a metabolomic approach, as it accurately reflects the current status of organisms and their specific events. However, transcriptomics and proteomics are insufficient for monitoring cellular function due to the lack of a straightforward correlation between mRNA or protein levels and metabolism.

Table 4. Application of metabolomics in antidiabetic action of natural products

Natural product	Metabolomics	Sample	Animal species	Main Target	References
Pueraria lobate (Willd.) Ohwi root (*Radix Puerariae*)	UPLC-Q-TOF/MS	Serum	Male Kunming mice	Glycerol phospholipid metabolism and fatty acid extension in mitochondria.	(Gong *et al.*, 2022)
Stachyose (*Rehmanniae radix*)	UPLC-ESI-Q-TOF-MS LC–MS/MS analysis (HILIC/MS)	Urine	Male Wistar rats	Citrate cycle (TCA cycle), alanine, aspartate and glutamate metabolism, glyoxylate and dicarboxylate metabolism.	(Liang *et al.*, 2020)
Red ginseng (*Ginseng Radix et Rhizoma Rubra*)	UHPLC-MS/MS	Serum	Male *Sprague-Dawley* rats	Amino acid metabolism, glycerol-phospholipid metabolism, and fatty acid metabolism.	(Yang *et al.*, 2022)
Ginseng berries (*Panax ginseng* C. A. Meyer)	UHPLC-Q-Orbitrap/MS	Serum Urine	Male Wistar rats	Arachidonic acid metabolism and cholesterol metabolism	(Wang *et al.*, 2021)
Scutellaria baicalensis Georgi	UHPLC-Q-TOF-MS	Serum	Male *Sprague-Dawley* rats	Glycerophospholipid metabolism, amino acids metabolism and retinol metabolism	(Men *et al.*, 2021)
Lycium barbarum polysaccharide	GC-TOF-MS	Liver	Male adult *Sprague-Dawley* rats	Citrate cycle, alanine, aspartate and glutamate metabolism, glyoxylate and dicarboxylate metabolism	(Xia *et al.*, 2019

UHPLC/Q-TOF-MS (Ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry); UPLC- ESI-Q-TOF-MS (Ultra-performance Liquid Chromatography-ESI/quadrupole-TOF high-definition MS); LC–MS/MS (Liquid chromatography–mass spectrometry/ mass spectrometry); HILIC/MS (Hydrophilic interaction chromatography/mass spectrometry); UPLC-Q-Orbitrap (Ultrahigh-performance liquid chromatography tandem hybrid quadrupole-Orbitrap mass spectrometry); HRMS/MS (High-resolution mass spectrometry/ mass spectrometry); ^{1}H NMR (Proton nuclear magnetic resonance); UHPLC- MS/MS (Ultra-high-performance liquid chromatography-mass spectrometry/ mass spectrometry); GC-TOF-MS (Gas chromatography time-of-flight mass spectrometry)

IV. CONCLUSION

Omics technologies provide very modern and sophisticated approaches for elucidating the antidiabetic mechanism of natural products derived antidiabetic agents. The various antidiabetic mechanism of novel natural antidiabetic agents explained by these studies in this review resulted in preventing and delaying the development of DM besides no or minimal side effects. The new insight into molecular mechanisms encourages the researchers to explore the identification and isolation of bioactive compounds in these natural products that possess antidiabetic activities.

Nonetheless, the solution for several obstacles in related to these omics' approaches should be addressed such as complexity, experimental cost and sample with a wide dynamic range, before popularising these technologies that could be figured out by consistent refinement in this area and bioinformatics technology. The best way to determine the MOA of natural products would be to conduct an integrated study utilising various omics technologies, as each technique has unique characteristics in terms of its constraints and the possibility of producing results.

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