SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Metabolites alterations associated with obesity: A scoping review

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ABSTRACT

Introduction: Obesity can be considered a major public health concern throughout the world. Various studies have been conducted to combat the rising number of cases of this health problem. Therefore, identifying the roots of the disease is critical in developing the desperately needed treatment approaches. However, in order to fully understand the origin of this disease, figuring out the metabolites present, and the alterations that occurred in a particular metabolism are crucial, and the information regarding the metabolites involved is limited. The aim of this study is to analyse the literature relevant to the metabolites involved in obesity conditions through a scoping review.

Materials and Methods: This review utilises three databases (SCOPUS, Science Direct, and PubMed). The search phrases used are (Metabolomic* OR Metabolite*) for metabolomic study, (3T3-L1 OR Adipocyte OR "Adipose Tissue") for experimental design, and (Obesity) for obesity condition. Each of the search keywords was separated by an "AND" term in the databases. Other terms related to obesity, such as insulin resistance, heart disease, type 2 diabetes, muscular disorders, respiratory problems, and psychological problems were omitted because they did not contribute to the total number of studies discovered.

Results: A total of 27 research publications were included in this scoping review. Most of the study focuses on metabolomics in obesity. Metabolites detected were found in various metabolic pathways including amino acids, carbohydrates, lipids as well as other metabolisms. Most of these metabolites discovered in obese conditions showed an alteration when compared to the level of the metabolite in normal conditions.

Conclusion: Unfortunately, these studies had some limitations in which the metabolites detected varied between the articles and the information concerning the relationship between the technique or instrument utilised and the metabolites detected in the samples were not well described. Therefore, using the findings obtained in this study, it can help to determine the direction of the study in the future.

KEYWORDS:
Metabolism, metabolites, metabolomics, obesity, review

INTRODUCTION

Obesity can be considered a major public health concern throughout the world. According to the World Health Organization (WHO), obesity and overweight are characterised as abnormal or excessive fat accumulation that is harmful to one's health.[1] Obese patients are at a higher risk of developing a variety of comorbid conditions, such as cardiovascular disease (CVD), gastrointestinal disorders, type 2 diabetes mellitus (T2DM), joint and muscular disorders, respiratory problems, and psychological problems, all of which can have a significant impact on their daily lives and increase mortality risks.[2,3] Various research had been done to address the rising cases of this health issue. Therefore, understanding the roots of the disease is critical in developing the desperately needed treatment approaches. Principally, this condition is linked to an increase in the size of adipocytes,[4] which arise from fat cell multiplication through adipogenesis and increased cytoplasmic triglyceride accumulation.[5]

Adipogenesis is the process through which fat-laden cells (adipocytes) grow and deposit as adipose tissue at numerous locations throughout the body, including subcutaneous fat and depots.[6,7] This complex multi-step process involves coordinated changes in shape, hormone sensitivity, and adipogenic gene expression.[5]

The primary functions of these adipocytes are to store energy as fat when energy intake exceeds expenditure and to utilise this stored energy when energy expenditure exceeds intake.[6] During adipogenesis, countless metabolites from various metabolism including amino acids, carbohydrates, and lipids such as isoleucine, valine, lysine, phenylalanine,[8] betaine, carnitine, choline,[9] lactate, acetate, and succinate[10] were analysed. In order to detect these metabolites, metabolomic profiling should be performed.

The analysis of various small molecule metabolites in biological samples such as body fluids (urine, blood, saliva), tissues, etc., is also known as metabolomic study. In comparison to genomics, transcriptomics, and proteomics, metabolomics is seen as a relatively new addition to the "omics" platforms, but its roots lie in the old theory of analytical biochemistry.[11] In actuality, metabolites exist in a wide range of quantities and chemical diversity, making it impossible to assess all of the metabolites in a single assay with a single set of equipment. Instead, to get extensive

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coverage of metabolic space, practitioners of this approach typically use a suite of instruments, most often combining different combinations of liquid or gas chromatography coupled with mass spectrometry.[12]

The most common methods for metabolomic profiling are nuclear magnetic resonance (NMR) and mass spectrometry (MS). Individual analytes in the sample are separated based on their magnetic resonance shift or mass/charge ratio, resulting in a separation spectral profile.[11,13] NMR spectroscopy is a universal metabolite detection technology that allows samples to be evaluated directly with minimal processing and various classes of small metabolites to be detected at the same time. However, the major limitations in NMR for metabolomics include poor sensitivity and spectrum complexity, with signal superimposition at particular spectral regions compromising precise identification. While MS spectroscopy is more sensitive and specific compared to NMR spectroscopy, it usually necessitates a prior separation step, such as gas chromatography (GC), high-performance liquid chromatography (HPLC), or ultra-performance liquid chromatography (UPLC), and capillary electrophoresis (CE). Separation procedures in combination with MS are critical for reducing sample complexity and minimising ionisation suppression effects, hence increasing detection sensitivity and metabolome coverage.[2] Thus, in this scoping review, the studies focusing on the metabolomic study of obesity will be discussed and summarised. This review will also identify the research gaps in the particular subject, which then may serve as a roadmap for future research.

MATERIALS AND METHODS

This study investigated literature relevant to metabolomic studies in obesity through a scoping review. By including many types of study, scoping reviews are considered a beneficial tool for swiftly identifying research trends and outcomes connected to the research topic, as well as for quickly discovering usable basic resources and core concepts of corresponding domains. The scoping review was conducted in the order of the five research steps suggested by Arksey and O'Malley.[14]

Identify Research Question

This review aimed to investigate the diversity of metabolites related to obesity. This research question was created using the recommendation of Arksey & O'Malley[14] to start with a broad review topic to determine the data available before refining the search. The current authors are currently employing a metabolomic technique to investigate the metabolites related to obesity and are gathering further information from past correlated studies and published research. The development of research topics was critical for determining the direction of the review and the method for identifying and selecting relevant articles. Hence, the research questions for this review are: [1] What are the metabolites involved in obesity condition? [2] What are the metabolites altered in obese samples compared to normal?

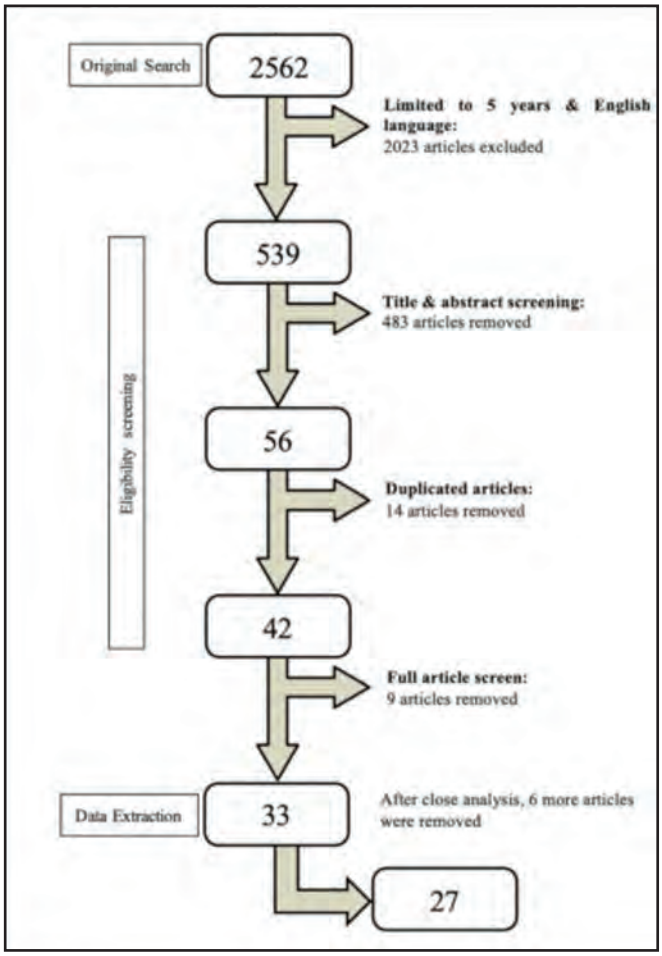

Fig. 1: Study selection for the scoping review. Articles identified from Scopus (n=203); Science Direct (n=2176); PubMed (n=183)

Identify Relevant Studies

Search Terms

To discover studies relating to the research questions outlined, key phrases were chosen. The following were the search phrases used: (Metabolomic* OR Metabolite*) for metabolomic study, (3T3-L1 OR Adipocyte OR "Adipose Tissue") for experimental design, and (Obesity) for obesity condition. Each of the search keywords was separated by an "AND" term in the databases. Other terms related to obesity, such as insulin resistance, heart disease, type 2 diabetes, muscular disorders, respiratory problems, and psychological problems were omitted. English language and articles published between 2017 and 2021 were chosen as the inclusion criteria. Older publications were eliminated or excluded because the goal of this scoping review was to find the most recent and relevant literature.

Databases

Based on the topic area, three databases were used in this study: SCOPUS (life and health sciences), ScienceDirect (science and medicine), and PubMed (life sciences and biomedical topics). Three databases were believed to be sufficient to rule out bias and would be able to access all the relevant papers within the area of interest. Using the above search criteria and databases, 2,562 articles were discovered.

Study Selection

In the study selection for this scoping review, out of the 2,562 articles discovered in three databases, articles published before 2017 until 2021 and languages other than the English language were removed, leaving 539 articles to be screened. All 539 titles of articles were read, and blatantly irrelevant papers were eliminated (e.g., Metabolomic profiling for the identification of novel biomarkers and mechanisms related to common cardiovascular diseases form and function), narrowing the total number of papers to 147. Next, the remaining abstracts were carefully evaluated and those that were irrelevant (n=91) were removed, leaving 56 publications for full-text screening. Then, duplicate titles (n=9) were discarded, leaving 42 articles to evaluate. The following stage was to read the full report, focusing on the methodology portion in particular. All the remaining articles were evaluated, resulting in a total of 33 articles. After close analysis during data extraction, a final 27 articles were selected to be included in the review. The flowchart of the study selection for this review is illustrated in Figure 1.

Data Charting

All the data from the chosen articles were collected and organised in the fourth research step of the scoping review framework. The gathered data points were title, author(s), year of publication, sample(s), experimental design, metabolomic technique used, and significant metabolites in obese conditions. The collected data points were summarised in Table I. While extracting and compiling the data for Table I, after close analysis was performed, six more publications were eliminated from this study because other metabolic syndromes were included (n=3), measurement of metabolites from other obese-related samples (n=2) and did not include metabolite in obesity condition (n=1).

Collating, Summarizing and Reporting Results

The final research step suggested by Arksey & O'Malley[14] was to organise the relevant findings into themes, sorting and prioritising the findings based on their relevance to the research objectives and putting a strong emphasis on the intervention type. The sample, experimental design, methodology, and outcomes were all covered in the study. The executive summary in Table I contain all the information.

RESULTS

Based on the Arksey & O'Malley[14] methodology and the inclusion criteria described above, 27 peer-reviewed papers related to the study topic were discovered. Considering the experimental design of all the related publications, the majority of the studies were conducted in mice (n=16, 59.3%), while eight (29.6%) in human serum, plasma, or urine and one (3.7%) each in adipocyte, hamster, and rabbit. Of all the experimental designs, the samples were divided into serum (n=6, 22.2%), plasma (n=4, 14.8%), adipose tissue (n=6, 22.2%), adipocyte (n=2, 7.4%), liver (n=4, 14.8%), urine (n=3,11.1%) and faecal (n=2, 7.4%). The interventions and data collection techniques are detailed in Table I. The metabolites analysed were further grouped by the type of metabolism it took place which are carbohydrate metabolism, amino acid metabolism, and lipid metabolism.

Carbohydrate Metabolism

According to the studies related to the metabolites in obesity, the majority of metabolites discovered involved in carbohydrate metabolism include glucose, lactate, succinate, citrate, fumarate, and 2-oxoglutarate. Most of these metabolites can be found in glycolysis and the tricarboxylic acid (TCA) cycle. Significant increases were reported in glucose and fumarate.[10,15,16] However, some studies found that glucose and fumarate metabolites were decreased when compared to normal conditions.[8,17,18] Besides, out of 27 studies discovered, four papers stated that there was an increase in lactate,[8–10,16] while one paper showed that lactate was decreased.[19] Moreover, although some publications identified a notable decrease in citrate,[10,15,17,19,20] there were also papers that demonstrated that citrate was increased compared to normal.[16,21] Several other papers also found a few metabolites such as aconitate, hippurate, galactose, pyruvate, mannose, maltose, glutathione, sucrose, acetyl-CoA, and alpha-ketoglutarate were related to obesity. Pyruvate,[9,20] hippurate,[19] alpha-ketoglutarate,[22] and acetyl-CoA[23] were some of the elevated metabolites that were revealed in obese samples. Remarkable decreases were also shown in aconitate,[20] galactose,[21] mannose,[24] sucrose,[19] maltose, and glutathione.[10]

Amino Acid Metabolism

Based on the papers related to the study, the most common metabolites found involved in amino acid metabolism are tyrosine, phenylalanine, isoleucine, leucine, alanine, lysine, valine, glutamine, and glycine. In obese conditions, the result for tyrosine, phenylalanine, and valine showed a significant increase when compared to normal.[8–10,18,19,25,26] In addition, a notable increase was also revealed in isoleucine and leucine.[9,18,25–28] However, even though multiple papers demonstrated a significant increase in these metabolites, according to Airaksinen, et al.,[29] these metabolites were lower when compared to the normal group. Meanwhile, glycine is one of the metabolites in amino acid metabolism that was found to be markedly decreased.[17,21,24,25,30] Other than these commonly analysed metabolites that are involved in amino acid metabolism, there were also studies reported that in obese subjects or samples that were induced with a high-fat diet, the results exhibited an increase in creatinine,[9,19] 2-oxoisocaproate,[9,16] glutamate,[10,17,19] and histamine.[10] On the other hand, several studies showed that aspartic acid,[24,31] cystine, and anserine[10] were significantly reduced. Apart from the variety of results reported among the metabolites found in amino acid metabolism, carnitine however, exhibited quite inconsistent results where there was an increase[9], decrease[29], and no remarkable change[31] observed when compared to the normal condition.

Lipid Metabolism

In accordance with 27 peer-reviewed papers related to the study topic, most of the metabolites detected that were related to lipid metabolism are comprised of betaine, choline, and taurine. Four studies found that betaine was one of the decreased metabolites when compared to the normal group.[8,10,19,29] In contrast,[9,16] showed that betaine was increased in the serum sample. Choline, however, exhibited an elevation based on the studies done by Wang, et al.,[8] Duft, et al.,[9] Guo, et al.,[16] and Osawa, et al.[30] but conversely, it was decreased in research done by Airaksinen, et al.[29] In addition

Table I: The sociodemographic among respondents

Author	Sample	Metabolomic Technique	Significant Metabolites Observation in Obese Condition
Wang et al.[8]	Liver	Proton nuclear magnetic resonance (^{1}H NMR analysis)	Isoleucine, Valine, Lysine, Phenylalanine, Lactate, Alanine, Acetate, Glutamine, Succinate, Taurine, Choline, Tyrosine, Uridine, 3-Hydroxybutyrate, Betaine, A-Glucose, Glycogen, Formate, Fumarate and Adenosine
Duft et al.[9]	Serum	Proton nuclear magnetic resonance (^{1}H NMR analysis)	Tyrosine, Histidine, 2-Oxoisocaproate, Pyruvate, Phenylalanine, Isoleucine, Choline, Betaine, Carnitine, Lysine, Glucose, Creatinine, Ornithine, Valine, Alanine, Leucine, Glutamine, Asparagine, 2-Aminobutyrate, Lactate
Sun et al.[10]	Serum and liver	Proton nuclear magnetic resonance (^{1}H NMR analysis)	1. Serum Low-density lipoprotein (LDL), Very low-density lipoprotein (VLDL), Isoleucine, Leucine, 3 Aminoisobutyrate, 3-Hydroxybutyrate, Valine, Lipid, Lactate, Alanine, Lysine, Acetate, Glutamate, Glutamine, Succinate, Citrate, Creatinine, Glucose 2. Liver Isoleucine, Leucin, Valine, Lactate, Alanine, Acetate, Glutamate, Glutamine, Glutathione, Succinate, Aspartate, Trimethylamine (TMA), Betaine, Trimethylamine oxide (TMAO), Taurine, Maltose, Glucose, Cystine, Inosine, Anserin, Uridin, Fumarate, Tyrosine, Histamine, Phenylalanine, 3-Methylxanthine, Nicotinamide adenine dinucleotide (NAD), Nicotinamide adenine dinucleotide phosphate (NADP), Nicotinurate
Bugáňová et al.[15]	Urine	Nuclear magnetic resonance (NMR-based metabolomics)	Hexanoylglycine, 2-Oxovalerate, N-Isovalerylglycine, Lactate, Putrescine, Vinyl Acetylglycine, Acetate, N-Acetyls of Amino Acids Derivatives, N-Carbamoyl-B-Alanine, Succinate, 2-Oxoglutarate, Citrate, Methylamine, Dimethylamine, Trimethylamine, N, N-Dimethylglycine, Creatine, Creatinine, Cis-Aconitate, Ethanolamine, Carnitine, Taurine, Glycine, N-methyl-4-pyridone-5-carboxamide (4PY), Ascorbate, Trigonelline, 1-Methylnicotinamide, Glucose, Galactose, Allantoin, Urea, Fumarate, N-methyl-2-pyridone-5-carboxamide (2PY), Phenylacetylglycine, 3-Indoxyl Sulfate, Hippurate, Nicotinamide-N-Oxide, Formate, Nicotinurate
Guo et al.[16]	Serum	Proton nuclear magnetic resonance (^{1}H NMR analysis)	2-Hydroxybutyrate, 2-Hydroxyisovalerate, 2-Oxoglutarate, 2-Oxoisocaproate, 3-Hydroxybutyrate, 3-Hydroxyisobutyrate, 3-Methyl-2-Oxovalerate, Alanine, Betaine, Choline, Citrate, Fumarate, Glucose, Glutamine, Lactate, Myo-Inositol, O-Acetylcarnitine, Proline, Tryptophan, Lysine, Arginine
Nishitani et al.[17]	Adipose and liver tissue	Capillary electrophoresis–mass spectrometry (CE-MS analysis)	1. White Adipose Tissue (Wat) Glycolysis- Glucose 6-Phosphate (G6P), Fructose 6-Phosphate (F6P), Fructose 1,6-Diphosphate (F1,6P), 3-Phosphoglycerate (3-PG), 2-Phosphoglycerate (2-PG), Phosphoenolpyruvate (PEP) TCA- Citrate, Cis-Aconitate (Cis-Aco), Succinate, Fumarate, Malate 2. Liver Glucose 6-phosphate (G6P), Fructose 6-phosphate (F6P), Citrate, Fumarate, Malate, Amino Acids, Alanine, Glycine, Glutamate, And Glutamine
Yde et al.[18]	Fecal	Nuclear magnetic resonance (NMR spectroscopy)	1. Short-Chain Fatty Acid (Acetate, Formate, Propionate, Isobutyrate, Valerate) 2. BCFA (2-Methyl Butyrate, 3-Methyl-2-Oxovalerate) 3. Alcohols 4. Amino Acids (Arginine, Isoleucine, Leucine, Lysine, Phenylalanine, Tryptophan, Tyrosine, Valine) 5. Metabolism (Glutarate, Malate, Fumarate, Glucose, Ribose, Succinate) 6. Others (Cadaverine, Trimethylamine)
Chen et al.[19]	Urine and fecal	Proton nuclear magnetic resonance (^{1}H NMR analysis)	1. Urine Acetoacetate, Creatine, Creatinine, Allantoin, Phenylacetate, Hippurate, Phenylalanine, Succinimide, N-Acetyl-Beta-D-Glucosaminidase (NAG), N-Acetylglutamate, Uracil, Valine, Levulinate, Alanine, 2-Methylglutarate, 4-Cresol, Leucine, Trimethylamine, 2-Hydroxybutyrate, N-Phenylacetylglycine and Glycogen, Phosphorylcholine, Ornithine, N-Nitrosodimethylamine, Glycerol, Citrate, Betaine, Sucrose, Glycine, Glycerophosphocholine, Propylene Glycol 2. Fecal Imidazole, Urocanate, 3-Phenylpropionate, Glutamate, Phenylacetate, Tyrosine, 2-Oxoglutarate, Cadaverine, Valine, Leucine, 5-Aminovalerate, Uracil, Arginine, Creatine, Malonate, α-Ketoisocaproate, Threonine, Lactate, α-Arabinose

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Table I: The sociodemographic among respondents

Author	Sample	Metabolomic Technique	Significant Metabolites Observation in Obese Condition
Sundekilde et al.[20]	Liver	High-Resolution Magic Angle Spinning (HRMAS) NMR Methods	Acetate, Glucose, Pyruvate, Fumarate, Cis-Aconitate, Citrate, Malate, Succinate, Taurine, Oxaloacetate, Oxoglutarate
Zhuang et al.[21]	Urine	Gas chromatography-mass spectrometry (GC-MS)	Glycine And Serine, Glutamine, L-Proline, L-Alanine, Glutamate, Acetic Acid, Lysine, D-Galactose, Citrate
Candi et al.[22]	Adipose tissue	Extensive gas chromatography/mass spectrometry (GC/MS) and liquid chromatography/mass spectrometry (LC/MS/MS) analyses	1. Ceramide and Sphingolipid Metabolism Behenoyl Sphingomyelin, Tricosanoyl Sphingomyelin, Lignoceroyl Sphingomyelin 2. Plasmalogens and Lysoplasmalogens 1-(1-Enyl-Palmitoyl)-GPE, 1-(1-Enyl-Oleoyl)-GPE and 1-(1-Enyl-Stearoyl)-GPE), 1-(1-Enyl-Palmitoyl)-2 Palmitoyl-GPC, 1-(1-Enyl-Palmitoyl)-2-Arachidonyl-GPC, 1-(1-Enyl-Palmitoyl)-2-Arachidonyl-GPE, and 1-(1-Enyl-Stearoyl)-2-Arachidonoyl-GPE) 3. Phospholipids and Lysolipids Glycerol Phosphorylcholine (GPC), Glycerol Phosphoethanolamine, 1,2-Dipalmitoyl-GPC, 1-Stearoyl-2-Arachidonoyl-GPC, 1-Palmitoyl-2-Arachidonoyl-GPC, 1-Steroyl-2-Arachidonoyl-GPI, 1-Steroyl-2-Arachidonoyl-GPE, 1-Palmitoyl-2-Steroyl-GPC, 1-Stearoyl-2-Oleoyl-GPG, and 1-Stearoyl-2-Linoleoyl-GPS), 1-Palmitoyl-GPC, 1-Stearoyl-GPC, 1-Palmitoyl-GPE, 1-Stearoyl-GPE, 1-Stearoyl-GPI, and 1-Stearoyl-GP) 4. Glucose Related Metabolites
Li et al.[23]	Liver	Chromatographic separation was performed by using an Acquity UPLC HSS T3 column	Acetyl-Coa, L-Glutamic Acid, N-Acetyl-D-Galactosamine, 1,1,1-Tri-Fluoroacetone, 1-Linoleoyl-Sn-Glycero-3-Phosphocholine, 2-C-Methylerythritol 4-Phosphate, Bis(2-Ethylhexyl) Phthalate, Methyl 3,3,3-Tri-Fluoro-2-Oxopropanoate, Muramic Acid, Taurine, Isoleucine, L-Phenylalanine, Methionine, Spermidine
Ammar et al.[24]	Serum	Gas chromatography/mass spectrometry (GC/MS)	Aminobutyric Acid, Butyric Acid, Glycine, Phenylethanolamine, Urea, D-Glucopyranose, Ethanol Hydroxybutyric Acid, D-Glucose, L-Alanine, L-Aspartic Acid, L-Glutamine, D-Mannose (Glucose-2-Epimer)
Dadson et al.[25]	Serum	High-throughput (HTP) nuclear magnetic resonance (NMR) metabolomic	Apob/Apoa-1, Glycine, Isoleucine, Leucine, Valine, Phenylalanine, Tyrosine, GlycA
Brennan et al.[26]	Plasma	Liquid Chromatography Triple Quadrupole Mass Spectrometry (LC-MS/MS)	Lactic Acid, Hypoxanthine, Pyruvic Acid, Inosine, Alpha-Ketoglutaric Acid,2-Ketoisovaleric Acid, Ketoisocaproic Acid, Xanthosine, Kynurenine, Anthranilic Acid, Indole-3-Carboxylic Acid, Allantoin
Jokinen et al.[27]	Plasma	Liquid Chromatography Triple Quadrupole Mass Spectrometry (LC-MS/MS)	Leucine, Propionylcarnitine, Isobutyrylcarnitine, Valine, Isovalerylcarnitine, Isoleucine
Piro et al.[28]	Adipose tissue	Samples were divided into five fractions: -Two for analysis by two separate reverse phases (RP)/UPLC-MS/MS methods with positive ion mode electrospray ionisation (ESI) -One for analysis by RP/UPLC-MS/MS with negative ion mode ESI -One for analysis by HILIC/UPLC-MS/MS with negative ion mode ESI -One sample was reserved for backup	Leucine, Isoleucine, Valine, 4-Methyl-2-Oxopentanoate, 3-Methyl-2-Oxovalerate, 3-Methyl-2-Oxobutyrate, 2-Methylbutyrylcarnitine

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Table I: The sociodemographic among respondents

Author	Sample	Metabolomic Technique	Significant Metabolites Observation in Obese Condition
Airaksinen et al.[29]	Adipose tissue	Liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS)	1. Subcutaneous Adipose Tissue (SAT) L-Carnitine, Hydroxybutyrylcarnitine, Hydroxyhexanoylcarnitine, Hydroxy-Isovaleryl-Carnitine, Isobutyryl-Carnitine, Methylmalonylcarnitine, Hexadecenoyl Carnitine, Citrulline, L-Histidine, L-Leucine, L-Isoleucine, L-Lysine, 1-Methylhistamine, L-Methionine, Pantothenic Acid, L-Phenylalanine, Proline, Uric Acid 2. Visceral Adipose Tissue (VAT) Butyryl-Carnitine, Hexanoylcarnitine, Palmitoyl-L-Carnitine, Choline, Propionylcarnitine, Pantothenic Acid, Tetradecanoylcarnitine, Hexadecenoyl Carnitine, Histidine, Lysine
Osawa et al.[30]	Adipocyte	Capillary electrophoresis time of flight mass spectrometer (CE-TOF/MS)	Choline, Cystathionine, Threonine, Glycine, Citrulline, Hypoxanthine, 5-phosphoribosyl 1-diphosphate (PRPP)
Li et al.[31]	Fecal	The ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UHPLC/Q-TOF-MS)	1. Amino Acids (Leucine, Phenylalanine, Tryptophan, Glycine, Methionine, Proline, Lysine, Citrulline, Isoleucine, Aspartic Acid, Ornithine) 2. Short Chain Fatty Acids 3. Unsaturated Fatty Acids 4. Sphingolipids 5. Carnitines
Shao et al.[32]	Adipose tissue	Ultrahigh-performance liquid chromatography-tandem mass spectrometry (UHPLC–MS/MS) Analysis	Glycerophospholipids, Polyketides, Sterol Lipids, Arachidonic Acid (AA), L-Dopa, Cholecalciferol, Hydrocortisone, Pyridoxamine
Jang et al.[33]	Plasma	Ultra performance liquid chromatography-mass spectrometry (UPLC MS)	3-Methoxybenzenepropanoic Acid, 3-Oxodecanoic Acid, 4-Aminobutyraldehyde, 4'-Apo-B-Carotenal, Lysopc (18:4), MG (0:0/18:2/0:0), N-Arachidonoyl, Retinyl Ester
Luo & Liu.[34]	Serum	Ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-QTOF-MS)	Thyroxine, Phosphatidylcholine (PC), Triglycerides (TG), Lysophosphatidylcholine (Lysopc), Lysophosphatidylethanolamine (Lysope), Glucosylceramide, 1D-Myo-Inositol 1, 3,4,6-Tetrakisphosphate, Alpha-Linolenic Acid, Cholesterol Sulfate, 1-Arachidonoyl glycerophosphoinositol), Arachidonic Acid, Glycerophospholipid, Glycosphingolipid, Linoleate, Omega-3 Fatty Acid, Phosphatidylinositol Phosphate, Tyrosine
Eniafe & Jiang.[35]	Plasma	Ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF/MS) analysis	Avenoleic Acid, 2R-Hydroxy-Oleic Acid, PC 16:0/18:2(9Z,12Z), 20:3 Cholesteryl Ester
Herman et al.[36]	Adipose tissue and serum	The ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UHPLC/Q-TOF-MS)	21 Amino Acids, 5 Carbohydrate, 2 Energy, 67 Lipid, 2 Xenobiotics, 3 Cofactors and Vitamins, 6 Nucleotides
Hsieh et al.[37]	3T3-L1 adipocyte	Liquid Chromatography–Time of Flight Mass Spectrometry	Hydroxyphenyllactic Acid, 2-Hydroxycaproic Acid, Creatine, Lactate, Ketoleucine or 2-Ketohexanoic Acid, Alanine or Beta-Alanine, Lysine, Arginine, Isoleucine or Alloisoleucine or Norleucine
Qiu et al.[38]	Liver	Ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-QTOF-MS)	1. Fatty Acid Metabolism 2. PPAR Signalling Pathway 3. AMPK Signalling Pathway 4. Insulin Signalling Pathway 5. Fatty Acid Degeneration

to the differential results shown in betaine and choline, taurine also exhibited an inconsistent alteration which resulted in significant elevation,[8] decrease,[15,23] and no change[10] when compared to the sample of normal condition. Other than that, there were also a few metabolites discovered in lipid metabolism when analysed in obesity conditions which are short-chain fatty acids, unsaturated fatty acids, sphingolipids,[31] sterol lipids, and glycerophospholipids.[32]

Other Metabolism

According to the obesity-related publications that were reviewed, there were few metabolites reported involved in energy metabolism and these include nicotinamide adenine dinucleotide (NAD), nicotinamide adenine dinucleotide phosphate (NADP), trimethylamine (TMA), and trimethylamine N-oxide (TMAO). Out of 27 papers identified, only one study discussed the metabolites involved in energy metabolism. Sun, et al.[10] found that in the liver, there was a significant increase in NAD+, TMAO, and a slight increase in NADP+. However, TMA in the liver sample showed a notable reduction when compared to the normal group. In proportion to the 26 refereed journals related to the metabolomic study of obesity, seven papers reported that metabolites associated with nucleotide metabolism were altered and these include allantoin, urea, uric acid, hypoxanthine, inosine, and uridine. Among these observed metabolites, allantoin showed an elevation when compared to the normal condition.[15,19] On the contrary, urea[24] and uric acid[29] were demonstrated to be at a lower level in obesity samples. However, even though uridine was found in a high-fat diet-induced sample, there was no significant difference as opposed to the normal diet.[10] Furthermore, a study conducted by Brennan, et al.[26] also found that there was a notable change in allantoin, hypoxanthine, and inosine. Other than that, metabolites resulting from the metabolism of cofactors and vitamins which are retinyl ester[33] and nicotinurate[10] were also reported to be slightly reduced and increased respectively.

DISCUSSION

This scoping review analysed 27 peer-reviewed research articles related to the metabolomic study of obesity. The main finding from these papers was the metabolites found in obesity conditions. Based on the papers reviewed, there were abundant metabolites analysed including metabolites that are discovered in carbohydrate, amino acid, lipid, energy, and nucleotide metabolism, also, most of these observed metabolites were varied in each article. However, in all of the articles included, the information regarding the relationship between the technique or instrument used and the metabolites detected in the samples was not properly discussed in detail. Within these metabolites examined, there were several elements particularly related to obesity that should be thoroughly investigated.

Carbohydrate Metabolism

Through its nuanced actions at both the organ and systemic levels, adipose tissue plays a critical role in controlling whole-body energy and glucose homeostasis.[34] Glycolysis, gluconeogenesis, TCA cycle, and pyruvate metabolism are among the pathways involved in carbohydrate metabolism. According to the scholarly articles reviewed, a large number of metabolites were discovered in this metabolism, however, these 27 studies provided contradicting results were inconsistent levels of metabolites were demonstrated. According to Sundekilde et al.,[20] the TCA cycle is a critical metabolic mechanism that links carbohydrate, protein, and fat metabolism by converting pyruvate to energy and carbon dioxide. An increase in TCA metabolites indicates the increase of gluconeogenesis consistent with pyruvate-driven gluconeogenesis, and higher TCA cycle flux, both of which have been seen as a result of diet-induced obesity. Thus, these explain the elevated metabolites involved in carbohydrate metabolism. Similarly, research done by Sun, et al.[10] also reported that in reaction to hyperlipidemia, glucose levels were increased.

Even so, some findings have indicated that when compared to normal conditions, some metabolites commonly found in the TCA cycle which are responsible for the generation of cellular energy[35] such as citrate, sucrose, and aconitate were lowered. This is owing to the fact that HFD may obstruct the entrance of TCA intermediates into the cycle, resulting in lipid build up in both serum and liver samples.[16] This view was also complemented by Chen, et al.[19] when the study explained that in obese conditions, energy consumption is reduced, resulting in an energy surplus and fat formation. The excess energy storage in the body suppresses the metabolism in the TCA cycle. Several other papers have also reported the downregulation of metabolites in carbohydrate metabolism.[10,15,17,19–21,24] In other words, the reductions observed in carbohydrate metabolism may reflect the body's energy metabolism level.[19]

Amino Acid Metabolism

From the data collected and evaluated from these 27 peer-reviewed articles, metabolites involved in amino acid metabolism were the most abundant metabolites exhibited. The relevance of these findings was supported by Herman, et al.36 that highlights while adipose tissue is well-known for its role in glucose and lipid homeostasis, it is less well-recognised for its role in systemic protein and amino acid metabolism. In vitro and in vivo experiments suggested that adipose tissue can metabolize large amounts of branched-chain amino acids (BCAAs). In obesity, most of the amino acid metabolites such as tyrosine, phenylalanine, valine, isoleucine, leucine, 2-oxoisocaproate, glutamate, and histamine showed increasing levels when compared to the normal group. These elevated results were supported by a study done by Duft, et al.[9] that stated obese individuals have increased BCAA levels and breakdown products in their blood. In the same vein, Mccormack, et al.[39] additionally reported that obesity and insulin resistance are linked to increased levels of BCAAs in the bloodstream. On top of that, She, et al.[40] mentioned that BCAA levels may be higher in obese people simply because they eat more food, and this is also influenced by the impairment of the BCAA catabolic pathway.[41] She, et al.[40] also stated that increase protein catabolism as a result of insulin resistance is another plausible cause for the rise in BCAAs in obesity.

On the contrary, there were also some metabolites, when compared to the normal diet showed a lower level of amino

acid metabolites. According to Ammar, et al.,[24] the study of obesity in rats revealed the amino acid metabolic pathway was found to be highly altered in obese rats, resulting in reduced levels of several amino acids such as glycine, aspartic, alanine, and glutamine. Similarly, Etxeberria, et al.[42] also stated that obese rats were found to have reduced levels of amino acids. Amino acid depletion was observed in HFD-fed obese mice, implying a disruption in energy metabolism. Furthermore, the lower glycine level may have contributed to the occurrence of a catabolic state, in which muscle tissue secretes glutamine to help the liver maintain glucose homeostasis.[24]

Lipid Metabolism

Lipid metabolism can be defined as the synthesis of structural and functional lipids such as phospholipids, glycolipids, sphingolipids, cholesterol, prostaglandins, etc. The metabolism is always in a dynamic equilibrium condition which means that some lipids are constantly oxidised to meet the body's metabolic needs, while others are synthesised and stored in adipocytes as triglycerides.[43] Lipids or fat are predominantly stored in white adipocytes. In white adipocytes, triglycerides are formed through the esterification of energy-rich fatty acids and glycerol. Triglyceride hydrolysis (lipolysis) releases fatty acids from fat cells into the bloodstream.[44] These released products are considered as metabolites. As reported by Park, et al.,[45] metabolite profiling has demonstrated substantial changes in lipid profiles linked to HFD, obesity, and obesity-related diseases in a variety of animal and human research. Even though various metabolites linked to lipid metabolism were discovered both in the normal and in the obese group, the level of metabolites in the obese group was altered when compared to the normal group. Choline was discovered to be one of the upregulated metabolites in four studies when compared to the normal group. Betaine, on the other hand, was reduced. Likewise, Wang et al.[8] also reported an increased level of choline and the downregulation of betaine. These results indicate that the HFD may have blocked the choline to betaine pathway. Supposedly, choline is converted to betaine, which adds a methyl group to homocysteine to produce methionine and dimethylglycine.[46] Hence, in HFD, when the choline to betaine pathway is blocked, the choline cannot be metabolised into betaine, eventually leading to an elevation of the choline level and reduction of the betaine. Moreover, Wang, et al.[8] draw on the work of Lever & Slow[47] who suggested that alterations in betaine, together with taurine and choline changes, suggested that these metabolites changes occurred may be due to the abnormal fatty acid metabolism.

LIMITATION AND SUGGESTION

The major shortcoming of the scoping review methodology is the absence of quality assessment of the papers evaluated. This is because the purpose of a scoping review is to simply identify research that has been done, not necessarily to assess the quality of the papers. According to Arksey & O'Malley,[14] the scoping study does not intend to examine the quality of evidence and hence cannot identify whether particular research yields robust or generalizable findings. Although quality assessment may not be a purpose of the study, the quality should be taken into account before using the findings to evaluate the metabolites related to obesity. Moreover, only three databases were utilised for article searching and the results are further limited as only papers published in English from the year 2017 until 2021 were selected. Therefore, these criteria may cause some bias in reviewing the results.

Concerning the articles analysed that were included in this review paper, one of the gaps discovered is that there were some variations in the metabolites analysed. Even though several metabolites detected were similar, the concentrations of each metabolite were different. Thus, this will limit the understanding of metabolites study in obesity as the changes in normal conditions and obese conditions remain unsettled. This particular knowledge is very useful as it may help researchers identify a possible obesity biomarker. Moreover, another limitation noted was the information regarding the relationship between the metabolites detected and the technique utilised. The instrument may play some crucial roles in the spectrum of the metabolites analysed. Hence, the lack of explanation concerning this relationship limits the information with regard to the metabolomic study in obesity.

CONCLUSION

In conclusion, this scoping review sheds light on the metabolomic study in obesity. According to current research, metabolomic profiling has been done to analyse the abundance of metabolites present in obesity conditions. All of these discovered metabolites were found mainly in carbohydrate, amino acid, lipid, energy, and nucleotide metabolism. Nevertheless, in discussions involving metabolisms, the pathways usually are always interconnected with each other. Thus, this review has evaluated and summarised the published literature concerning the majority of the metabolites found in obesity which may be a potential biomarker reference that might help in the future clinical management of obese patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

AUTHORS CONTRIBUTION

Conceptualisation and drafting of the manuscript: AA, NH; review of the manuscript: NH, EM, MIMY, MRS; All of the authors have read and approved the final manuscript.

REFERENCES

1. Chooi YC, Ding C, and Magkos F. The Epidemiology of Obesity. Metabolism 2019; 92: 6-10.
2. Klassen A, Faccio AT, Canuto GAB, Cruz PLRD, Ribeiro HC, Tavares MFM, and Sussulini A. Metabolomics: Definitions and Significance in Systems Biology. Adv Exp Med Biol. 2017; 965: 3-17.

3. Fruh SM. Obesity: Risk factors, Complications, and Strategies for Sustainable Long-Term Weight Management. J Am Assoc Nurse Pract 2017; 29(S1): S3-S14.
4. Gutierrez DA, Puglisi MJ, Hasty AH. Impact of Increased Adipose Tissue Mass on Inflammation, Insulin Resistance, and Dyslipidemia. Curr Diab Rep. 2009 Feb; 9(1): 26-32.
5. Park HJ, Cho JY, Kim MK, Koh PO, Cho KW, Kim CH, et al. Anti-obesity Effect of Schisandra chinensis in 3T3-L1 Cells and High Fat Diet-Induced Obese Rats. Food Chemistry 2012; 134(1): 227-34.
6. Lane MD. Adipogenesis. Encyclopedia of Biological Chemistry 2013; 52–6.
7. Berry DC, Stenesen D, Zeve D, and Graff JM. The Developmental Origins of Adipose Tissue. Development 2013; 140(19): 3939-49.
8. Wang D, Wang X, Zhang P, Wang Y, Zhang R, Yan J, et al. The fate of technical-grade chlordane in mice fed a high-fat diet and its roles as a candidate obesogen. Environ Pollut 2017; 222: 532-42.
9. Duft RG, Castro A, Bonfante ILP, Brunelli DT, Chacon-Mikahil MPT, Cavaglieri CR. Metabolomics Approach in the Investigation of Metabolic Changes in Obese Men after 24 Weeks of Combined Training. J Proteome Res 2017; 16(6): 2151-9.
10. Sun Q, Li M, Yang X, Xu X, Wang J, Zhang J. Dietary salecan reverts partially the metabolic gene expressions and NMR-based metabolomic profiles from high-fat-diet-induced obese rats. J Nutr Biochem 2017; 47: 53-62.
11. Shah SH, Kraus WE, Newgard CB. Metabolomic Profiling for the Identification of Novel Biomarkers and Mechanisms Related to Common Cardiovascular Diseases: Form and Function. Circulation 2012; 126(9): 1110-20.
12. Emwas AH, Roy R, McKay RT, Tenori L, Saccenti E, Gowda GN, et al. NMR spectroscopy for metabolomics research. Metabolites 2019; 9(7): 123.
13. Castelli FA, Rosati G, Moguet C, Fuentes C, Marrugo-Ramírez J, Lefebvre T, et al. Metabolomics for Personalized Medicine: The Input of Analytical Chemistry from Biomarker Discovery to Point-Of-Care Tests. Anal Bioanal Chem 2022; 414(2): 759-89.
14. Arksey H, O'Malley L. Scoping Studies: Towards a Methodological Framework. International Journal of Social Research Methodology 2005; 8(1): 19-32.
15. Bugáňová M, Pelantová H, Holubová M, Šedivá B, Maletínská L, Železná B, et al. The Effects of Liraglutide in Mice with Diet-Induced Obesity Studied by Metabolomics. J Endocrinol 2017; 233(1): 93-104.
16. Guo F, Han M, Lin S, Ye H, Chen J, Zhu H, et al. Enteromorpha prolifera Polysaccharide Prevents High-Fat Diet-Induced Obesity in Hamsters: A NMR-Based Metabolomic Evaluation. J Food Sci 2021; 86(8): 3672-85.
17. Nishitani S, Fukuhara A, Jinno Y, Kawano H, Yano T, Otsuki M, et al. Metabolomic Analysis of Diet-Induced Obese Mice Supplemented with Eicosapentaenoic Acid. Exp Clin Endocrinol Diabetes 2020; 128(8): 548-55.
18. Yde CC, Jensen HM, Christensen N, Servant F, Lelouvier B, Lahtinen S, et al. Polydextrose with and Without Bifidobacterium animalis Ssp. Lactis 420 Drives the Prevalence of Akkermansia and Improves Liver Health in A Multi-Compartmental Obesogenic Mice Study. PloS one 2021; 16(12): e0260765.
19. Chen M, Lu B, Li Y, Wang Y, Zheng H, Zhong D, et al. Metabolomics Insights into The Modulatory Effects of Long-Term Compound Polysaccharide Intake in High-Fat Diet-Induced Obese Rats. Nutr Metab (Lond) 2018; 15: 8.
20. Sundekilde UK, Yde CC, Honore AH, Caverly Rae JM, Burns FR, Mukerji P, et al. An Integrated Multi-Omics Analysis Defines Key Pathway Alterations in A Diet-Induced Obesity Mouse Model. Metabolites 2020; 10(3): 80.
21. Zhuang T, Liu X, Wang W, Song J, Zhao L, Ding L, et al. Dose-Related Urinary Metabolic Alterations of a Combination of Quercetin and Resveratrol-Treated High-Fat Diet Fed Rats. Front Pharmacol 2021; 12: 655563.
22. Candi E, Tesauro M, Cardillo C, Lena AM, Schinzari F, Rodia G, et al. Metabolic Profiling of Visceral Adipose Tissue from Obese Subjects with or without Metabolic Syndrome. Biochem J. 2018; 475(5): 1019-35.
23. Li X, Huang Y, Song L, Xiao Y, Lu S, Xu J, et al. Lactobacillus plantarum Prevents Obesity Via Modulation of Gut Microbiota and Metabolites in High-Fat Feeding Mice. Journal of Functional Foods 2020; 73: 104103.
24. Ammar NM, Farag MA, Kholeif TE, Metwally NS, El-Sheikh NM, El Gendy AN, at al. Serum Metabolomics Reveals the Mechanistic Role of Functional Foods and Exercise for Obesity Management in Rats. J Pharm Biomed Anal 2017; 142: 91-101.
25. Dadson P, Rebelos E, Honka H, Juárez-Orozco LE, Kalliokoski KK, Iozzo P, et al. Change in Abdominal, But Not Femoral Subcutaneous Fat CT-Radiodensity Is Associated with Improved Metabolic Profile After Bariatric Surgery. Nutr Metab Cardiovasc Dis 2020; 30(12): 2363-71.
26. Brennan AM, Tchernof A, Gerszten RE, Cowan TE, Ross R. Depot-Specific Adipose Tissue Metabolite Profiles and Corresponding Changes Following Aerobic Exercise. Front Endocrinol (Lausanne) 2018; 9: 759.
27. Jokinen R, Rinnankoski-Tuikka R, Kaye S, Saarinen L, Heinonen S, Myöhänen M, et al. Adipose Tissue Mitochondrial Capacity Associates with Long-Term Weight Loss Success. Int J Obes (Lond) 2018; 42(4): 817-25.
28. Piro MC, Tesauro M, Lena AM, Gentileschi P, Sica G, Rodia G, et al. Free-Amino Acid Metabolic Profiling of Visceral Adipose Tissue from Obese Subjects. Amino Acids 2020; 52(8): 1125-37.
29. Airaksinen K, Jokkala J, Ahonen I, Auriola S, Kolehmainen M, Hanhineva K, et al. High-Fat Diet, Betaine, and Polydextrose Induce Changes in Adipose Tissue Inflammation and Metabolism in C57BL/6J Mol Nutr Food Res 2018; 62(23): 1800455.
30. Osawa S, Kato H, Maeda Y, Takakura H, Ogasawara J, Izawa T. Metabolomic Profiles in Adipocytes Differentiated from Adipose-Derived Stem Cells Following Exercise Training or High-Fat Diet. Int J Mol Sci 2021; 22(2): 966.
31. Li M, Xu J, Zhang Y, Chu S, Sun S, Huo Y, et al. Comparative Analysis of Fecal Metabolite Profiles in HFD-Induced Obese Mice After Oral Administration of Huangjinya Green Tea Extract. Food Chem Toxicol 2020; 145: 111744.
32. Shao J, Pan T, Wang J, Tang T, Li Y, Jia X, et al. Integrated Proteomics and Metabolomics Analysis of Perirenal Adipose Tissue in Obese Rabbits Treated with a Restricted Diet. Biology 2021; 10(4): 321.
33. Jang HY, Han Y, Yoo HJ, Lee JH, Kim M. Effects of Short-Term Dietary Restriction on Plasma Metabolites and the Subcutaneous Fat Area According to Metabolic Status in Obese Individuals: A Case–Control Study. Diabetol Metab Syndr 2021; 13(1): 62.
34. Luo L, and Liu M. Adipose tissue in control of metabolism. J Endocrinol 2016; 231(3): R77-R99.
35. Eniafe J, Jiang S. The Functional Roles of TCA Cycle Metabolites in Cancer. Oncogene 2021; 40(19): 3351-63.
36. Herman MA, She P, Peroni OD, Lynch CJ, Kahn BB. Adipose Tissue Branched Chain Amino Acid (BCAA) Metabolism Modulates Circulating BCAA Levels. J Biol Chem 2010; 285(15): 11348-56.
37. Hsieh CC, Chiu HH, Wang CH, Kuo CH. Aspirin Modifies Inflammatory Mediators and Metabolomic Profiles and Contributes to the Suppression of Obesity-Associated Breast Cancer Cell Growth. Int J Mol Sci. 2020; 21(13): 4652.
38. Qiu Y, Yu H, Hu Y, Guo S, Lei X, Qin Y, et al. Transcriptomic and Metabonomic Profiling Reveal the Anti-Obesity Effects of Chikusetsusaponin V, A Compound Extracted from Panax japonicus. J Pharm Pharmacol. 2021; 73(1): 60-9.
39. McCormack SE, Shaham O, McCarthy MA, Deik AA, Wang TJ, Gerszten RE, et al. Circulating branched-chain amino acid concentrations are associated with obesity and future insulin resistance in children and adolescents. Pediatr Obes 2013; 8(1): 52-61.

40. She P, Van Horn C, Reid T, Hutson SM, Cooney RN, Lynch CJ. Obesity-Related Elevations in Plasma Leucine Are Associated with Alterations in Enzymes Involved in Branched-Chain Amino Acid Metabolism. Am J Physiol Endocrinol Metab 2007; 293(6): E1552-E1563.
41. Siddik MAB, Shin AC. Recent Progress on Branched-Chain Amino Acids in Obesity, Diabetes, and Beyond. Endocrinol Metab (Seoul) 2019; 34(3): 234-46.
42. Etxeberria U, de la Garza AL, Martínez JA, Milagro FI. Diet-Induced Hyperinsulinemia Differentially Affects Glucose and Protein Metabolism: A High-Throughput Metabolomic Approach in Rats. J Physiol Biochem 2013; 69(3): 613-23.
43. Gyamfi D, Awuah EO, and Owusu S. Lipid Metabolism: An Overview. The Molecular Nutrition of Fats 2019; 17-32.
44. Spalding KL, Bernard S, Näslund E, Salehpour M, Possnert G, Appelsved L, et al. Impact of Fat Mass and Distribution on Lipid Turnover in Human Adipose Tissue. Nat Commun 2017; 8(1): 15253.
45. Park S, Sadanala KC, Kim EK. A Metabolomic Approach to Understanding the Metabolic Link Between Obesity and Diabetes. Mol Cells 2015; 38(7): 587.
46. Friesen RW, Novak EM, Hasman D, Innis SM. Relationship of Dimethylglycine, Choline, and Betaine with Oxoproline in Plasma of Pregnant Women and Their Newborn Infants. J Nutr 2007; 137(12): 2641-6.
47. Lever M, Slow S. The Clinical Significance of Betaine, an Osmolyte with A Key Role in Methyl Group Metabolism. Clin Biochem 2010; 43(9): 732-44.