ABSTRACT

Worldwide soybean oil consumption is high as it is used in processed food. Many studies reported that use of soybean oil has a risk of developing metabolic syndrome, but there is no scientific claim that soybean oil has developed metabolic syndrome. Similarly, nowadays, most of the increase in fructose consumption is derived from refined sugars and processed foods. Hence, the present study dealt to imply the probable proteins modulated in metabolic syndrome. The structural information of bioactive phytoconstituents was retrieved from different open source databases. Compounds were then predicted for their hits with the probable targets involved in the metabolic syndrome. The modulated protein pathways identified by using the REACTOME pathway analysis. Network was constructed proteins involved in metabolic syndrome with phytoconstituents. The phytoconstituents namely linolenic acid, linoleic acid and oleic acid were majorly targeted by the modulated proteins involved in metabolic syndrome. In conclusion, the present study reflects the combination of soybean oil and fructose can provide the better model for metabolic syndrome.

Keywords: Metabolic syndrome, Soybean oil, Fructose, Network pharmacology.

INTRODUCTION

Metabolic syndrome is defined as a group of diseases that includes hypertension, hyperglycemia, central obesity, and dyslipidemia. The rate of occurrence of obesity and metabolic syndrome is on the rise in India and other South Asian countries and has led to increased incidences of cardiovascular diseases and diabetes mellitus type 2 related mortality and morbidity[1, 2].

Evidence of metabolic syndrome can be found in approximately a third of the urban South Asian population[3]. Prevalence rates of metabolic syndrome based on age-standardized studies are known to be 42.3% in females, 24.9% in males and 33.5% overall. The factors playing an active part in increasing the risk of metabolic syndrome are noted to be age, female gender, and obesity, reduced fruit intake, high cholesterol levels, and raised socioeconomic status[4]. Lifestyle changes such as a sedentary lifestyle, change in traditional diet, and an increased consumption of sugar and fructose (found in most soft drinks) have been instrumental in leading to a spike in the prevalence of type 2 diabetes mellitus and metabolic syndrome in the region. Increased dietary fat has also led to a decline in the overall health of the population[5, 7].

The soybean or soya bean is an East Asian species of legumes widely cultivated for its edible bean. Oil derived from the seeds of the soybean plant (soybean oil) is a product that is widely used across the globe in making margarines, salad dressings, various processed foods, and packaged snack foods[8]. Soybean oil (100 g) has 16 g of saturated fat, 23 g of monounsaturated fat, and 58 g of polyunsaturated fat. Compared to other vegetable oils, liquid soybean oil contains no trans-fat, has a high level of unsaturated fats (both poly- and monounsaturated) and is low on saturated fats. It is also a rich source of omega-3 fatty acids and vitamin E. [9] A diet rich in ω-3 polyunsaturated fatty acids helps to reduce glucose oxidation, increase lipid oxidation, and increase glycogen storage in the liver (Jump, Depner, Tripathy, & Lytle, 2015). The composition of omega-3 polyunsaturated fatty acids includes alpha linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid [10].

Preliminary studies had reported soybean to have a tendency to cause obesity and diabetes. They have also reported an inflammation and an increase in the blood glucose levels in mice and a raised lipid profile in rats on administration of soybean oil. [8, 10, 13] It has also been reported that administration of fructose caused metabolic syndrome in rats but it also caused weight loss.
Fructose is a monosaccharide, a type of sugar that cannot be hemolyzed to give a simpler sugar. Glucose and galactose also belong to the same class of sugars. In nature, fructose can be found in fruits and vegetables but increased fructose consumption in the present day comes from refined sugars.[7].

In modern-day pharmacy, there is a trend to utilize the “lock and key” concept to create ligand molecules aimed at acting on selective targets. There are also attempts to design a single drug that can modulate multiple protein molecules and act as a “master key” that can unlock multiple locks.[12]. Metabolic syndrome is a polygenic condition involving a complex interlinked multi-gene network making a single drug-protein interaction incompetent to treat the condition. Hence the present study aimed to assess the synergistic effect of soybean oil and fructose in metabolic syndrome using multiple in silico tools.[13, 14, 15]

Material and methods

Mining of compounds

Phytoconstituent of soybean oil were mined from the published literature, and articles. The database was constructed for the phytoconstituent, their types, canonical SMILES, and PubChem CID. The canonical SMILES of each phytoconstituent were retrieved from PubChem database.

Identification of metabolic syndrome target

Table 1: List of compounds from soybean oil

<table>
<thead>
<tr>
<th>Phytoconstituent</th>
<th>Canonical SMILES</th>
<th>Molecular weight (g/mol)</th>
<th>Molecular formula</th>
<th>PubChem CID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linoleic acid</td>
<td>CCC=CCC=CCC=CCCCCCCCC (O) O</td>
<td>274.8</td>
<td>C_{30}H_{50}O_{2}</td>
<td>5280934</td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>CCCCCCCCCCCCCCC (O) O</td>
<td>256.42</td>
<td>C_{30}H_{48}O_{2}</td>
<td>985</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>CCCCCCCCCCCCCCC (O) O</td>
<td>282.5</td>
<td>C_{30}H_{50}O_{2}</td>
<td>445639</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>CCCCCCCCCCCCCCC (O) O</td>
<td>284.5</td>
<td>C_{30}H_{52}O_{2}</td>
<td>5281</td>
</tr>
</tbody>
</table>

Identification of target in Metabolic Syndrome

Four hundred twelve targets were identified from therapeutic target database which are involved in metabolic syndrome. Out of which ninety were found in obesity, two hundred twenty four were found in diabetes, eighty three targets were found in cardiovascular disease, and thirteen were found in dyslipidemia.

Table 2: Proteins modulated by fructose and compounds of soybean oil.

<table>
<thead>
<tr>
<th>Soybean oil</th>
<th>Disease</th>
<th>Count</th>
<th>Gene code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linoleic acid</td>
<td>Obesity</td>
<td>03</td>
<td>PPARD, PPARG, HSD11B1</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>Diabetes</td>
<td>08</td>
<td>LOC114353661, NR3C1, PPARA, PPARG, GCGR, HSD11B1, HSD11B2, PPARD</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>Cardiovascular</td>
<td>08</td>
<td>HMGCR, AR, G6PD, PPARA, PL2G1B, EDNRB, FABP1, NOS2</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>Dyslipidemia</td>
<td>03</td>
<td>HMGCR, PPARA, PPARD</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>Obesity</td>
<td>03</td>
<td>PPARD, PPARG, HSD11B1</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>Diabetes</td>
<td>07</td>
<td>SCD, CCKBR, MC4R, PPARA, PPARG, GCGR, PPARD</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>Cardiovascular</td>
<td>08</td>
<td>HMGCR, AR, ACE, G6PD, PPARA, TRX2AR, CACNA2D1, FABP1</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>Dyslipidemia</td>
<td>03</td>
<td>HMGCR, PPARA, PPARD</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>Obesity</td>
<td>08</td>
<td>FASN, GCGR, PPARD, PPARG, DGATT1, MC4R, GCG,HSD11B1</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>Diabetes</td>
<td>03</td>
<td>PPARA, PPARG, PPARD</td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>Cardiovascular</td>
<td>06</td>
<td>HMGCR, AR, G6PD, FABP1, CACNA2D1, TRX2AR</td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>Dyslipidemia</td>
<td>03</td>
<td>HMGCR,PPARA,PPARD</td>
</tr>
<tr>
<td>Palmitic acid</td>
<td>Obesity</td>
<td>02</td>
<td>PPARA,HSD11B1</td>
</tr>
</tbody>
</table>

The target of each compound present in soybean oil and fructose were predicted using Swiss target prediction then each target were confirmed for their role in obesity diabetes, dyslipidemia and hypertension.

Enrichment analysis

REACTOM was used to understand the protein-protein interaction by submitting the set of protein code and the respective pathway involved in metabolic syndrome was identified by using the published literature.

Network construction

Cytoscape 3.7.1 [16] was used to construct the network between compounds, target proteins, and pathways. The command “Network Analyzer” was used to analyze the network by treating the network as directed. The map node size was set from “low values to small sizes” and map node color from “low values to bright colors” based on edge count for both settings.

Results

Identification of compound

Five different phytoconstituent were identified in soybean oil from open-source records (Table 1). These phytoconstituent were identified as fatty acid that occurs naturally in plant oil and vegetable oil.

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### Figure 1: Pathways modulated by fructose and soybean oil.
Network analysis

The network identified linoleic acid and linolenic acid to be more interactive targets involved in metabolic syndrome. Similarly, PPARA protein was majorly targeted by multiple constituents. Likewise proteins involved in diabetes are majorly regulated. The pathways modulated by fructose and soybean oil is represented in fig. 1 and with multiple proteins is summarized in fig. 2.

Discussion

After understanding and assimilating the above, it seems a reasonable hypothesis that a combination of soybean oil and fructose can lead to metabolic syndrome. Therefore, the aim of the current study is to assess the possibility of this hypothesis using systems biology tools. The reported phytoconstituents of fructose as well as those of soybean oil were identified and their targets were predicted. Multiple pathways modulated by the phytoconstituents present in the soybean oil were identified using gene enrichment analysis. The multiple proteins that are manifest in dyslipidemia, obesity, diabetes and general cardiovascular complications were also identified for each phytoconstituent (Table. 2). Although target prediction failed to pinpoint the proteins involved in the pathogenesis of dyslipidemia, it was successful in showing the protein in a majority of these compounds that was involved in obesity and diabetes. It was also revealed that a majority of the fructose-modulated proteins involved in diabetes such as HTR2A, HTR2C, AKR1B1, MGAM, PYGM, KDR, IL2, TLR4, TLR9 as well as ADRA1D could have a prominent role in the pathogenesis of Insulin Resistance (Type 2 Diabetes Mellitus).

Twenty five common pathways were identified with the help of enrichment analysis. Other than this, soybean oil was also predicted in the regulation of gene expression associated with lipid metabolism, lipogenesis, glucocorticoid biosynthesis, nuclear receptor transcription pathway, steroid biosynthesis, glucagon signaling in metabolic regulation, and the circadian clock. There have been previous reports suggesting that these events play a significant role in the development of metabolic syndrome. One major limitation of fructose-induced pathogenesis in metabolic syndrome is decreases in body weight which could be due to involvement of adrenoceptors, adrenaline signaling, glycogenolysis, metabolism of steroid hormones and interleukin 10 signaling.

Regulation of development, reproduction, and metabolism of lipids, drugs and energy is done by nuclear receptors (NR) which are a superfamily of ligand-activated transcription factors. A typical example of the significance of this family of proteins in metabolic disease is the use of NR ligands in clinical trials and in clinical treatment of metabolic disorders such as diabetes mellitus, dyslipidemia, and hypercholesterolemia. The functioning of NR ligand in regulating lipid metabolism is disrupted by the combination of soybean oil and fructose. [17] Liver and kidneys express the PPARgene whose role is to regulate fatty acid oxidation and apolipoprotein synthesis. The gene induces hepatic peroxisomal fatty acid oxidation and the combination of soybean oil and fructose tends to mislead the fatty acid oxidation event. While regulating lipid and glucose metabolism, PPARs tends to be a culprit gene for the risk of metabolic syndrome and diabetes mellitus Type 2. Leu162Val (rs1800206) has been shown to be significantly related with the risk of diabetes mellitus Type 2 in a different population. Flavell et al reported that a variant of Leu162Val was associated with increased plasma levels of total cholesterol, HDL cholesterol, and apoAI, indicating that PPARα gene variation influences the onset and progression of Type 2 diabetes mellitus [18-22].
Steroid hormones increase both the volume and distribution of body fat. Glucocorticoids are known to stimulate lipogenesis and inhibit lipolysis. The most visible effects of this are fat deposits in the abdomen, the nape of the neck, and the face. The effect of glucocorticoids in these sites may be more dominant as a result of a higher expression of glucocorticoid receptors and a relatively high level of activity of 11βHSD type 1 regenerating cortisol from inactive cortisone here. There is not much information available regarding steroid metabolism in patients with impaired glucose tolerance or diabetes mellitus Type 2. However, there is a possibility that soybean oil and fructose may alter the SUMOylation pathway leading to dyslipidemia and diabetes. Present study identifies the modulation of the multiple compounds and proteins via a single compound. Likewise, the interaction of compound and proteins can be visualized via network pharmacology approach and in silico dockings.

**CONCLUSION**

The current study projected as a potential to interact with majority of proteins that are implicated in the pathogenesis of Metabolic Syndrome. The network analysis result demonstrated linolenic acid and linoleic acid are majorly interactive targets. Further, the combination of soya oil and fructose could provide the better model for metabolic syndrome.

**Conflict of interest**

The authors declare no conflict of interest.

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**REFERENCES**


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