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Original article

Considerable Effects of Caffeinated Coffee on Mouse Liver Function

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Abstract

Background and objectives: Coffee is a favorable drink in the world with advantages that are documented during different investigations. In the present study, the effect of caffeine which is one of the important compounds of coffee has been evaluated on function of mice liver via network analysis and gene ontology enrichment. **Methods:** Results of GSE53131 from Gene Expression Omnibus (GEO) were analyzed and the differentially expressed genes (DEGs) were assessed via protein-protein interaction (PPI) network analysis and gene ontology. Cytoscape software and STRING database were used to analyze the data. **Results:** Effect of caffeine on mice liver was appeared in the gene expression profiles of the mice liver which were fed with caffeinated and decaffeinated coffee. Acat2, Acly, Acss2, Akr1d1, Ehhadh, Elovl2, Fasn, Fdps, Gsta3, Hmgcr, Ldlr, Lss, Mmab, Mvd, Mvk, Nsdhl, Prodh, Rdh11, and Thrsp that are related mostly to lipid metabolism and cholesterol biosynthesis were pointed out as the discriminator genes in response to caffeine effect on liver function. **Conclusion:** In conclusion, assessment of mice liver gene expression profiles revealed that lipid metabolism of the mice liver was affected considerably by consumption of caffeinated coffee versus liver of mice that were fed with decaffeinated coffee. Using caffeine as a preventing factor for hepatic disorders is recommended base on the findings of present study.

Keywords: coffee; decaffeinated; lipid metabolism; liver

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Introduction

Coffee is a common favorable drink in the world. Several advantages such as reduced risk of mortality and chronic diseases, including cancer are reported for coffee drinking. Presence of biological compounds such as diterpenes, caffeine , polyphenols as well as volatile components and heterocyclic substances, and caffeic acid in coffee supports advantageous impact of its consumption [1]. Based on literature, there is an inverse correlation between coffee consumption and risk of type-2 diabetes [2]. Role of coffee consumption in patients with non-alcoholic fatty liver disease has been investigated. The findings are consistent with protective role of coffee drinking on significant liver fibrosis [3]. Caffeine as the main compound of coffee is a

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pan-antagonist of adenosine receptors. There are diverse reports about role of caffeinated and decaffeinated coffee in blocked liver fibrosis. It has been expressed that liver fibrosis is blocked by caffeinated coffee but the decaffeinated coffee has not shown such property [4]. Since the effect of coffee and caffeine drinking in disorders such as cardiovascular diseases is controversial, it seems that understanding the mechanism of coffee consumption effects need more details [5,6].

To find the molecular mechanism of coffee drinking, several genomic studies have been administrated. Barnung et al. have published the results of an investigation about coffee consumption and whole-blood gene expression. Cancer in the Norwegian women is evaluated in this post-genome cohort research [7].

Bioinformatics and the related methods are tied to the genomics and proteomics investigations. Such as the many subjects, coffee consumption has been studied via genomics and bioinformatics [8]. A suitable method which has attracted the attention of researchers is PPI network analysis and is applied widely in medicine, pharmacognosy, and nutrition. Our previously investigation via PPI network analysis led to introducing cholesterol metabolism pathway as a main target of coffee [9]. Using PPI network analysis in pharmacognosy is a progressive trend. Vafaee et al. have investigated cancer preventive effects of red proplois via PPI network analysis [10]. In the present study, gene expression profiles of mice liver (mice fed with high fat diet) after consumption of caffeinated coffee versus the profiles of the ones which were fed with decaffeinated coffee were extracted from GEO and analyzed via PPI network analysis to explore the role of caffeine in the control fat metabolism in body.

Material and Methods

Ethical considerations

This project was approved by Shahid Beheshti University of Medical Sciences (IR.SBMU.AEC.1401.044).

Data collection

To evaluate the effect of caffeine on fatty liver disease, GSE53131 was selected for assessing the effect of caffeinated and decaffeineted coffee on livers of C57BL/6J mice fed with a high-fat diet. Gene expression profiles of GSM282830-GSM282832 as the caffeinated group versus the decaffeinated group (GSM282833-GSM282835) were compared with GEO2R. Box plot analysis was administrated to find possibility of comparison of the selected gene expression profiles. The significant DEGs which discriminated the two equated groups were selected based on p-value ≤ 0.01 and FC ≥ 1.5. The significant DEGs were included in STRING database via "protein query" and the recognized individuals were interacted by Cytoscape software. The PPI network was created by using undirect edges. The shaped network was examined by "Network Analyzer" and the centrality parameters of the nodes were identified. To find the related biological terms, the elements of the main connected component were weighed via gene ontology enrichment by ClueGO. The determined biological terms were grouped based on kappa score. Regulatory relationships including binding, activation, inhibition, reaction, catalysis, and post translation modification between nodes of the main connected component were explored by CluePedia.

Statistical analysis

To find the significant DEGs p-value ≤ 0.01 and fold change ≥ 1.5 were considered. The PPI network was form based on confidence (score) cutoff = 0.40.

Results and Discussion

Gene expression profiles of the mice which received caffeinated coffee were compared with the gene expression profiles of the individuals that were fed with decaffeinated coffee in Figure 1. All profiles are median center and comparable. Number of 68 significant DEGs (based on p value and fold change) were determined for more assessment. Among the 68 queried DEGs, 62 ones were recognized by STRING database. The recognized DEGs were organized in 29 isolated genes, two paired nodes, triple DEGs, and a main connected component of 28 nodes (Figure 2).

Biological terms related to the elements of the main connected component are shown in the Figure 3. Nineteen groups of biological terms which were associated to the 19 nodes of the main connected component are shown in Figure 3. Actions between nodes of the main connected component are presented in Figure 4. Among binding, activation, inhibition, reaction, catalysis, and post translation modification relationships, binding and activation appeared in Figure 4. The other actions were not identified.

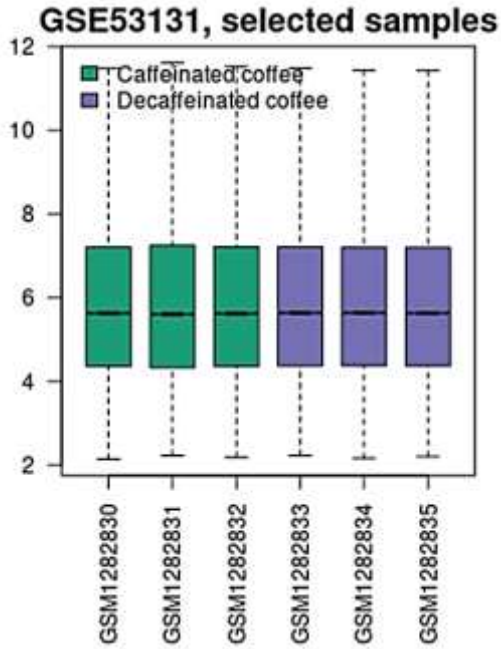

Figure 1. Box plot of the studied gene expression profiles

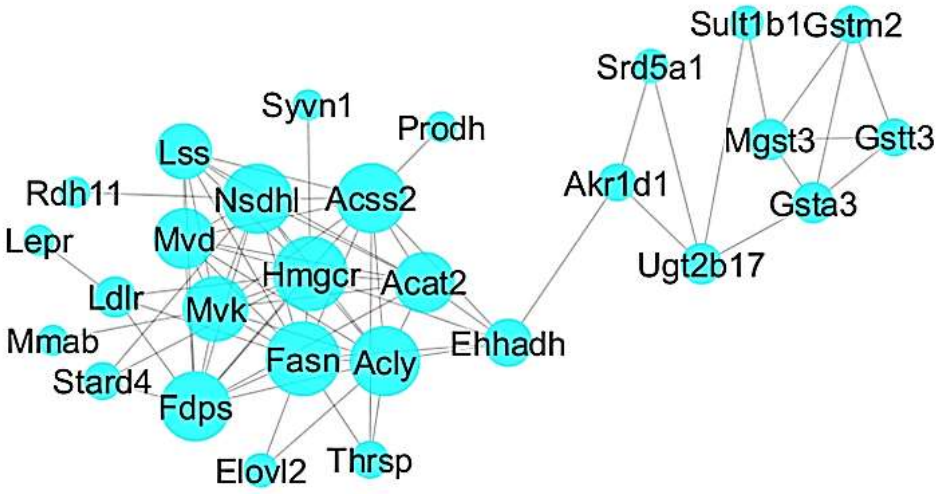

Figure 2. Main connected component of the PPI network. Nodes are layout based on degree value

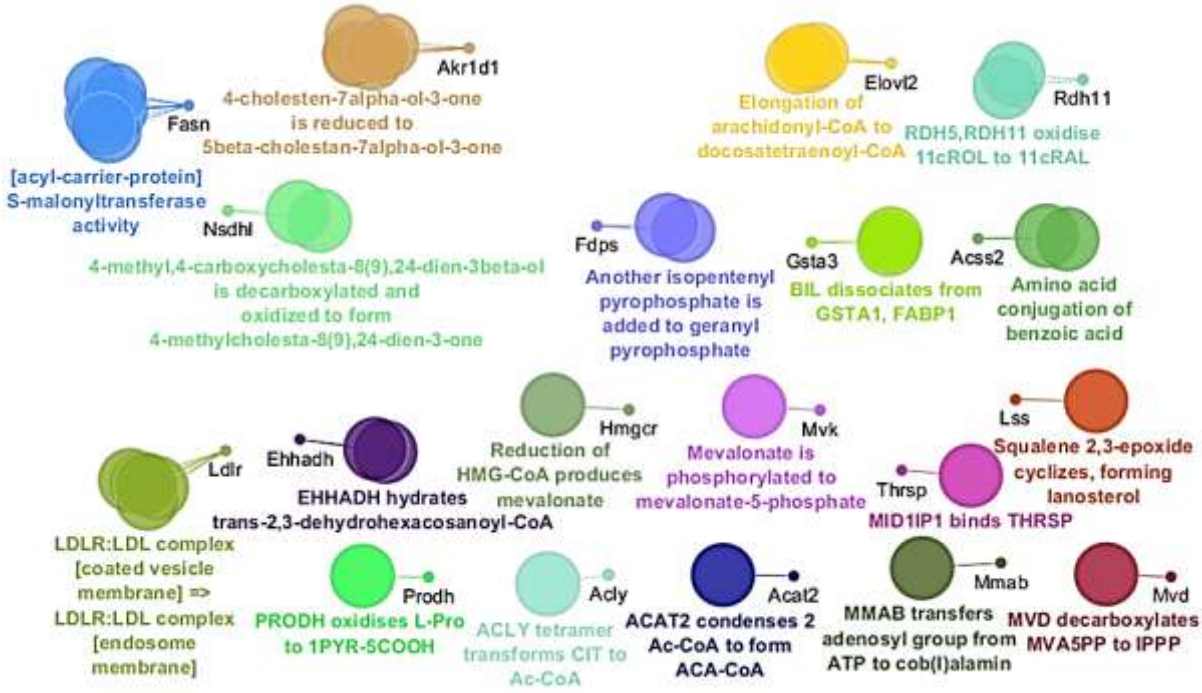

Figure 3. 19 groups of biological terms related to the nodes of the main connected component; the associated genes are labeled with black color

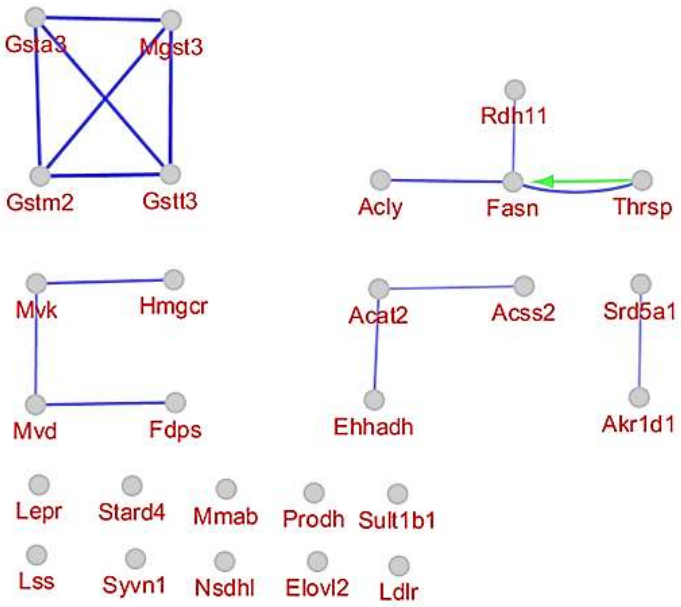

Figure 4. Regulatory relationships between nodes of the main connected component. Blue and green (as the single like) colors refer to binding and activation actions

Gene expression investigation revealed the advantages of coffee consumption to delay hepatitis and suppress inflammation [11]. It can be expected that gene expression profiles of mice be sensitive to consumption of coffee. As it is depicted in the Figure 1, gene expression profiles of mice in response to consumption of caffeinated and decaffeinated coffee are analogous and more analysis is possible. It seems that the 28 elements of the main connected component are the suitable factors to discriminate the mice which consumed caffeinated coffee from the individuals that were fed with decaffeinated coffee. Adan et al. published the results of an investigation about consumption of caffeinated and decaffeinated drink in 688 healthy undergraduate volunteers. They found that caffeine arouse effects were induced in all post-consumption records, but the results of decaffeinated drink were only outward at 10 minutes. Response of men was different from women [12].

Gene ontology enrichment revealed that 19 groups of biological terms were related to the 19 nodes of the main connected component. In the following section it has been tried to organize the biological terms based on common function:

1."[acyl-carrier-protein] S-malonyltransferase activity" refers to malonyl-CoA + acyl carrier protein ⇌ CoA + malonyl-[acyl-carrier-protein] reaction which is related to the fatty acid synthesis [12]. 2. "4-cholesten-7alpha-ol-3-one is reduced to 5beta-cholestan-7alpha-ol-3-one" is related to the activity of hepatic cholesterol 7α-hydroxylase [13]. As like item 2, "4-methyl,4-carboxycholesta-8(9),24-dien-3beta-ol is decarboxylated and oxidized to form 4-methylcholesta-8(9),24-dien-3-one" is related to metabolism of cholesterol. 4. "Elongation of arachidonyl-CoA to docosatetraenoyl-CoA" reflexes arachidonic acid metabolism [14]. 5. "Squalene 2,3-epoxide cyclizes, forming lanosterol" is also related to biosynthesis of cholesterol [15]. 6. "LDLR:LDL complex [coated vesicle membrane] => LDLR:LDL complex [endosome membrane]" is the another group that is related to the Low-density lipoprotein and its receptor [16]. 7. "EHHADH hydrates trans-2,3-dehydrohexacosanoyl-CoA" point out to activity of EHHADH which is responsible for the hydration and dehydrogenation steps in fatty acid β-oxidation [17]. 8. "Mevalonate is phosphorylated to mevalonate-5-phosphate" refers to the role of mevalonate which is involved in several important cellular function as like synthesizing sterol isoprenoids, such as cholesterol, and non-sterol isoprenoids, such as dolichol [18]. 9. "MVD decarboxylates MVA5PP to IPPP" as like item 8 is associated with mevalonate metabolism [19]. 10. "Reduction of HMG-CoA produces mevalonate" term is tied to the items 8-9. 11. "Another isopentenyl pyrophosphate is added to geranyl pyrophosphate" is related to the biosynthesis of terpenoids [20]. 12. "MMAB transfers adenosyl group from ATP to cobalamin" is linked to the MMAB gene. Metabolism Of Cobalamin Associated B (MMAB) encodes a protein which catalyzes the last step in the change of vitamin B_{12} into adenosylcobalamin [21]. As it is reported in the literature that MMAB encourages negative feedback control of cholesterol homeostasis [22].

As it was discussed, most of the introduced biological terms are related to the metabolism of lipids and especially cholesterol. It can be concluded that there are essential differences between caffeinated and decaffeinated coffee considering effect on the metabolism of cholesterol. Action between the studied nodes of the main component is shown in the Figure 4. Except THRSP-FASN relationship, the other connections are binding types. The only activation link connects THRSP to FASN. The two biological terms related to THRSP and FASN are "MID1IP1 binds THRSP" and "[acyl-carrier-protein] S-malonyltransferase activity". Activation of FASN induced more alteration in fatty acid synthesis [23]. Since binding action is considered in the PPI network, the other sub-networks in Figure 4 were not discussed in details.

Conclusion

In conclusion, gene expression profiles of mice liver showed that there were set of genes that are targeted by caffeinated coffee and are active on lipid metabolism especially cholesterol biosynthesis while decaffeinated coffee is not able to induce such effects. The results of this research can be applied to use of caffeine as an additive compound in the other nutrients to prevent the fatty liver disease and hepatic cirrhosis.

Acknowledgment

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Author contributions

Mostafa Rezaei Tavirani, Babak Arjmand, Mahmood Khodadoost and Zahra Razzaghi were involved in project design, data collection and analysis; all authors were involved in project administration and approved the final draft of the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

GEO: gene expression omnibus; DEGs: differentially expressed genes; PPI: protein-protein interaction.