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Galaxy Publication

Systems Biology Evaluation of Coffee Compounds and Metformin in Type 2 Diabetes Management

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ABSTRACT

Studies have underscored the favorable impact of coffee intake on maintaining blood glucose levels in humans. In contrast, metformin serves as the standard pharmacological treatment for type 2 diabetes. The present investigation aimed to examine potential roles for coffee either as an adjunct to metformin or as a standalone approach in managing type 2 diabetes. Proteomic information concerning the influence of caffeine and trigonelline—the two principal bioactive components in coffee—on alleviating diabetes was collected and evaluated using protein-protein interaction (PPI) network analysis along with gene ontology enrichment. Whole-blood gene expression data from metformin-responsive diabetic individuals versus healthy controls were retrieved from the GSE83983 dataset in the Gene Expression Omnibus (GEO) repository. After preliminary screening with the GEO2R tool, the markedly differentially expressed genes (DEGs) underwent PPI network analysis and regulatory network examination. Both caffeine and trigonelline actively modulate glycolysis-related pathways to combat diabetes. Metformin substantially impacted several diabetes-associated genes, including HSP90AA1, TLR4, RELA, ARRB, LRRK2, STAT5B, LYN, and TLR2. Findings suggest that regular coffee intake may support blood glucose control in diabetic individuals in ways akin to metformin. Appropriate levels of coffee consumption could potentially function as a regulator of blood sugar in patients with diabetes.

Keywords: Coffee, Diabetes, Gene, Metformin

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Introduction

Research has demonstrated that drinking coffee exerts a meaningful influence on blood glucose homeostasis. Caio E.G. Reis *et al*. compiled evidence from numerous studies regarding coffee's role in human glucose management. According to their summary, acute intake (1-3 h) tends to elevate the glucose response area under the curve, whereas chronic consumption (2–16 weeks) correlates with lowered glucose levels and heightened insulin sensitivity, possibly enhancing overall glycemic control [1]. Additional evidence links coffee drinking to reduced risk of various chronic illnesses, such as diabetes mellitus, Parkinson's disease, and certain cancers, though connections to cardiovascular issues have also been documented [2].

Muhammad Shahid *et al*. investigated caffeine's effects on the proteome of bladder epithelial cells, identifying 32 upregulated and 25 downregulated proteins. Their analysis revealed that caffeine primarily affected gene sets related to “glycolysis” and “PI3K/AKT/MTOR” signaling [3]. Peerapen *et al*. provided proteomic insights into how caffeine and trigonelline affect liver cells, reporting significant dysregulation in 47 proteins. Notably, they found that caffeine-mediated downregulation predominantly targeted proteins in the glycolytic pathway [4].

Metformin stands as the leading therapeutic option for diabetes and is widely prescribed today. Its broad application and multiple health advantages across different conditions highlight its therapeutic and preventive

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value [5]. Beyond its core indication for type 2 diabetes (T2D), metformin has shown effects in areas like aging, oncology, and cardiovascular health. Key proposed actions involve redox-dependent suppression of liver glucose production and blockage of glycerol-3-phosphate dehydrogenase, thereby elevating cytosolic redox potential [6]. Giusti *et al*. detailed metformin's protective effects against cytokine-driven damage in human pancreatic islet cells using multidimensional shotgun proteomics [7]. Li *et al*. explored how genetic differences influence metformin efficacy through a genome-wide association analysis [8].

Computational biology tools have helped reveal additional aspects of metformin's protective mechanisms against diverse pathologies [9-11].

Protein-protein interaction (PPI) network analysis is a powerful technique for uncovering molecular pathways in various disorders. It excels at processing extensive gene datasets to pinpoint pivotal elements [12]. Here, the potential benefits of coffee in preventing or mitigating T2D were reviewed from existing literature. These insights were then contrasted with network-based findings from blood gene expression in metformin-treated patients (drawn from the GEO repository) to detect any shared mechanistic similarities between coffee intake and this established T2D therapy.

Materials and Methods

Data collection

To investigate the potential of coffee consumption in lowering blood glucose levels, multiple search terms including “diabetes”, “coffee”, “proteomics”, “genomics”, and “bioinformatics” were used in Google Scholar. Relevant differentially expressed proteins (DEPs), differentially expressed genes (DEGs), and associated biological terms were chosen for further examination. Given that caffeine and trigonelline are recognized as the primary bioactive compounds in coffee, the proteomic data from Peerapen *et al*., which examined changes in the human hepatocyte proteome induced by caffeine and trigonelline, were selected for detailed analysis. As stated in that study, concentrations of 100 µM for both caffeine and trigonelline reflect levels achievable through regular coffee intake [4]. According to their findings, 26 proteins were significantly dysregulated by caffeine and 25 by trigonelline, with four proteins commonly affected in both conditions. Accounting for these overlaps, a total of 47 unique proteins were identified. To assess the human body's response to metformin, the dataset GSE153315 was retrieved from the GEO database (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=gse153315>). This dataset contains whole-blood gene expression profiles from 10 type 2 diabetic patients who responded to metformin compared to 10 healthy controls.

Data evaluation

The GSE153315 dataset was assessed using box plot and UMAP visualizations through the GEO2R tool. Suitable gene expression profiles were selected based on the results of box plot and corresponding UMAP analyses. The overlap between significant DEGs and all DEGs distinguishing treated samples from controls was illustrated in a Venn diagram. The distribution of upregulated and downregulated genes according to log2 (fold change) was displayed in a volcano plot.

PPI network analysis

The 47 dysregulated DEPs reported by Peerapen *et al*. [4] and the 653 significant DEGs from GSE153315 were subjected to protein-protein interaction (PPI) network analysis. Data were uploaded to the “Protein query” section of the STRING database using Cytoscape software version 3.7.2 to build the PPI networks. Interactions between identified DEPs and DEGs were represented as undirected edges. The resulting networks were evaluated with the “Network Analyzer” tool in Cytoscape and visualized according to node degree values.

In the primary connected component of the metformin PPI network, the top 10% of nodes ranked by degree were designated as hubs. Bottlenecks were defined as the top 5% of nodes based on betweenness centrality. Nodes that qualified as both hubs and bottlenecks were classified as hub-bottleneck nodes.

To identify associated biological processes, all DEPs from the coffee-related analysis were analyzed using the ClueGO v2.5.7 plugin in Cytoscape. The significant DEGs from the metformin analysis were examined for regulatory networks with the CluePedia v1.5.7 plugin in Cytoscape.

Statistical analysis

Significant DEGs were defined by criteria of |Fold change| > 2 and Padj < 0.05. A default confidence score of 0.4 was used to construct the metformin PPI network, while a confidence score of 0.4 was also applied for the coffee-related analysis. For gene ontology enrichment, thresholds of term p-value, term p-value corrected with Bonferroni step down, group p-value, and group p-value corrected with Bonferroni step down < 0.001 were applied.

Results and Discussion

Figure 1 displays the box plot for 10 whole-blood gene expression profiles obtained from diabetic patients versus healthy controls. According to **Figure 1**, the metformin-treated samples GSM4640272 and GSM4640273, as well as control samples GSM4640277 and GSM4640278, were excluded from further evaluation due to unsuitability. This variability among samples was confirmed through UMAP visualization **(Figure 2),** where clear clustering between treated and control groups was lacking. Analyses conducted after removing GSM4640272, GSM4640273, GSM4640277, and GSM4640278 are presented in **Figures 3 and 4.** The box plot and UMAP outcomes supported the appropriateness of the retained profiles for continued analysis, demonstrating adequate distinction between the groups. Venn diagram results showed that, from a total of 17159 DEGs separating treated and control samples, 653 met significance criteria. **Figure 6** highlights that many of these DEGs displayed marked upregulation or downregulation.

In the coffee compound analysis, STRING identified connections for 46 DEPs in human hepatocytes, forming a network with one isolated node and a primary cluster of 45 nodes **(Figure 7).**

Table 1 lists the top 10 nodes ranked by degree and betweenness centrality. Of the 653 significant DEGs, STRING recognized 442. The constructed PPI network consisted of 128 singleton genes, 26 pairs, 4 triplets, and a major component containing 284 nodes linked by 637 edges. This major component is illustrated in **Figure 8.** The hub-bottleneck nodes comprised eleven genes: HSP90AA1, TLR4, RELA, ARRB2, PPIG, HIST1H4F, MAPT, LRRK2, STAT5B, LYN, and TLR2 **(Table 2).**

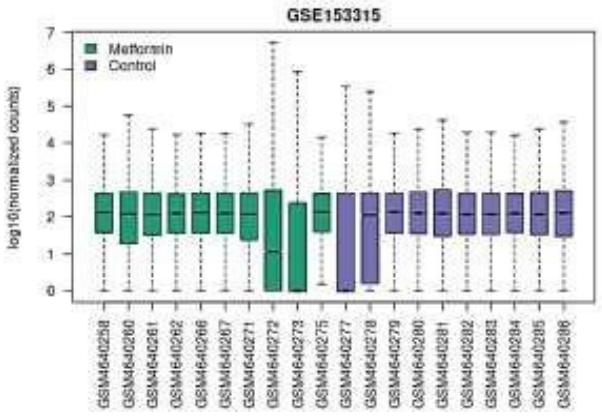

Figure 1. Box plot representing 10 whole-blood gene expression profiles from metformin-treated diabetic patients compared to healthy controls.

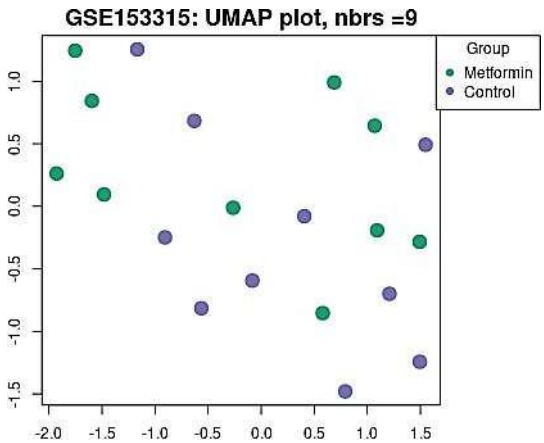

Figure 2. UMAP visualization of whole-blood gene expression data from metformin-treated patients versus healthy controls.

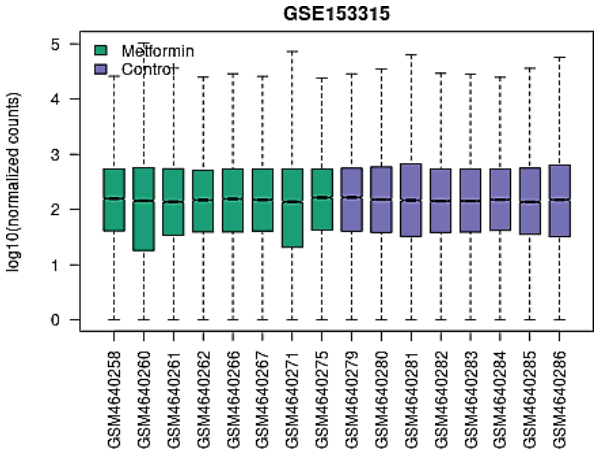

Figure 3. Box plot of 8 validated whole-blood gene expression profiles from metformin-treated diabetic patients versus healthy controls.

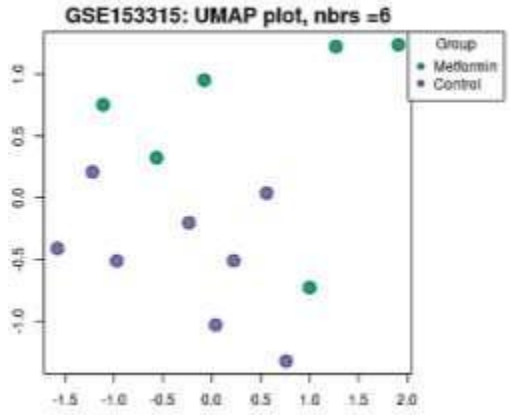

Figure 4. UMAP visualization of validated whole-blood gene expression profiles from metformin-treated patients versus healthy controls.

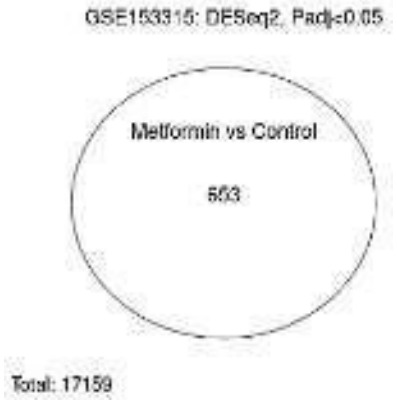

Figure 5. Venn diagram illustrating overlaps in gene expression profiles from whole-blood samples of metformin-treated patients versus healthy controls.

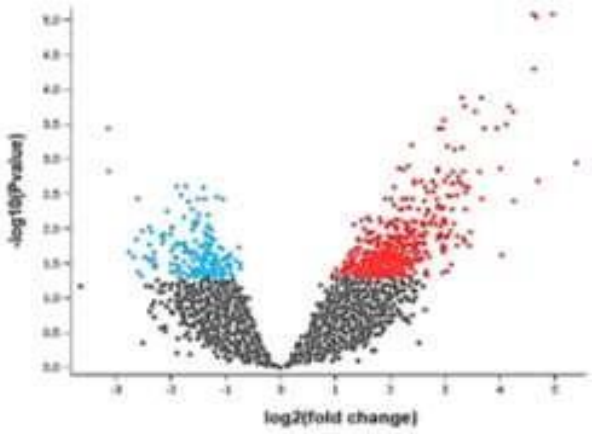

Figure 6. Volcano plot for whole-blood gene expression in metformin-treated diabetic patients versus healthy controls. Red and blue points denote significantly upregulated and downregulated DEGs, respectively. Metformin vs. control, padj < 0.05.

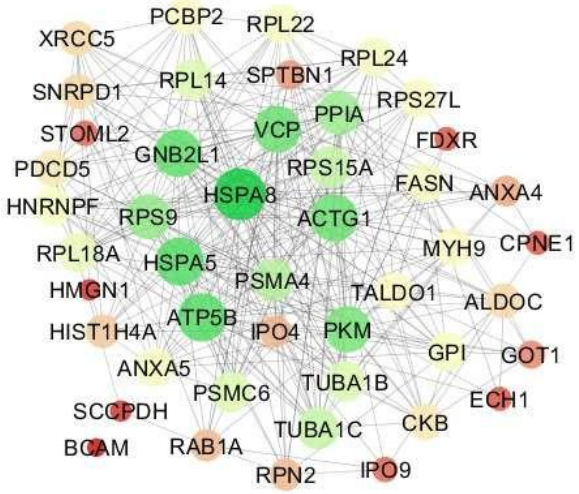

Figure 7. PPI network depicting impacts of coffee components (caffeine and trigonelline) on human hepatocytes; node positioning reflects degree value, with increasing size and red-to-green gradient indicating higher degree.

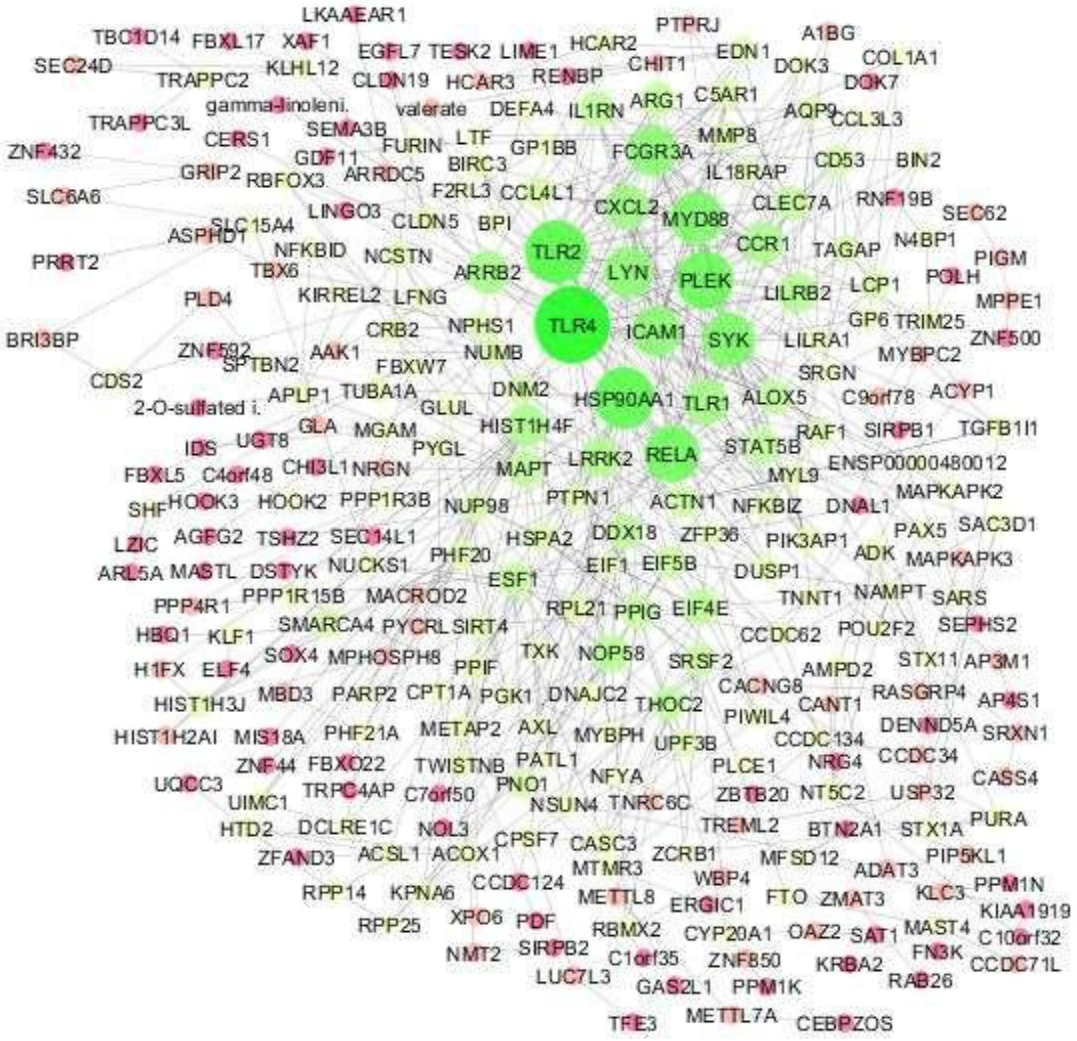

Figure 8. Primary connected component of the PPI network based on whole-blood gene expression in metformin-treated diabetic patients versus healthy controls; node positioning by degree value, with increasing size and red-to-green gradient signaling higher degree (likely hubs appear greener and larger).

Table 1. Top 10 nodes in the coffee compound PPI network according to degree value and betweenness centrality. Proteins appearing in both lists are highlighted in bold.

No	Top nodes based on betweenness centrality		Top nodes based on degree	
	Display name	**Betweenness centrality**	**Display name**	**Degree**
1	ACTG1	0.081	HSPA8	33
2	HSPA8	0.076	HSPA5	28
3	HSPA5	0.068	ATP5B	28
4	ATP5B	0.064	GNB2L1	27
5	VCP	0.048	ACTG1	26
6	PKM	0.036	VCP	26
7	GNB2L1	0.031	PKM	25
8	PSMA4	0.031	RPS9	23
9	RAB1A	0.028	PPIA	22
10	PDCD5	0.027	PSMA4	20

Table 2. Hub-bottleneck nodes within the primary connected component of the PPI network derived from whole-blood gene expression analysis in metformin-treated diabetic patients versus healthy controls.

No.	Display name	Degree	Betweenness centrality
1	HSP90AA1	27	0.208

2	TLR4	36	0.185
3	RELA	24	0.144
4	ARRB2	16	0.133
5	PPIG	11	0.108
6	HIST1H4F	15	0.081
7	MAPT	12	0.069
8	LRRK2	14	0.067
9	STAT5B	12	0.057
10	LYN	20	0.055
11	TLR2	28	0.051

Enriched gene ontology terms for the coffee compound effects are outlined in **Figure 9**, revealing eight distinct biological process groups: “protein targeting to ER”, “ATP biosynthetic process”, “glycolytic process through fructose-6-phosphate”, “regulation of mitochondrial membrane potential”, “response to interleukin-12”, “cellular response to interleukin-4”, “chaperone-mediated protein folding”, and “ribosome assembly”. Specific terms belonging to the “glycolytic process through fructose-6-phosphate” group are detailed in **Table 3.**

Table 3. Specific biological terms in the “glycolytic process through fructose-6-phosphate” group.

No	Biological process
1	Canonical glycolysis
2	Glycolytic process through glucose-6-phosphate
3	NADH regeneration
4	Hexose catabolic process
5	Glucose catabolic process
6	Glucose catabolic process to pyruvate
7	Glycolytic process through fructose-6-phosphat

Terms originated from GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_08.05.2020_00h00. Significance required term p-value, term p-value corrected with Bonferroni step down, group p-value, and group p-value corrected with Bonferroni step down < 0.001.

Interactions among significant DEGs—covering activation, inhibition, and expression—are mapped in **Figure 10.** Beyond many standalone DEGs, the network featured eight pairs, one triplet, two quadruplets, and a dominant connected component. Among the 11 hub-bottlenecks, eight—HSP90AA1, TLR4, RELA, ARRB, LRRK2, STAT5B, LYN, and TLR2—were also present as nodes in this regulatory network **(Figure 10).**

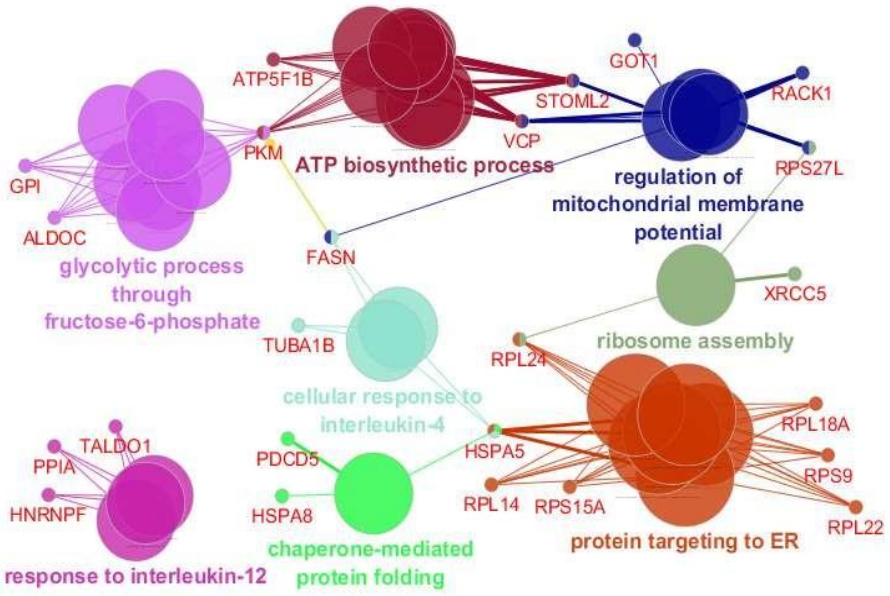

Figure 9. Enriched biological processes linked to DEPs from coffee compound analysis; small circles indicate individual DEPs, bold labels mark process categories. Category size reflects the number of included

terms. Terms sourced from GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_08.05.2020_00h00. Significance thresholds: term p-value, term p-value corrected with Bonferroni step down, group p-value, and group p-value corrected with Bonferroni step down < 0.001.

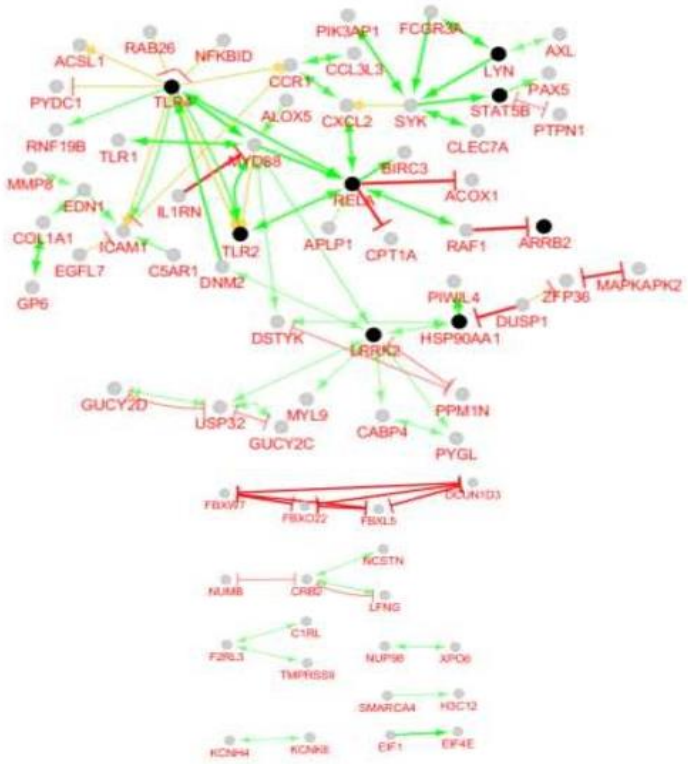

Figure 10. Regulatory relationships among significant DEGs; green denotes activation, red inhibition, and yellow expression links. Black nodes (showing high incoming and outgoing directed connections) correspond to hub-bottlenecks incorporated in the regulatory network.

Network analysis of the effects of caffeine and trigonelline revealed that HSPA8, HSPA5, ATP5B, GNB2L1, ACTG1, VCP, PKM, and PSMA4 represent key proteins targeted by coffee components. Chiva-Blanch *et al.* demonstrated that diabetic individuals exhibit elevated levels of the HSPA8/Hsp90/CSK2α stress-related protein complex compared to nondiabetic individuals [13]. As illustrated in **Figure 9**, both HSPA8 and HSPA5 are associated with the "chaperone-mediated protein folding" biological process. Research by Bravard *et al.* showed a significant reduction in ATP5B levels in the muscle tissue of patients with type 2 diabetes [14]. In contrast, coffee compounds upregulated ATP5B in the studied samples. **Figure 9** also links ATP5B and VCP to the "ATP biosynthetic process". Multiple studies have highlighted the involvement of pyruvate kinase M2 (PKM2) in diabetes [15-17]. The associations of PKM with both "glycolytic process through fructose-6-phosphate" and "ATP biosynthetic process" are evident in **Figure 9**. **Table 3** indicates that the majority of terms in the "glycolytic process through fructose-6-phosphate" cluster pertain to glucose metabolism. These observations underscore the important regulatory influence of coffee compounds on glucose homeostasis in diabetic states.

Metformin is a long-established and widely used medication for type 2 diabetes. Existing literature confirms its safety and efficacy over many years [18]. Nevertheless, studies have identified metformin resistance in certain individuals [19]. As evident in **Figures 1 and 2**, considerable heterogeneity exists in gene expression responses among metformin-sensitive diabetic patients, with inconsistent patterns in box plots and poor sample separation in the UMAP plot. This variability, potentially attributable to genetic differences among patients, prompted the exclusion of unsuitable samples, leading to analysis of only validated profiles **(Figures 3 and 4). Figures 5 and 6** demonstrate that metformin significantly alters the expression of numerous genes. Protein-protein interaction (PPI) network analysis identified an interactome comprising 284 significant DEGs **(Figure 8).** This analysis highlighted 11 central nodes. Prior research has established that central nodes in PPI networks correspond to critically affected elements central to major altered biological processes [20].

Of these 11 central nodes, eight DEGs—HSP90AA1, TLR4, RELA, ARRB, LRRK2, STAT5B, LYN, and TLR2—overlapped with components of the primary regulatory network. This concordance between PPI and regulatory network findings validates the experimental approach. Consequently, this gene set was designated as the core group responsive to metformin. Similarly to metformin, coffee compounds influenced the expression of HSP90AB2.

Literature indicates that members of the toll-like receptor (TLR) family play crucial roles in innate immunity and contribute to the pathogenesis of type 2 diabetes [21]. The RELA gene encodes the p65 transcription factor, whose involvement in diabetes has been explored. Ke *et al*. reported enhanced hepatic insulin sensitivity following RELA inactivation [22]. Yang *et al*. found markedly elevated expression of leucine-rich repeat kinase 2 (LRRK2) in rats with 24-week diabetes compared to controls [23]. Tyrosine-protein kinase LYN has been shown to mediate tyrosine phosphorylation and activation of signal transducer and activator of transcription 5 (STAT5) [24]. Elevated saturated fatty acids in type 2 diabetes patients have been linked to upregulation of signaling lymphocytic activation molecule family member 3 (SLAMF3) through the STAT5-PI3K/Akt pathway [25]. The tight linkage between LYN and STAT5 is depicted in **Figure 10.**

Independent analyses confirmed the beneficial effects of both coffee compounds and metformin in combating diabetes. Given the challenges of drug resistance and inter-patient genetic variability, coffee may be proposed as a valuable adjunct or alternative to metformin. Appropriate levels of coffee intake could represent an effective strategy against diabetes.

Conclusion

The results demonstrate that the two primary coffee compounds (caffeine and trigonelline) can enhance blood glucose control in diabetic individuals in a manner comparable to metformin. As the clinical dosing of metformin is well-established for diabetic management, it is proposed that suitably calibrated coffee consumption could exert a synergistic effect with metformin in countering hyperglycemia in diabetic patients.

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Conflict of Interest: None

Financial Support: None

Ethics Statement: This study was approved by the Ethical Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.140).

References

1. Reis CE, Dórea JG, da Costa TH. Effects of coffee consumption on glucose metabolism: a systematic review of clinical trials. J Tradit Complement Med. 2019; 9(3): 184-91.
2. Butt MS, Sultan MT. Coffee and its consumption: benefits and risks. Crit Rev Food Sci Nutr. 2011; 51(4): 363-73.
3. Shahid M, Kim M, Yeon A, Andres AM, You S, Kim J. Quantitative proteomic analysis reveals caffeine-perturbed proteomic profiles in normal bladder epithelial cells. Proteomics. 2018; 18(20): 1-20.
4. Peerapen P, Chanthick C, Thongboonkerd V. Quantitative proteomics reveals common and unique molecular mechanisms underlying beneficial effects of caffeine and trigonelline on human hepatocytes. Biomed Pharmacother. 2023; 158: 1-13.
5. Triggle CR, Mohammed I, Bshesh K, Marei I, Ye K, Ding H, et al. Metformin: is it a drug for all reasons and diseases? Metabolism. 2022; 133: 1-34.
6. LaMoia TE, Shulman GI. Cellular and molecular mechanisms of metformin action. Endocr Rev. 2021; 42(1): 77-96.
7. Giusti L, Tesi M, Ciregia F, Marselli L, Zallocco L, Suleiman M, et al.The protective action of metformin against pro- inflammatory cytokine-induced human islet cell damage and the mechanisms involved. Cells. 2022; 11(15): 1-29.
8. Li JH, Perry JA, Jablonski KA, Srinivasan S, Chen L, Todd JN, et al. Identification of genetic variation

influencing metformin response in a multi-ancestry genome-wide association study in the diabetes prevention program (DPP). Diabetes. 2022: 72(8): 1161-72.
9. Yang L, Yang J, Liang X, Huang W, Zhang X, Li R. Uncovering antiobesity-related hypertension targets and mechanisms of metformin, an antidiabetic medication. Bioengineered. 2021; 12(1): 4757-67.
10. Zhao Z, Wang C, Jia J, Wang Z, Li L, Deng X, et al. Regulatory network of metformin on adipogenesis determined by combining high- throughput sequencing and GEO database. Adipocyte. 2022; 11(1): 56-68.
11. Guimarães TA, Farias LC, Santos ES, de Carvalho Fraga CA, Orsini LA, de Freitas Teles L, et al Metformin increases PDH and suppresses HIF-1α under hypoxic conditions and induces cell death in oral squamous cell carcinoma. Oncotarget. 2016; 7(34): 55057-68.
12. Mansouri V, Arjmand B, Hamzeloo-Moghadam M, Tavirani MR, Razzaghi Z, et al. Introducing critical genes in response to photodynamic therapy: a network analysis. J Lasers Med Sci. 2023; 14: 1-5.
13. Chiva-Blanch G, Peña E, Cubedo J, García- Arguinzonis M, Pané A, Gil PA. et al. Molecular mapping of platelet hyperreactivity in diabetes: the stress proteins complex HSPA8/Hsp90/CSK2α and platelet aggregation in diabetic and normal platelets. Transl Res. 2021; 235: 1-14.
14. Bravard A, Lefai E, Meugnier E, Pesenti S, Disse E, Vouillarmet J. et al. FTO is increased in muscle during type 2 diabetes, and its overexpression in myotubes alters insulin signaling, enhances lipogenesis and ROS production, and induces mitochondrial dysfunction. Diabetes. 2011; 60(1): 258-68.
15. Gordin D, Shah H, Shinjo T, St-Louis R, Qi W, Park K,et al. Characterization of glycolytic enzymes and pyruvate kinase M2 in type 1 and 2 diabetic nephropathy. Diabetes Care. 2019; 42(7): 1263-73.
16. Qi W, Keenan HA, Li Q, Ishikado A, Kannt A, Sadowski T, et al. Pyruvate kinase M2 activation may protect against the progression of diabetic glomerular pathology and mitochondrial dysfunction. Nat Med. 2017; 23(6): 753-62.
17. Wang H, Chu W, Das SK, Ren Q, Hasstedt SJ, Elbein SC. Liver pyruvate kinase polymorphisms are associated with type 2 diabetes in northern European Caucasians. Diabetes. 2002; 51(9): 2861-5.
18. Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo- controlled, dose-response trial. Am J Med. 1997; 103(6): 491-7.
19. Park JE, Jeong GH, Lee IK, Yoon YR, Liu KH, Gu N,et al. A pharmacometabolomic approach to predict response to metformin in early-phase type 2 diabetes mellitus patients. Molecules. 2018; 23(7): 1-13.
20. Rezaei Tavirani M, Rezaei Tavirani S, Mansouri V, Rostami Nejad M, Rezaei Tavirani M. Protein- protein interaction network analysis for a biomarker panel related to human esophageal adenocarcinoma. Asian Pac J Cancer Prev. 2017; 18(12): 3357-63.
21. Liu F, Lu W, Qian Q, Qi W, Hu J, Feng B. Frequency of TLR 2, 4, and 9 gene polymorphisms in Chinese population and their susceptibility to type 2 diabetes and coronary artery disease. J Biomed Biotechnol. 2012; Article ID 373945.
22. Ke B, Zhao Z, Ye X, Gao Z, Manganiello V, Wu B, et al. Inactivation of NF-κB p65 (RelA) in liver improves insulin sensitivity and inhibits cAMP/PKA pathway. Diabetes. 2015; 64(10): 3355-62.
23. Yang S, Xia C, Li S, Du L, Zhang L, Hu Y. Mitochondrial dysfunction driven by the LRRK2- mediated pathway is associated with loss of Purkinje cells and motor coordination deficits in diabetic rat model. Cell Death Dis. 2014; 5(5): 1-11.
24. Tóthová Z, Tomc J, Debeljak N, Solár P. STAT5 as a key protein of erythropoietin signalization. Int J Mol Sci. 2021; 22(13): 1-13.
25. Zhou T, Wang G, Lyu Y, Wang L, Zuo S, Zou J, et al. Upregulation of SLAMF3 on human T cells is induced by palmitic acid through the STAT5- PI3K/Akt pathway and features the chronic inflammatory profiles of type 2 diabetes. Cell Death Dis. 2019; 10(8): 1-10.