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Assessing Biological Effects of Yoghurt Consumption against Acidified Milk: A System Biology Study

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Abstract

Background and Objective: Yoghurt is a fermented milk product by bacteria; a process including transformation of lactose and galactose to lactic acid. In other words, milk acidification is a critical step in the industrial process to produce various dairy foods and components such as yogurt and caseinates. This study aimed to assess yoghurt effects on gene expression of human whole blood against acidified milk.

Material and Methods: Whole blood gene expression changes of yoghurt consumers against individuals that received acidified milks were retrieved from gene expression omnibus (GEO) database and pre-assessed via GEO2R program to find significant differentially expressed genes (DEG). Significant DEGs were assessed via director protein-protein interaction (PPI) network analysis and gene ontology enrichment to investigate critical genes and targeted biological processes.

Results and Conclusion: Pre-assessment analysis showed that whole blood gene expression profiles of the yoghurt group changed (characterized by 37 significant DEGs) while samples of acidified milk consumers included no significant alterations. Moreover, PPI network analyses showed that RPSA, RPS5, RPS14, PABPC1, DDX60L, FEN1, MRPL12 and KAT6A were the highlighted significant DEGs. Based on the gene ontology, enrichment biosynthesis of ceruloplasmin was addressed as the targeted biological process.
It was concluded that yoghurt included significant effects on gene expression profiles of whole blood while acidified milk did not. Downregulation of genes that were involved in ceruloplasmin production and function was highlighted as the major event in blood of yoghurt consumers.
Conflict of interest: The authors declare no conflict of interest.

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1. Introduction

Lactic acid bacteria are used to convert milk to yoghurt via the fermentation process. Lactose and galactose of milk transform to lactic acid via fermentation; a process which is accompanied with nutrient, physical and chemical modifications of the milk matrix [1]. Several factors such as starter cultures, fermentation conditions and milk

characteristics can affect milk fermentation for yoghurt production. Improvement of the fermentation process leads to the production of quality products [2]. There are evidence that lactic acid bacteria modify microbiota of the yoghurt consumers through fermentation [3]. Acidified milk foods are well-known products worldwide [4]. Milk acidification is an essential step of the industrial production process of various dairy products and components such as cheeses, yogurts and caseinates [5]. Investigations indicate that glucono-*δ*-lactone as a milk acidifier induces coagulation of milk proteins [6]. Studies have shown advantages of fermented dairy consumption such as decreased lipid parameters, decreased circulating parameters of inflammation and regulation of glycemia [7-9]. Significant characteristics of milk fermentation that affects metabolism correspond to lactose metabolism in people worldwide, who cannot eat milk due to its lactose [10].

Liver plays critical roles in copper homeostasis. Investigations indicate that most of the copper is transferred from the liver to plasma in form of ceruloplasmin [11]. Ceruloplasmin is involved in the metabolic balance of iron. Contribution of ceruloplasmin in neurodegenerative diseases such as Alzheimer's disease, Wilson's disease and Parkinson's disease is verified by the researchers. Its roles in metabolic diseases such as obesity, diabetes and hyperlipidemia are reported by the researchers as well [12].

Sample collection is a critical step in analytical experiments. Whole blood is an available source of genomic DNA, which has widely been used in services worldwide [13,14]. High-throughput technologies such as genomics, proteomics and transcriptomics can provide large numbers of data on gene products [15]. Bioinformatics as an appropriate tool is close to genomics to solve numerous problems in medicine and biology [16]. The PPI network analysis as a bioinformatics technique has been interested by the scientists to analyze genomic data. Genes or proteins are included in networks and play various roles in the networks based on their characteristics. The PPI network analysis is used in various fields of medicine and nutrition [17-19]. There are investigations about the effects of yoghurt consumption on gene expression profiles of blood cells. Roles of yoghurt and acidified milk consumptions in modulation of inflammation are documented [20]. In the present study, transcriptomic data of the whole blood of seven young men, who consumed yoghurt and acidified milk, were extracted from the GEO database and compared to each other using PPI network analysis. Critical genes were identified and assessed via gene ontology to find targeted biological terms. Findings open new windows to possible advantages of yoghurt consumption as a public nutrient.

2. Materials and Methods

2.1. Data collection

To investigate effects of fermentation on the quality of milk and the consequence results on human health, GSE98645 was searched within the GEO database. Whole blood transcriptomes of seven healthy young men (mean (±SEM) age of 24.6 y ±4.7) after consuming probiotic yoghurt or acidified milk were compared with those before interventions. Data were published as an original article [21]. The yoghurt was fermented by *Lactobacillus delbrueckii* spp. *bulgaricus*, *Streptococcus thermophilus* and *L. rhamnosus* and the acidified milk was prepared using d-(+)-glucono-*δ*-lactone (2%). Details of the method were described by Burton et al. [21]. The acidified milk mimicked physical characteristics, pH and texture of yoghurt [22]. The dairy product was consumed once (800 g) for 15 min (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=gse98645). The postprandial assay was completed after an overnight fast. Venous blood sampling was completed in the fasting state and during the 6-h postprandial time following dairy intakes [21]. Then, RNA was extracted using Paxgene whole-blood samples and sequenced using Illumina HiSeq platform.

2.2. Pre-assessment analysis

Gene expression profiles of the samples linked to the consumed yoghurt and acidified milk were compared with those of control individuals using GEO2R program. Moderated t-statistic method was used in GEO2R analysis. Distribution of data was assessed via a box plot to investigate equivalence characteristics of the samples. Significant up and down-regulated DEGs were visualized using volcano plot. Significant DEGs were identified and cleaned (uncharacterized genes were removed) based on an adjusted *p*-value of less than 0.05.

2.3. Protein-protein interaction network analysis

Significant DEGs were included in CluePedia v.1.5.7 of Cytoscape software v.3.7.2 to form a directed PPI network to find the critical genes. Nodes were connected by the activation, inhibition, expression, reaction, catalysis and post-translation modification actions. Undirected PPI network was used to find binding actions between the recognized significant DEGs. Significant DEGs were included in the "protein query" of the STRING database to construct a PPI network using Cytoscape software. A confidence score of 0.1 was used to maximize connections between the nodes. The network was analyzed via the "Network analyzer" plugin of Cytoscape software. Element of the major connected component was visualized and sorted through the degree values. Associated biological terms were assessed via gene ontology enrichment. Significant DEGs were enriched using ClueGO v.1.5.7 plugin of Cytoscape software. Biological terms were

extracted from GO_BiologicalProcess-EBI-UniProt-GOA-ACAP-ARAP_08.05.2020_00h00, GOCellularComponent-EBI-UniProt-GOA-ACAP-ARAP_08.05.2020_00h00,EACTOME_Reactions_08.05.2020 ontology sources. Clustering of biological terms was carried out using default kappa score. Corrected statistical *p*-values were generated via Bonferroni step-down correction method.

2.4. Statistical analysis

Significant DEGs were identified based on adjusted *p*-values of less than 0.05. Undirected PPI network was constructed regarding confidence scores of 0.1. Biological terms were achieved based on the corrected *p*-values via Bonferroni step-down correction method.

Enrichment/depletion (two-sided hypergeometric test) statistical test was used as well. A network specificity less than detailed was addressed.

3. Results and Discussion

3.1. Pre-assessment analysis

A box plot of compared whole blood gene expression profiles of the yoghurt group (seven samples) with control group is present in Figure 1. Samples were median-centric and comparable statistically. A linked volcano plot of yoghurt-control analysis is shown in Figure 2. Significant up and down-regulated DEGs are visualized in Figure 2. The box plot of compared seven whole-blood gene expression profiles of the acidified milk group with those of the control groups is illustrated in Figure 3. Samples were matched statistically. Volcano plot of the acidified milk-control analysis is shown in Figure 4. As shown in the figure, no significant DEGs were detected. This analysis was ignored for further assessments. Assessment showed 37 significant DEGs (adjusted *p*-value < 0.05) from separating the yoghurt group from the controls. A list of the significant DEGs is present in Table 1.

3.2. Protein-protein interaction network analysis

Significant DEGs were assessed via a directed PPI network to find prominent relationships between DEGs. The PPI network included two subnetworks and the isolated nodes. The two subnetworks of the directed PPI network of yoghurt–control analysis including the significant DEGs are shown in Figure 5. Activation, inhibition, expression, reaction, catalysis and post-translation modification actions were used to form the network. In general, activation, reaction, catalysis and post-translation modification actions included relationships between nodes of the identified subnetworks. The constructed undirected PPI network of yoghurt-control analysis is mapped in Figure 6. The 22 nodes of the major connected component of the PPI network were connected by 51 edges. Isolated and paired nodes are shown in Figure 6. However, undirected PPI network was small and was not a scale-free network, nodes were layout based on degree values to show various centrality characteristics of the nodes.

3.3. Gene ontology enrichment

Gene ontology results for yoghurt–control analysis are present in Figure 7. A total number of 54 biological terms of biological processes, cellular components and reactions were identified as the linked biological terms. Biological terms were clustered in four groups [“formation of translation initiation complexes yielding circularized ceruloplasmin mRNA in a 'closed-loop' conformation”, “positive regulation of nuclear-transcribed mRNA poly(A) tail shortening”, “rDNA heterochromatin assembly” and “protein import into mitochondrial matrix”] were as the targeted terms. List of the biological terms is shown in Table 2.

Pre-assessment analyses, including box plots and volcano plots (Figures 1, 2), indicated that whole-blood gene expression profiles of the participants who consumed yoghurt were comparable with those of the controls. Significant DEGs were visualized in the volcano plot. Rundblad et al. reported effects of fermented dairy product intakes on gene expression responses of the peripheral blood mononuclear cells associated with less inflammation [23]. As shown in Figure 1, box plot of Figure 3 corres-ponds to a similar analysis. However, no significant DEGs were reported (Figure 4). Results indicated that yoghurt included significant effects on gene expression profiles of the whole bloods while acidified milk did not.

A list of 37 significant DEGs, including 14 upregulated and 13 downregulated genes responsible for consuming yoghurt, is present in Table 1. Importance of the biomarkers of food intake is highlighted in the literature [24]. An investigation by Rezaei et al. showed that consumption of yoghurt led to beneficial effects on blood pressure, blood glucose, serum lipid and glycated hemoglobin. However, C-reactive protein level, high-density lipoprotein and cholesterol were not affected by yoghurt consumption [25].

To screen the 37 significant DEGs, actions between the studied genes were mapped (Figure 5). Technically, RPSA, RPS5, RPS14, PABPC1, DDX60L, FEN1, MRPL12, H4C11, H4C12 and KAT6A were addressed as the interacted DEGs. From the ten highlighted DEGs, H4C11 and H4C12 were not present in the PPI network while others were appeared as the central nodes (Figure 6). Gene ontology assessment is an appropriate tool to assess a set of genes [26]. Results of gene ontology enrichment of the 37 DEGs are illustrated in Figure 7. As depicted in Figure 7, two clusters of biological processes including “rDNA heterochromatin assembly” and “formation of translation initiation complexes yielding circularized ceruloplasmin mRNA in ‘closed-loop’ conformation” were associated to the RPSA, RPS5, RPS14, PABPC1, H4C11 and H4C12. It seems that “formation of translation initiation complexes

yielding circularized ceruloplasmin mRNA in ‘closed-loop’ conformation” was the major targeted group of biological processes.

The most complex characteristics of translation in eukaryotes include the established initiation process. It needs at least 11 eukaryotic initiation factors with coordinated interactions [27]. There is a model that corresponds with the formation a closed-loop structure by mRNA in the initiation of protein synthesis in eukaryotic organisms [28]. More than 95% of plasma copper is associated with ceruloplasmin.

This serum ferroxidase belongs to the multicopper oxidase family, which needs copper for its function. Investigations indicate that malfunction of ceruloplasmin leads to aceruloplasminemia; a neurodegenerative disease [29]. As depicted in Table 2 and Figure 7, “formation of translation initiation complexes yielding circularized ceruloplasmin mRNA in ‘closed-loop’ conformation” includes 16 biological processes and is associated to RPSA, RPS5, RPS14, PABPC1 and DHX30 genes. As discussed previously, RPSA, RPS5, RPS14 and PABPC1 were highlighted as critical genes. Relationships between these four critical genes are shown in Figure 5. As present in Figure 5, RPS14 is affected directly and indirectly by RPS5, RPSA and PABPC1. Downregulation of RPSA, RPS5 and RPS14 is shown in Table 1.

It could be concluded that yoghurt consumption was accompanied by decreased yield of “formation of translation initiation complexes yielding circularized ceruloplasmin mRNA in ‘closed-loop’ conformation” biological processes group, meaning that blood ceruloplasmin level decreased in the yoghurt consumers. Studies demonstrate that ceruloplasmin is the most abundant protein in milk containing β-casein variant A1A1 [30]. Raia et al. reported effects of ceruloplasmin deficiency on the impairment of brain iron metabolisms and behaviors in mice [31]. They showed that ceruloplasmin deficiency played roles in dysregulation of lipid metabolism in the liver and adipose tissues of mice [32]. As shown in Figure 7, “formation of translation initiation complexes yielding circularized ceruloplasmin mRNA in a 'closed-loop' conformation” was connected to five associated DEGs; hence, it could be concluded that ceruloplasmin deficiency was a specific change in gene expression profiles of the yoghurt consumers. Benefits of this finding need further studies.

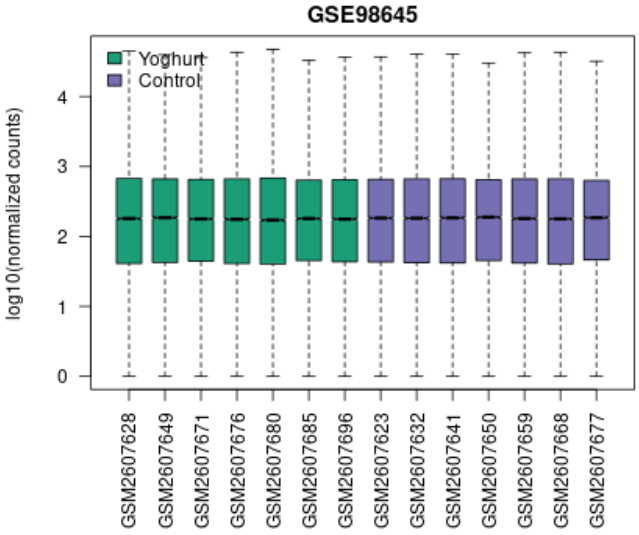

Figure 1. Box plot of the whole-blood gene expression profiles of yoghurt and control groups.

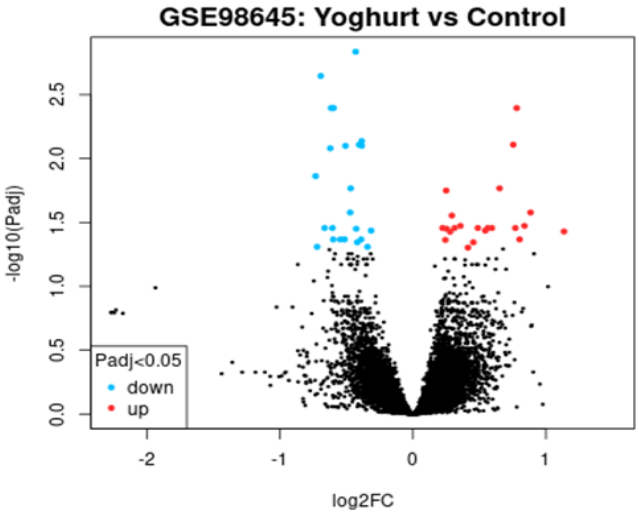

Figure 2. Volcano plot linked to yoghurt-control analysis. Significant differentially expressed genes are colored.

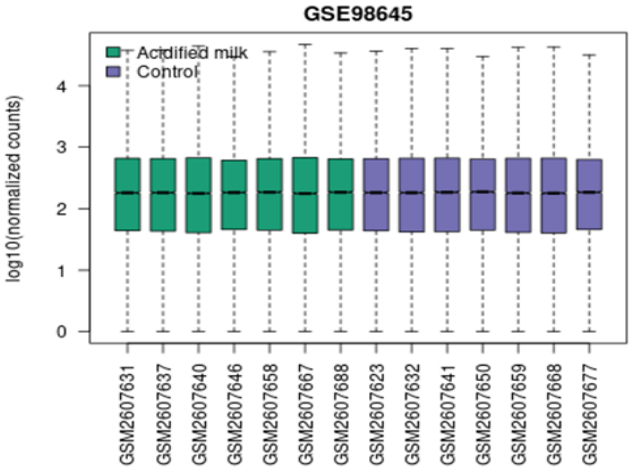

Figure 3. Box plot of the whole-blood gene expression profiles of acidified milk and control groups.

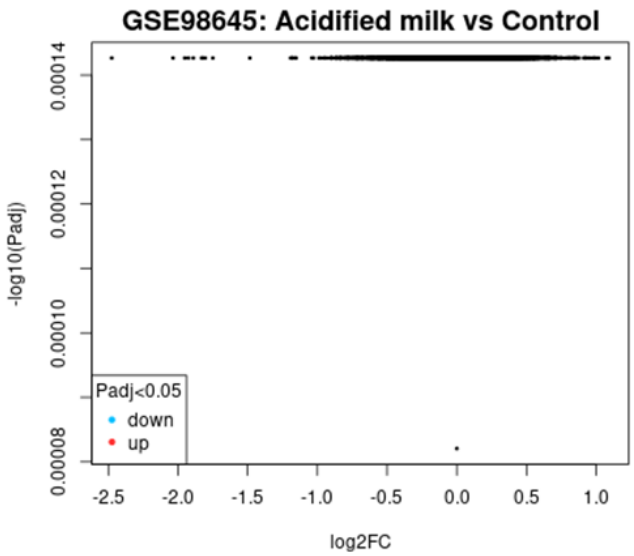

Figure 4. Volcano plot linked to acidified milk control analysis. Except for one-point, other spots are distributed approximately around one log value (adjusted *p*-value).

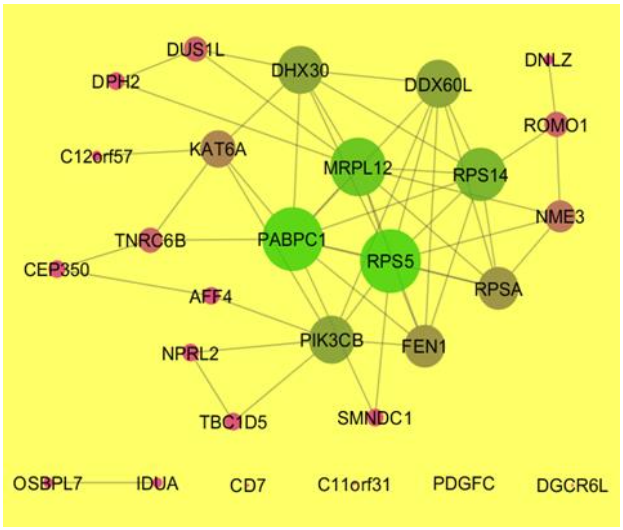

Figure 6. Protein-protein interaction network of the recognized significant differentially expressed genes of yoghurt-control analysis. The 22 nodes of the major connected component are connected via 51 edges. Nods are layout based on degree values.

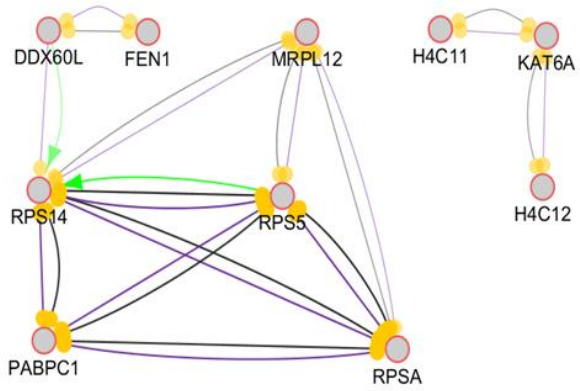

Figure 5. Subnetworks of directed PPI network linked to the yoghurt-control analysis. Activation, reaction, reaction, catalysis and post-modification actions are respectively shown in green, black, pink and purple. Except for the activation links, other connections correspond to mutual relationships between the nodes.

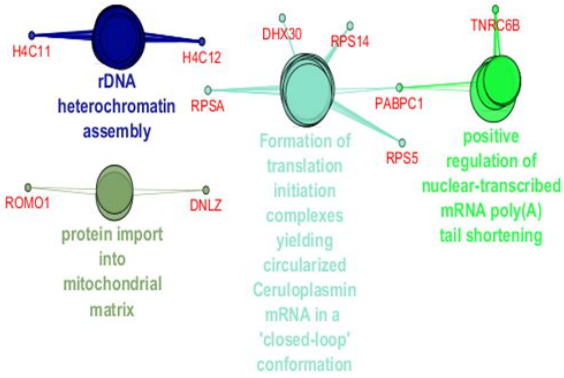

Figure 7. Gene ontology results including biological processes, cellular components and reactions for yoghurt-control analysis. The ten associated genes are labeled in red. Terms of groups (except those with names of the groups) are not labeled to avoid complexity.

Table 2. List of the targeted biological terms in yoghurt-control analysis. Bold terms are correspond to names of the four groups of terms. The biological terms are linked to the ROMO1, DNLZ, H4C11, H4C12, RPSA, DHX30, RPS14, PABPC1, RPS5 and TNRC6B DEGs.

Group	GO Term	% Associated Genes
1	Protein transmembrane import into intracellular organelle	5.56
	Protein import into mitochondrial matrix	10.53
2	**Positive regulation of nuclear-transcribed mRNA poly(A) tail shortening**	16.67
	Regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay	10.00
	Nuclear-transcribed mRNA poly(A) tail shortening	5.56
	Positive regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay	11.11
	Regulation of nuclear-transcribed mRNA poly(A) tail shortening	14.29
3	**Formation of translation initiation complexes yielding circularized Ceruloplasmin mRNA in a 'closed-loop' conformation**	6.90
	Association of phospho-L13a with GAIT element of Ceruloplasmin mRNA	6.78
	Formation of translation initiation complexes containing mRNA that does not circularize	5.26
	18SE pre-rRNA in pre-40S particles is nucleolytically processed during translocation from the nucleus to the cytosol	5.77
	eIF2: GTP is hydrolyzed, eIFs are released	5.17
	Ribosomal scanning	5.26

	Translation initiation complex formation	6.90
	Activation of the mRNA upon binding of the cap-binding complex and eIFs and subsequent binding to 43S	6.78
	eIF3 and eIF1A bind to the 40S subunit	6.25
	Formation of the 43S pre-initiation complex	5.88
	Formation of the ternary complex and subsequently, the 43S complex	5.88
	Start codon recognition	5.17
	Ribosomal scanning and start codon recognition	5.17
	Cytosolic small ribosomal subunit	5.77
	Ribosome assembly	5.63
	Ribosomal small subunit assembly	13.64
4	Elongator complex acetylates replicative histone H3, H4	6.06
	ATF2 acetylates histone H2B, H4	6.06
	NSL acetylates histone H4	8.70
	MSL acetylates histone H4	11.11
	Type B histone acetlytransferase complex acetylates histone H4	12.50
	CLOCK acetylates lysine-10 of histone H3, H4	7.14
	SUMOylation of Histone H4 with SUMO3	12.50
	SUMOylation of Histone H4 with SUMO1	12.50
	CLOCK acetylates lysine-15 of histone H3, H4	7.14
	PRMT1, PRMT6 methylate arginine-4 of histone H4	12.50
	COPRS: CCND1: CDK4: PRMT5:pT5-WDR77 methylates arginine-4 of histone H4 (H4R3)	5.88
	DNMT3A binds Me2sR4-HIST1H4	13.33
	SETD8 (KMT5A) methylates lysine-21 of histone H4 (H4K20)	13.33
	PHF8 demethylates MeK21-histone H4	13.33
	SUV420H1 (KMT5B), SUV420H2 (KMT5C), (possibly SMYD3 (KMT3E)) methylate methyl-lysine-21 of histone H4 (H4K20)	11.76
	SUV420H1, SUV420H2, (possibly SMYD3 (KMT3E)) methylate dimethyl-lysine-21 of histone H4 (H4K20)	11.76
	JMJD6 demethylates MeR4-HIST1H4	13.33
	JMJD6 demethylates Me2sR4-HIST1H4	13.33
	PRMT1, PRMT6 methylate methyl-lysine-4 of histone H4	12.50
	WICH phosphorylates H2AFX on Y142	5.56
	ATM phosphorylates MDC1	5.00
	ATM phosphorylates histone H2AFX on S139 at DNA DSBs	5.13
	MDC1 associates with gamma-H2AFX at nuclear foci	5.00
	ATM recognizes H2AFX-Nucleosomes	5.13
	Elongator complex acetylates H3, H4	6.06
	Clock acetylates histones H3, H4	7.14
	rDNA heterochromatin assembly	5.00
	Nuclear nucleosome	5.00
	DNA replication-dependent nucleosome organization	6.25
	Negative regulation of megakaryocyte differentiation	11.11
	DNA replication-dependent nucleosome assembly	6.25

4. Conclusion

In conclusion, yoghurt includes significant effects on gene expression of whole bloods while acidified milk does not. Totally, 37 significant DEGs were highlighted as a result of yoghurt consumption. Downregulation of genes that are associated with the production and function of ceruloplasmin was highlighted in the blood of yoghurt consumers. Further studies, including detailed experiments on ceruloplasmin in bloods of yoghurt consumers, validation of the introduced critical DEGs via the associated methods such as quantitative reverse transcription-polymerase chain reaction (qRT-PCR) and larger size samples, are needed to investigate complete molecular metabolisms associated to yoghurt consumption.

5. Ethical Code

This study was approved via IR.SBMU.RETECH.-REC.1403.260 ethical code

6. Acknowledgements

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7. Conflict of Interest

Mostafa Rezaei-Tavirani contributed to the conception and design of the study and literature review. All authors participated equally in project administration and writing of the primary draft of the manuscript, providing critical revision and editing. All authors approved the final version of the manuscript.

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ارزیابی اثرات بیولوژیکی مصرف ماست در مقایسه با شیر اسیدی شده: یک مطالعه سیستم بیولوژی

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چکیده

سابقه و هدف: ماست فراورده‌ای از شیر تخمیر شده توسط باکتری است؛ فرآیندی که شامل تبدیل لاکتوز و گالاکتوز به اسید لاکتیک می‌باشد. از طرفی، اسیدی شدن شیر مرحله مهمی در فرآیند صنعتی تولید فرآورده‌ها و ترکیبات گوناگون شیری مانند ماست و کازئینات است. این مطالعه با هدف بررسی اثرات ماست بر بیان ژن‌ها در خون انسان در مقایسه با شیر اسیدی شده انجام شده است.

مواد و روش ها: تغییرات بیان ژنی خون مصرف‌کنندگان ماست در برابر افرادی که شیرهای اسیدی دریافت کرده بودند از پایگاه داده بیان ژنی Gene Expression Omnibus بازیابی و از طریق برنامه GEO2R برای یافتن ژن‌های که افتراقی بیان شده بودند (DEGs) پیش-ارزیابی شدند. DEGهای مهمی از طریق آنالیز شبکه تعامل پروتئین-پروتئین (PPI) جهت دار تعیین و از طریق هستی شناسی ژنی بررسی تا فرآیندهای زیستی هدف تعیین گردند.

یافته‌ها و نتیجه‌گیری: تجزیه و تحلیل پیش-ارزیابی نشان داد که پروفایل‌های بیان ژن در خون گروه مصرف کننده ماست تغییر کرده است (۳۷ DEG مشخص شد). در حالی‌که نمونه‌های مصرف‌کنندگان شیر اسیدی شده تغییر قابل توجهی نداشتند. علاوه بر این، تجزیه و تحلیل شبکه PPI نشان داد که RPSA، RPS5، RPS14، PABPC1، DDX60L، FEN1، MRPL12 و KAT6A، ژن‌های مهم هدف واقع شده می باشند. بر اساس هستی‌شناسی ژنی، بیوسنتز سرولوپلاسمین به عنوان فرآیند زیستی مهم تغییریافته معرفی شد. نتیجه‌گیری کلی این است که ماست دارای اثرات قابل توجهی بر پروفایل بیان ژنی خون است در حالی که شیر اسیدی شده تاثیری ندارد. کاهش ژن‌هایی که در تولید و عملکرد سرولوپلاسمین دخیل بودند به‌عنوان رخداد اصلی در خون مصرف‌کنندگان ماست برجسته شد.

تعارض منافع: نویسندگان اعلام می‌کنند که هیچ نوع تعارض منافعی مرتبط با انتشار این مقاله ندارند.

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- شیر اسیدی شده
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- تجزیه و تحلیل شبکه
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- ماست

نویسنده مسئول

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