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Original article

Onion Extract on Cell Gene Expression Profile: a System Biology Approach

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Abstract

Background and objectives: Widespread consuming of onion as a nutrient in the world implies more investigations about useful and harmful aspects of this common supplementary food. Assessment of molecular mechanism of yellow onion extract on cell line Caco-2 was the aim of this study. **Methods:** Data was extracted from gene expression omnibus (GEO) database. The gene expression profiles of Caco-2 cells in the presence of yellow onion extract versus control cells were analyzed via GOE2R software. The significant differentially expressed genes (DEGs) were assessed via network analysis and the central nodes were enriched via gene ontology. **Results:** Thirteen central nodes including JUN, ATF3, DUSP1 VEGF, CDKN1A, SNAI1, HSPB1, MCL1, SQSTM1, SREBF1, MAP1LC3B, EZR, and DUSP5 were identified. The related biological terms in five groups were introduced. JUN as a crucial DEG was highlighted. **Conclusion:** Based on findings, yellow onion extract effects on the wide range of cellular function such as apoptosis, cell proliferation and more other vital functions. The significant role of c-Jun proto-oncogene (among JUN, ATF3, and DUSP1 as hub-bottlenecks) and "c-Jun-ATF3 complex" biological term group as the affected individuals by yellow onion extract were pointed in this study.

Keywords: gene; gene ontology; JUN gene; network; onion

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Introduction

One of the common vegetables with beneficial characteristics is onion including white, yellow, red, and yellow individuals. Several reported properties of onion are anti-mitogen, anti-cholesterol, and anti-oxidant activities [1,2]. Also, based on investigation of Saba Ahmadi et al, onion extract has shown antiviral activity against avian influenza virus [3].

The high throughput methods such as proteomics, genomics, and metabolomics are suitable tools to assess wide range of events which happen in the molecular levels for the studied organisms [4].

Herbal medicine is a field that is concerned deeply by proteomics, metabolomics, and genomics to analyze diseases and the related subjects [5,6]. Since bioinformatics is tied to the omics methods to analyze the finding, application of bioinformatics and omics methods in the field

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of traditional medicine is promoted and have resulted numerous outcomes in this regard [7]. Network analysis as a bioinformatics related method is used widely in medicine to evaluate different types of diseases. It is applied in the nutrition, planet sciences, herbal medicine and different fields in biology and biomedical related arenas [8]. It is reported that consumption of yellow onion is associated with decrease of hyperglycemia and insulin resistance in patients [9].

Protein-protein interaction network analysis is stablished based on interactions between the queried elements such as proteins or genes that play different roles in a network. In protein-protein interation (PPI) network, a few nodes are linked to large numbers of the first neighbors, these types of the nodes are known as hubs. Experiments have shown that the hubs of a network are the crucial elements of network and are responsible for the main related biological events that are concerned by the elements of the network. The other critical nodes of the network are the bottleneck nodes, the nodes that participate in some shortest paths. Common hubs and bottlenecks are known as hub-bottlenecks. Hub-bottleneck nodes are the main elements of a network which control the biological processes and biochemical pathways and are related to the function of network [10-13].

PPI network analysis has been used to explore anticancer property of human cervical cancer. The contradictory effects of 6-shogoal on the treated cells were reported. In another investigation, tumor inhibition of rosemary was evaluated via network analysis while Zamanian-Azodi et al. published a document about anticancer property of ghost pepper by using PPI network analysis [14-16]. In the present study the effect of yellow onion extract on Caco-2 cell line proteome was downloaded from GEO and analyzed via PPI network analysis to explore the crucial effect of onion on the cell function.

Material and Methods

Ethical considerations

This project was approved by the following ethical code: IR.SBMU.RETECH.REC.1400.1065 by Shahid Beheshti University of Medical Sciences.

Data collection

GSE83893 which is published entitled as “The effect of onion exposure on gene expression profiles in intestinal Caco-2 cells” was selected from GEO. GSM2221098, GSM2221101, and GSM2221104 as control samples and GSM2221100, GSM2221103, and GSM2221106 as treated human Caco-2 cells 6 hour incubated with in vitro digested yellow onion extract (YOD) were candidate to be assessed regarding gene expression change analysis. More details of methods is described in investigation of Nicole J W de Wit et al. [17].

Network analysis

The significant DEGs were included a network via “protein query” of STRING database by cytoscape software. To make maximum interactions between the nodes, 80 first neighbors from STRING database were added to the queried DEGs. The main connected component was analyzed by “NetworkAnalyzer” plugin of cytoscape software. Top 5% of the queried DEGs based on degree value and betweenness centrality were identified as hubs and bottlenecks respectively.

Gene ontology

To explore the role of the central nodes, the related biological terms were searched from clueGO application of cytoscape software. The terms were extracted via detailed mode of search and grouped based on Kappa-score.

Action map analysis

Regulatory interactions between the identified central DEGs were assessed via CluePedia plugin of cytoscape software. Activation, inhibition, expression, and reaction actions were determined.

Statistical analysis

The expression profiles were compared by GEO2R and the meandiff plot, volcano plot, and expression density graph were illustrated. In the present investigation, log2 (fold change)>0.6 and log2 (fold change) <-0.6 were identified as the up-regulated and down-regulated genes, respectively. Density as a function of expression value is schemed in the expression density graph for the six assessed samples. Volcano plot refer to a positive scale of -log10 (p-value) as a function of log2 (fold change). This plot was plotted for the six control and treated samples to show the significant dysregulated genes. The significant DEGs were selected based on fold change>1.5 and p-value<0.05.

Results and Discussion

To compare the studied gene expression profiles, meandiff plot is shown in the Figure 1. Log2 (fold change) as a function of log2 expression is presented in the meandiff plot (Figure 1). The presented plot shows the significant gene expression process. The up-regulated and the down-regulated genes (as dots) appeared in the up and down parts of Figure 1 respectively. Expression density graphs (Figure 2) indicated that the profiles had a similar pattern. As it is shown in Figure 3, large numbers of genes are significantly dysregulated individuals (the colored points).

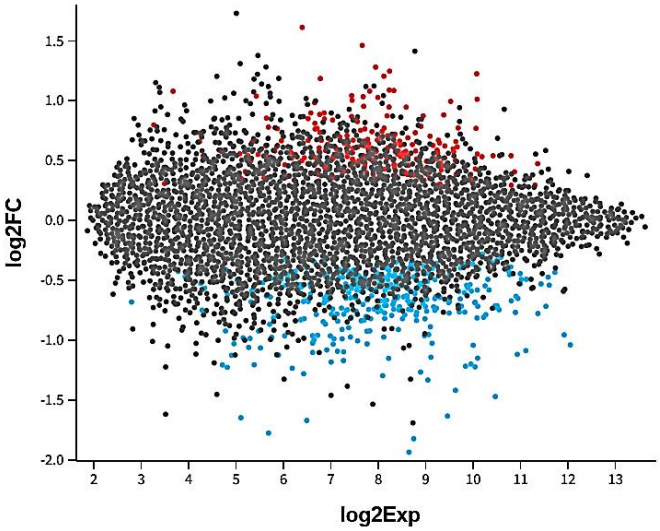

Figure 1. Meandiff plot of the gene expression profile of the treated Caco-2 cells with yellow onion extract versus controls. The red and blue dots represent up and down-regulated individuals, respectively.

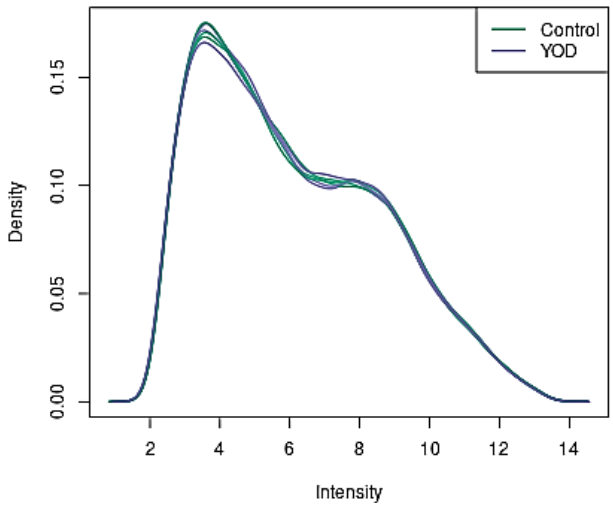

Figure 2. The comparable expression density plot of the six gene expression profiles of the treated Caco-2 cells with yellow onion extract (YOD) and the control cell profiles

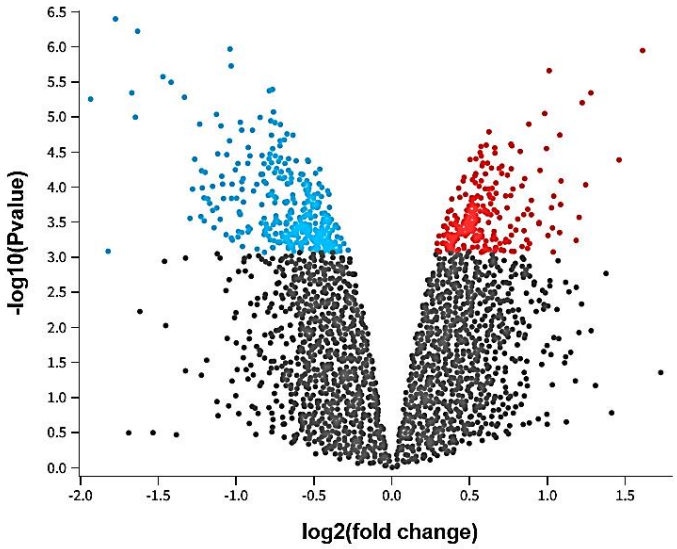

Figure 3. Volcano plot of the gene expression profiles of the treated Caco-2 cells with yellow onion extract versus controls. The colored genes with logFC < -0.6 and 0.6 < logFC are significant DEGs. The red and blue dots refer to up and down-regulated individuals, respectively.

Numbers of 162 characterized significant DEGs were selected from GSE83893. Among 162 queried DEGs, 151 individuals were recognized by STRING database. The DEGs were included in a PPI network and connected to each other by 117 undirected edges (Figure 4). About 60% of the nodes were not included in the main connected component of the created network, hence 80 first neighbors were added to the queried DEGs and the network was reconstructed. The network including 36 isolated nodes, 2 paired DEGs and a main connected component consisted of 193 genes and 3123 edges was reformed. The main connected component is shown in Figure 5. Network analysis led to exploring the central nodes. The hubs, bottlenecks, and hub-bottleneck nodes are presented in Table 1. JUN, ATF3, and DUSP1 as hub-bottleneck nodes and VEGF, CDKN1A, SNAI1, HSPB1, and MCL1 as hubs and SQSTM1, SREBF1, MAP1LC3B, EZR, and DUSP5 as bottlenecks are listed in Table 1.

Gene ontology enrichment led to introducing the investigated biological terms. Five groups of biological terms including 38 individual that are related to the central nodes were determined (Table 2).

As it is depicted in Table 2, the identified groups are related to the limited numbers of DEGs. Regulatory relationship between the central nodes was investigated by action map analysis. Activation, co-expression, and reaction actions were identified as the relationship connections between the analyzed central nodes (Figure 6). As it is depicted in Figure 6, 50% of the assessed genes were included in the main sub-network.

Effects of herbal extracts on cells and organisms were investigated via network analysis and led to exploring new protein targets in the evaluated samples [18]. Gene expression profiles of the treated cells and controls were compared to show the possible dysregulated genes. As it shown in Figures 1 and 3, there are several DEGs that are characterized by fold change above 1.5 and p-value less than 0.05. These genes can be considered as the significant DEGs that discriminate the two cell groups in the absence and the presence of onion extract. Expression density graph (Figure 2) refers to comparable gene expression profiles.

The network analysis is corresponded to the weak interactions between the selected DEGs (as the significant dysregulated genes). However, adding suitable numbers of first neighbors to the queried DEGs led to constructing a scale free network. Scale free networks are the networks that are applied frequently to interpret biological findings [19,20]. The queried DEGs interact in a more connected network by the added first neighbors.

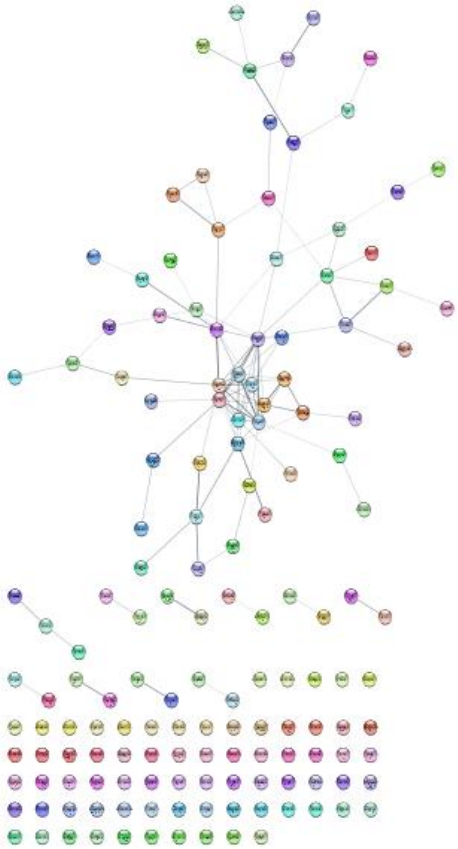

Figure 4. Protein-protein interaction network of the queried DEGs related to the treated Caco-2 cells with yellow onion extract versus controls. Some genes are remained isolated or appeared as the paired individuals.

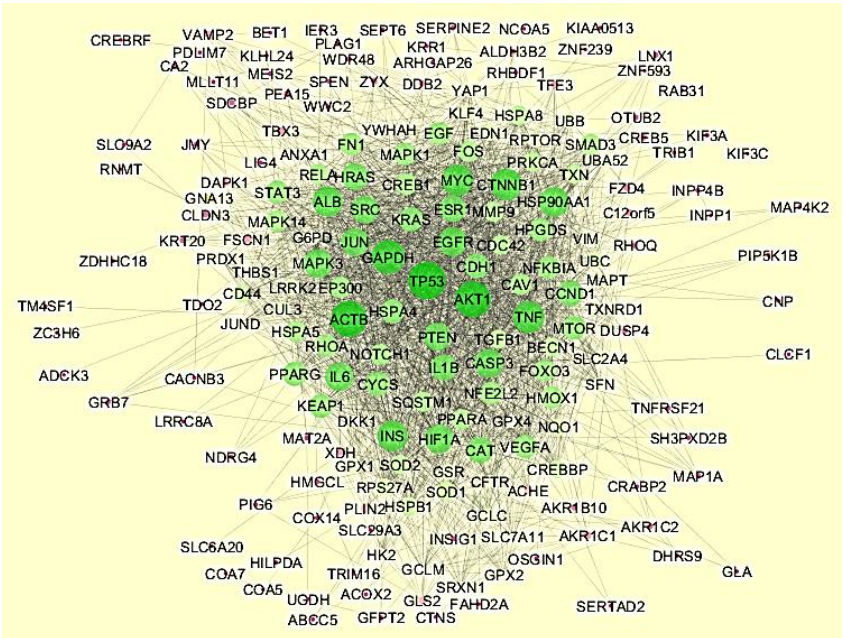

Figure 5. Protein-protein interaction network of the queried DEGs related to the treated Caco-2 cells with yellow onion extract versus controls plus the added first neighbors; red to green refers to increase of degree value

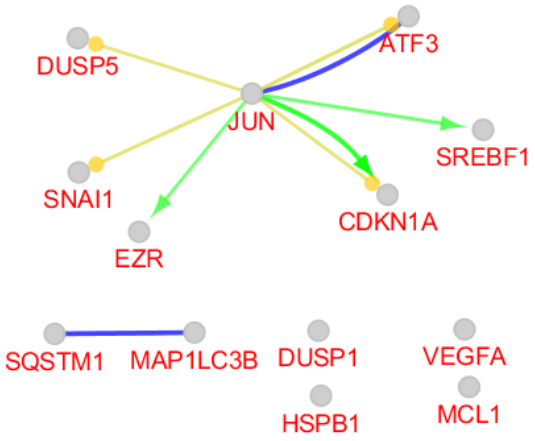

Figure 6. Action map of the central nodes including a main connected component and six other genes. Green, yellow, and blue colors refer to activation, co-expression, and reaction, respectively

Table 1. Central nodes of protein-protein interaction network related to the queried DEGs which discriminate the treated Caco-2 cells from controls

No.	Display name	Degree	Betweenness centrality	Centrality type
1	JUN	97	0.0392	Hub-Bottleneck
2	VEGFA	68	0.0036	Hub
3	CDKN1A	60	0.0036	Hub
4	ATF3	57	0.0127	Hub-Bottleneck
5	SNAI1	55	0.0042	Hub
6	DUSP1	54	0.0294	Hub-Bottleneck
7	HSPB1	49	0.0070	Hub
8	MCL1	49	0.0013	Hub
9	SQSTM1	43	0.0138	Bottleneck
10	SREBF1	34	0.0136	Bottleneck
11	MAP1LC3B	32	0.0209	Bottleneck
12	EZR	27	0.0241	Bottleneck
13	DUSP5	20	0.0288	Bottleneck

As it is shown in Table 1, 13 central nodes are introduced as the important affected genes by yellow onion extract. JUN, ATF3, and DUSP1 among the 13 central nodes are hub-bottlenecks. Due to critical role of hub-bottlenecks in the function of the analyzed network [21], it seems these three nodes are crucial DEGs of the network. JUN is characterized as the potent hub-bottleneck node in Table 1. It is ranked as the top node with highest values of degree and betweenness centrality parameters. Importance of JUN as a crucial node is reflected in Figure 6. JUN over-expresses ATF3 (the other crucial central node) and activates SERBF1, EZR, CDKN1A. SERBF1 and EZR are two bottleneck nodes and CDKN1A is a hub gene. JUN up-regulates DUSP5, SNAI1, and CDKN1A. SNAI1 and DUSP5 are hub and bottleneck nodes respectively.

JUN proto-oncogene, AP-1 transcription factor subunit (JUN) encodes c-Jun proto-oncogene in human. c-Jun proto-oncogene is the major component of the 12-O-tetradecanoyl phorbol 13-acetate (TPA)-inducible transcription factor AP-1 [22,23]. There are many documents about biological roles of c-Jun proto-oncogene. This protein is involved in the several vital cell activities such as apoptosis, cell proliferation, tumorigenesis, cell survival, and tissue morphogenesis [24]. It has reported that c-Jun c-JUN regulates target genes directly in different types of cancer cells which leads to functional changes in affected cells [25]. Kumar M et al. published data about effect of onion extract on c-Jun N-terminal kinase signaling pathway to reduce expression of tissue factor in human umbilical vein endothelia [26].

Table 2. Gene ontology results of the central nodes

No.	Gene Ontology Term	Ontology Source	Group No.	Associated genes
1	**SNAI1, SNAI2 bind the PTEN gene promoter**	RRs	1	[SNAI1]
2	Negative regulation of cell differentiation involved in embryonic placenta development	GOBP	1	[SNAI1]
3	Translocation of Ezrin to plasma membrane	RRs	2	[EZR]
4	**DCC interaction with Ezrin**	RRs	2	[EZR]
5	Phosphorylation and activation of Ezrin	RRs	2	[EZR]
6	Translocation of p21 to the nucleus	RRs	3	[CDKN1A]
7	PCBP4 modulates CDKN1A translation	RRs	3	[CDKN1A]
8	CEBPA binds CDKN1A (p21)	RRs	3	[CDKN1A]
9	PCNA-p21 complex	CC	3	[CDKN1A]
10	**PCNA-p21 complex**	GOCC	3	[CDKN1A]
11	Regulation of cardiac muscle tissue regeneration	GOBP	3	[CDKN1A]
12	Negative regulation of cardiac muscle tissue regeneration	GOBP	3	[CDKN1A]
13	Cyclin-dependent protein kinase activating kinase activity	GOBP	3	[CDKN1A]
14	Expression of Acetyl CoA Carboxylase 1 (ACACA, ACC1)	RRs	4	[SREBF1]
15	Expression of Acyl-CoA Desaturase (Stearoyl CoA Desaturase, SCD)	RRs	4	[SREBF1]
16	SREBP1A,1C,2 binds SREBP1A,1C,2 forming dimers	RRs	4	[SREBF1]
17	SREBP1A,2 binds the MVD promoter	RRs	4	[SREBF1]
18	SREBP1A,1C,2 binds the ELOVL6 promoter	RRs	4	[SREBF1]
19	SREBP1A,1C binds the ACACB promoter	RRs	4	[SREBF1]
20	SREBP1A,2 binds the LSS promoter	RRs	4	[SREBF1]
21	SREBP1A,1C,2 binds the ACACA promoter	RRs	4	[SREBF1]
22	SREBP1A,1C binds the SCD gene	RRs	4	[SREBF1]
23	SREBF1 gene expression is inhibited by FOXO1	RRs	4	[SREBF1]
24	**Sterol response element binding**	GOMF	4	[SREBF1]
25	Formation of Activated Protein 1 (AP-1) complex. ATF2/c-JUN heterodimer.	RRs	5	[JUN]
26	Expression of ATF3	RRs	5	[ATF3]
27	NOTCH4 gene transcription	RRs	5	[JUN]
28	ERK1/2-activated AP1 complex binds KDM6B promoter	RRs	5	[JUN]
29	AP-1 transcription factor binds IGFBP7 promoter	RRs	5	[JUN]
30	Formation of Activated Protein 1 (AP-1) complex. cFOS/c-JUN heterodimer.	RRs	5	[JUN]
31	AP-1 transcription factor binds IL1A promoter	RRs	5	[JUN]
32	JUN binds MAPK6 gene	RRs	5	[JUN]
33	JUN positively regulates MAPK6 gene expression	RRs	5	[JUN]
34	Activated JNK phosphorylates c-JUN	RRs	5	[JUN]
35	ESR1-JUN complex	CC	5	[JUN]
36	**c-Jun-ATF3 complex**	CC	5	[ATF3, JUN]
37	Leading edge cell differentiation	GOBP	5	[JUN]
38	Regulation of transcription from RNA polymerase II promoter in response to arsenic-containing substance	GOBP	5	[ATF3]

Term p-value, term p-value corrected with Bonferroni step down, group p-value, and group p-value corrected with Bonferroni step down were 0.00. RRs: REACTOME reactions; GOBP: gene ontology biological process; CC: CORUM CORUM; GOCC: gene ontology cellular component; GOMF: gene ontology molecular function; the head of biological term groups are shown in bold font.

As it is depicted in Table 2, five groups including 38 biological terms which are related to the central nodes were identified. The most important group including 14 biological terms was “c-Jun-ATF3 complex”. Jun is involved in the 12 terms among the 14 introduced individuals. Activating Transcription Factor 3 (ATF3) the other hub-bottleneck is involved in the “c-Jun-ATF3 complex”. There are documents about near function of ATF3 and JUN. SM Sykes et al. published documents about role of these genes in regulation of transcriptional yield of the unfolded protein response in acute myeloid leukemia [27]. In the other investigation involvement of ATF3/c-JUN/LGAL3 axis in central diabetes insipidus following hypothalamic injury was reported by Zhou M et al. [28]. It seems that JUN as a prominent DEG is the main target of yellow onion in the treated cells.

Conclusion

The findings indicate that yellow onion extract affects critical functions of the treated cells. C-Jun proto-oncogene was highlighted as the crucial affected protein. Considering the wide range of biological activities that are related to c-

Jun proto-oncogene, and introducing "c-Jun-ATF3 complex" as the important affected group of biological terms, it can be concluded that yellow onion consuming has prominent positive impact in human health.

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Author contributions
Mostafa Rezaei Tavirani planed the project and all authors have equal attribution in administration and publishing data.

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; YOD: yellow onion extract; PPI: protein-protein interaction; ATF3: activating transcription factor