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Low-Level Laser Therapy Effects on Rat Blood Hemostasis Via Significant Alteration in Fibrinogen and Plasminogen Expression Level

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Abstract

Introduction: There are many documents about the significant role of low-level laser therapy (LLLT) in different processes such as regenerator medicine and bone formation. The aim of this study is to assess the role of LLLT in blood hemostasis in rats via bioinformatic investigation.

Methods: The differentially expressed plasma proteins of treated rats via LLLT from the literature and the added 50 first neighbors were investigated via network analysis to find the critical dysregulated proteins and biological processes by using Cytoscape software, the STRING database, and ClueGO.

Results: A scale-free network including 55 nodes was constructed from queried and added first neighbor proteins. Fibrinogen gamma, fibrinogen alpha, and plasminogen were highlighted as the central genes of the analyzed network. Fibrinolysis was determined as the main group of biological processes that were affected by LLLT.

Conclusion: Findings indicate that LLLT affects blood hemostasis which is an important point in approving the therapeutic application of LLLT and also in preventing its possible complication.

Keywords: Laser therapy; Differentially expressed proteins; Bioinformatics; Rat; Blood hemostasis.

Introduction

The application of a laser in different fields of medicine implies more investigation to discover its molecular mechanism and possible complication.[1] Hemostasis as a process that is involved in the cessation of bleeding from a blood vessel is studied in the presence of many stress conditions.[2-4] There are many documents about the molecular aspect of low-level laser therapy (LLLT), which are concerned with proteomics, genomics, and bioinformatics.[5-7] Since the high throughput methods provide large numbers of data, bioinformatics as a useful tool is applied to organize and interpret the findings to present a new concept.[8]

Network analysis as one of the bioinformatics fields is an approach that studies the relationship between the assessed data. In this mode of analysis, the large numbers of proteins can include in a unique interacted unit to form a scale-free network. In the scale-free networks, there are few nodes (proteins in this study) that play crucial roles in network construction.[9] Centrality parameters of the studied nodes are important characters of the nodes of the network that rank the node as critical and usual nodes. Two significant central parameters are degree and betweenness centrality. The nodes that are characterized with high values of degree and betweenness centrality are known as hub and bottleneck nodes respectively. The common hubs and bottlenecks are hub-bottlenecks which are potent central elements of the analyzed network.[10-12] The central nodes of a network determine the possible function of the network.[13,14]

Gene ontology is a method that determines related biological processes, molecular functions, biochemical pathways, and cellular components for the studied genes.[15,16] Results of gene ontology are used to assess the molecular mechanism of many diseases.[17,18] In many cases, network analysis and gene ontology are tied together to

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solve the complexity of the studied systems.[19-21] In the present study, the limited numbers of dysregulated plasma proteins of rats that are treated via LLLT in interaction with the main numbers of the first neighbors are selected to be analyzed via network analysis. The central proteins are investigated via gene ontology to find the critical modulated biological processes after LLLT.

Methods

Six dysregulated rat plasma proteins after LLLT were extracted from the published data by Kilik et al.[22] Based on the methods of this article, 8 male Wistar rats in two groups, control group (C) and irradiated group (I), were investigated to find the effect of LLLT. Radiation is administrated by the gallium–aluminum–arsenide (GaAlAs) diode laser (Maestro/CCM, Medicom Prague, Czech Republic, λ = 830 nm, oval shape of beam-spot size * 1 cm^2, power density 450 mW/cm^2, total daily dose 60,3 J/cm^2, irradiation time 134 seconds) via transcutaneous irradiation for 9 days. Plasma proteins were analyzed via two-dimensional gel electrophoresis and the digested spots were identified by MALDI-TOF mass spectrometry. Details of the procedure are described in the published article.[22] The queried differentially expressed proteins (DEPs) plus 50 first neighbors from the STRING database were analyzed by using Cytoscape software v3.7.2. The central nodes were assessed via gene ontology by ClueGO plugin of Cytoscape. The related significant biological processes were selected from "GO, Biological Process, EBI, UniProt-GOA-ACAP-ARAP, 08.05.2020".

Results

Six identified proteins including haptoglobin (HP), hemopexin (HPX), fibrinogen gamma (FGG), fetuin-A (FETUA), Fetuin-B (FETUB), and alpha-1-antitrypsin (A1AT) were extracted from the published data by Kilik et al.[22] The first three proteins (HP, HPX, and FGG) are the up-regulated proteins while the other ones are de-regulated individuals. Among the 6 queried differentially expressed genes (DEGs), A1AT was not recognized by the STRING database. The network including 55 nodes (five queried DEPs and 50 added first neighbors) and 1034 edges was created (Figure 1). The nodes of the network and the centrality parameters of the nodes are presented in Table 1. The last queried DEP is located in the row of 23 in Table 1 and its degree is 40. The degree of 40 was selected as cutoff and the 24 nodes that were characterized by degree value above 40 were considered for more analysis. The results of gene ontology of the selected 24 proteins are presented in Table 2. 56 terms clustered in four classes of biological processes are presented in Table 2. Each one of the two first groups includes one term while the third group is characterized by 18 terms. The larger group contains 36 biological processes.

Discussion

As it is shown in Figure 1, the collection of queried DEPs and the added first neighbor proteins formed a scale-

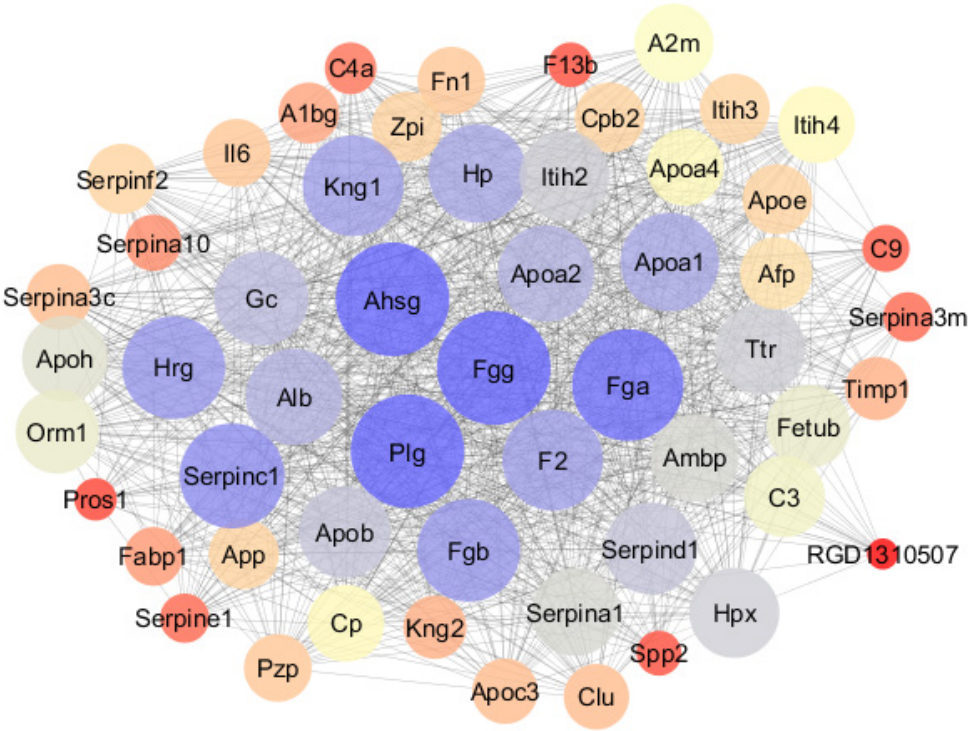

Figure 1. Network Including 5 Recognized Queried DEPs and 50 Added First Neighbors. The nodes are layout based on degree value. Red to blue color and increasing size of nodes refer to higher values of degree.

Table 1. The 55 nodes of the analyzed network and the related centrality parameters are presented

R	Display Name	Query Term	Degree	BC	CC	Stress
1	Ahsg	FETUA	54	0.017	1.000	902
2	Fgg	FGG	54	0.017	1.000	902
3	Plg		54	0.017	1.000	902
4	Fga		53	0.015	0.982	828
5	Serpinc1		50	0.013	0.931	694
6	Fgb		49	0.012	0.915	666
7	Hrg		49	0.013	0.915	692
8	F2		48	0.010	0.900	592
9	Kng1		48	0.011	0.900	602
10	Apoa1		47	0.009	0.885	540
11	Hp	HP	47	0.011	0.885	584
12	Alb		46	0.009	0.871	510
13	Apoa2		46	0.008	0.871	498
14	Gc		45	0.008	0.857	460
15	Apob		44	0.008	0.844	458
16	Serpind1		44	0.008	0.844	476
17	Hpx	HPX	43	0.007	0.831	434
18	Itih2		43	0.008	0.831	452
19	Ttr		43	0.006	0.831	396
20	Ambp		42	0.006	0.818	348
21	Serpina1		42	0.005	0.818	334
22	Apoh		41	0.005	0.806	314
23	Fetub	FETUB	40	0.006	0.794	316
24	Orm1		40	0.006	0.794	346
25	C3		39	0.005	0.783	314
26	A2m		38	0.005	0.771	292
27	Apoa4		37	0.005	0.761	272
28	Cp		37	0.004	0.761	258
29	Itih4		37	0.003	0.761	202
30	Afp		35	0.003	0.740	180
31	Apoe		34	0.003	0.730	180
32	App		34	0.003	0.730	198
33	Cpb2		34	0.003	0.730	180
34	Itih3		34	0.003	0.730	198
35	Serpinf2		34	0.005	0.730	254
36	Zpi		34	0.004	0.730	224
37	Fn1		33	0.003	0.720	188
38	Il6		33	0.003	0.720	170
39	Pzp		33	0.002	0.720	128
40	Apoc3		32	0.001	0.711	104
41	Clu		32	0.004	0.711	226
42	Serpina3c		32	0.002	0.711	106
43	Kng2		31	0.002	0.701	104
44	Timp1		31	0.003	0.701	164
45	A1bg		30	0.004	0.692	204
46	Fabp1		29	0.001	0.684	90
47	Serpina10		28	0.001	0.675	78
48	C4a		26	0.001	0.659	76
49	Serpina3m		25	0.001	0.651	96
50	Serpine1		25	0.002	0.651	100
51	C9		24	0.001	0.643	76
52	F13b		23	0.001	0.635	54
53	Spp2		23	0.000	0.635	36
54	Pros1		22	0.001	0.628	58
55	RGD1310507		17	0.000	0.593	8

Note: Three queried genes appear in the third column.

free network. In the many published documents, the importance of the scale-free network in the interpretation of the molecular mechanism is emphasized. Centrality analysis revealed that there are numbers of critical nodes that can play a role as central nodes. As it is represented in Table 1, FETUA and FGG are the top nodes based on degree value and also betweenness centrality; therefore, these two queried DEPs can be considered as hub-bottlenecks. Like FETUA and FGG, PLG and FGA appear as hub-bottleneck nodes (see Figure 1 and Table 1). Based on these results, it is possible that the two queried DEPs (FETUA and FGG) and also the two added first neighbors (PLG and FGA) be considered as the critical proteins which are dysregulated by laser irradiation.

As it is depicted in Table 2, the group of terms, which is categorized as "neutral lipid catabolic process" is not related to the central proteins. Then this group of terms was ignored from more analysis. FETUA (AHSG) is involved in the two terms of the top two groups of the term including "cysteine-type endopeptidase inhibitor activity" and "acute-phase response". FGG and PLG are involved in the 29 and 20 terms of the last group of terms respectively. FGA, the last central protein, is related to the 29 terms of the last group of terms.

It can be concluded that the critical group of terms is the group which is classed as "fibrinolysis" and the crucial proteins are FGG, FGA, and PLG. FGG is a queried up-regulated DEP and FGA and PLG are two added first neighbors. Fibrinolysis is a significant term which effects on hemostatic balance.[23] Fibrinolysis and platelet function are tied together to control blood coagulation. [24] As it can be seen in Table 2, most terms in the "fibrinolysis" group are characterized by platelet, coagulation, hemostasis, and fibrinolysis. The important role of fibrinogen in blood hemostasis and the pathological condition due to dysregulation of fibrinogen expression is described in many documents. Dysregulation of fibrinogen expression is highlighted in COVID-19 infection disease.[25] Plasminogen is an inactive form of plasmin, the enzyme that degrades fibrin and activates matrix metalloproteinases, which leads to extracellular matrix degradation.[26] The closed relationship between plasminogen and fibrinogen

Table 2. Biological processes related to the 24 top nodes of the analyzed network

GO Term	% AP	Associated protein found
Cysteine-type endopeptidase inhibitor activity	5.33	[Ahsg, Fetub, Hrg, Kng1]
Acute-phase response	7.55	[Ahsg, F2, Hp, Orm1]
Regulation of plasma lipoprotein particle levels	4.69	[Apoa1, Apoa2, Apob]
Plasma lipoprotein particle organization	8.57	[Apoa1, Apoa2, Apob]
Plasma lipoprotein particle remodeling	14.29	[Apoa1, Apoa2, Apob]
Protein-containing complex remodeling	13.64	[Apoa1, Apoa2, Apob]
Regulation of lipid catabolic process	4.62	[Apoa1, Apoa2, Apoh]
Protein-lipid complex subunit organization	7.69	[Apoa1, Apoa2, Apob]
Neutral lipid catabolic process	10.81	[Apoa1, Apoa2, Apob, Apoh]
Glycerolipid catabolic process	6.35	[Apoa1, Apoa2, Apob, Apoh]
Positive regulation of lipid catabolic process	10.00	[Apoa1, Apoa2, Apoh]
Intermembrane lipid transfer	6.82	[Apoa1, Apoa2, Apob]
Protein-lipid complex remodeling	14.29	[Apoa1, Apoa2, Apob]
Sterol transporter activity	9.38	[Apoa1, Apoa2, Apob]
Acylglycerol catabolic process	10.81	[Apoa1, Apoa2, Apob, Apoh]
Lipid transfer activity	6.82	[Apoa1, Apoa2, Apob]
Triglyceride catabolic process	11.54	[Apoa1, Apob, Apoh]
Cholesterol efflux	6.25	[Apoa1, Apoa2, Apob]
Sterol transfer activity	13.64	[Apoa1, Apoa2, Apob]
Cholesterol transfer activity	14.29	[Apoa1, Apoa2, Apob]
Regulation of coagulation	10.34	[Apoh, F2, Fga, Fgb, Fgg, Hrg, Kng1, Plg, Serpinc1]
Regulation of hemostasis	10.71	[Apoh, F2, Fga, Fgb, Fgg, Hrg, Kng1, Plg, Serpinc1]
Protein activation cascade	41.67	[Apoh, Fga, Fgb, Fgg, Serpinc1]
Blood coagulation	5.78	[Apoh, F2, Fga, Fgb, Fgg, Hrg, Kng1, Plg, Serpinc1, Serpind1]
Hemostasis	5.71	[Apoh, F2, Fga, Fgb, Fgg, Hrg, Kng1, Plg, Serpinc1, Serpind1]
Heterotypic cell-cell adhesion	6.78	[Apoa1, Fga, Fgb, Fgg]
Negative regulation of coagulation	15.09	[Apoh, F2, Fga, Fgb, Fgg, Hrg, Kng1, Plg]
Positive regulation of coagulation	12.90	[Apoh, F2, Hrg, Plg]
Negative regulation of hemostasis	15.38	[Apoh, F2, Fga, Fgb, Fgg, Hrg, Kng1, Plg]
Positive regulation of hemostasis	14.29	[Apoh, F2, Hrg, Plg]
Platelet activation	5.88	[F2, Fga, Fgb, Fgg, Hrg]
Blood coagulation, fibrin clot formation	62.50	[Apoh, Fga, Fgb, Fgg, Serpinc1]
Regulation of response to wounding	4.46	[Apoh, F2, Fga, Fgb, Fgg, Hrg, Kng1, Plg, Serpinc1]
Negative regulation of response to wounding	8.33	[Apoh, F2, Fga, Fgb, Fgg, Hrg, Kng1, Plg]
Positive regulation of response to wounding	4.60	[Apoh, F2, Hrg, Plg]
Regulation of blood coagulation	10.84	[Apoh, F2, Fga, Fgb, Fgg, Hrg, Kng1, Plg, Serpinc1]
Platelet aggregation	6.12	[Fga, Fgb, Fgg]
Positive regulation of blood coagulation	14.29	[Apoh, F2, Hrg, Plg]
Negative regulation of blood coagulation	15.69	[Apoh, F2, Fga, Fgb, Fgg, Hrg, Kng1, Plg]
Regulation of heterotypic cell-cell adhesion	16.00	[Apoa1, Fga, Fgb, Fgg]
Regulation of wound healing	5.66	[Apoh, F2, Fga, Fgb, Fgg, Hrg, Kng1, Plg, Serpinc1]
Negative regulation of wound healing	10.26	[Apoh, F2, Fga, Fgb, Fgg, Hrg, Kng1, Plg]
Positive regulation of wound healing	5.97	[Apoh, F2, Hrg, Plg]
Positive regulation of heterotypic cell-cell adhesion	21.43	[Fga, Fgb, Fgg]
Endothelial cell apoptotic process	5.08	[Fga, Fgb, Fgg]
Zymogen activation	5.97	[Apoh, Fga, Fgb, Fgg]

Table 2. Continued

GO Term	% AP	Associated protein found
Fibrinolysis	31.82	[Apoh, F2, Fga, Fgb, Fgg, Hrg, Plg]
Negative regulation of fibrinolysis	42.86	[Apoh, Hrg, Plg]
Positive regulation of vasoconstriction	6.38	[Fga, Fgb, Fgg]
Regulation of fibrinolysis	27.27	[Apoh, Hrg, Plg]
Negative regulation of epithelial cell apoptotic process	5.56	[Fga, Fgb, Fgg]
Plasminogen activation	16.00	[Apoh, Fga, Fgb, Fgg]
Regulation of extrinsic apoptotic signaling pathway via death domain receptors	5.56	[Fga, Fgb, Fgg]
Regulation of endothelial cell apoptotic process	5.45	[Fga, Fgb, Fgg]
Negative regulation of extrinsic apoptotic signaling pathway via death domain receptors	10.00	[Fga, Fgb, Fgg]
Negative regulation of endothelial cell apoptotic process	9.38	[Fga, Fgb, Fgg]

Note: Term *P* value, term *P* value corrected with Bonferroni step down, group *P* value, and group *P* value corrected with Bonferroni step down were less than 0.001. The four groups are shown in different colors and the name of the groups is bolded. %AP refers to the percentage of associated proteins.

in body hemostasis was studied about 50 years ago and is a well-known association.[27]

Many effects such as wound healing, improving muscular function, effect on bacterial growth, effect on oral mucositis in cancer patients, bone formation, dentistry, and many other subjects are attributed to LLLT.[28-31] In the present study, a significant effect of LLLT on blood hemostasis is highlighted. This finding may be a crucial point in the application of LLLT as a therapeutic tool or in preventing the disadvantage of using LLLT.

Conclusion

It can be concluded that LLLT results in the modulation of body blood hemostasis. Fibrinogen and plasminogen were highlighted as the two important elements in this process.

Ethical Considerations

This project was approved by the ethical committee of Shahid Beheshti University of Medical Sciences. (code: IR.SBMU.RETECH.REC.1400.006)

Conflict of Interests

There is no conflict of interest.

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References

1. Khalkhal E, Razzaghi M, Rostami-Nejad M, Rezaei-Tavirani M, Beigvand HH, Tavirani MR. Evaluation of laser effects on the human body after laser therapy. *J Lasers Med Sci*. 2020;11(1):91. doi: 10.15171/jlms.2020.15.
2. Smith SA, Travers RJ, Morrissey JH. How it all starts: Initiation of the clotting cascade. *Crit Rev Biochem Mol Biol.* 2015;50(4):326-36. doi: 10.3109/10409238.2015.1050550.
3. Austin AW, Wissmann T, von Känel R. Stress and hemostasis: an update. *Semin Thromb Hemost* 2013;39(08): 902-912. doi: 10.1055/s-0033-1357487
4. Raphael J, Mazer CD, Subramani S, Schroeder A, Abdalla M, Ferreira R, et al. Society of Cardiovascular Anesthesiologists clinical practice improvement advisory for management of perioperative bleeding and hemostasis in cardiac surgery patients. *J Cardiothorac Vasc Anesth.* 2019;33(11):2887-99. doi.10.1053/j.jvca.2019.04.003
5. Ogita M, Tsuchida S, Aoki A, Satoh M, Kado S, Sawabe M, et al. Increased cell proliferation and differential protein expression induced by low-level Er: YAG laser irradiation in human gingival fibroblasts: proteomic analysis. *Lasers Med Sci*. 2015;30(7):1855-66. doi: 10.1007/s10103-014-1691-4.
6. Trajano L, Sergio L, Silva C, Carvalho L, Mencalha A, Stumbo A, et al. Low-level laser irradiation alters mRNA expression from genes involved in DNA repair and genomic stabilization in myoblasts. *Laser Phys Lett*. 2016;13(7):075601. doi:10.1088/1612-2011/13/7/075601
7. Arjmand B, Vafaee R, Razzaghi M, Rezaei-Tavirani M, Ahmadzadeh A, Rezaei-Tavirani S, et al. Central Proteins of Plasma in Response to Low-Level Laser Therapy Involve in Body Hemostasis and Wound Repair. *J Lasers Med Sci*. 2020;11(4 Suppl.):S55-S9. doi: 10.34172/jlms.2020.S9.
8. Zhong X-Z, Li X-X, Zeng Y, Wang S-P, Sun Z-Y, Tang Y-Q. Dynamic change of bacterial community during dairy manure composting process revealed by high-throughput sequencing and advanced bioinformatics tools. *Bioresour. Technol.* 2020;306:123091. doi: 10.1016/j.biortech.2020.123091
9. Azodi MZ, Arjmand B, Razzaghi M, Tavirani MR, Ahmadzadeh A, Rostaminejad M. Platelet and Haemostasis are the Main Targets in Severe Cases of COVID-19 Infection; a System Bioinformatics Study. *Arch Acad Emerg Med.* 2021;9(1):e27. doi: 10.22037/aaem.v9i1.1108
10. Wu J, Vallenius T, Ovaska K, Westermarck J, Mäkelä TP, Hautaniemi S. Integrated network analysis platform for protein-protein interactions. *Nat Methods*. 2009;6(1):75-7. doi: 10.1038/nmeth.1282.
11. Tsai C-J, Ma B, Nussinov R. Protein–protein interaction networks: how can a hub protein bind so many different partners?. *Trends Biochem. Sci.* 2009;34(12):594-600. doi: 10.1016/j.tibs.2009.07.007

12. Safaei A, Tavirani MR, Oskouei AA, Azodi MZ, Mohebbi SR, Nikzamir AR. Protein-protein interaction network analysis of cirrhosis liver disease. *Gastroenterol Hepatol Bed Bench.* 2016;9(2):114-23. doi: 10.22037/ghfbb.v9i2.896
13. Wuchty S, Almaas E. Peeling the yeast protein network. *Proteomics*. 2005;5(2):444-9. doi: 10.1002/pmic.200400962.
14. Rabieian R, Abedi M, Gheisari Y. Central nodes in protein interaction networks drive critical functions in transforming growth factor beta-1 stimulated kidney cells. *Cell J.* 2017;18(4):514-531. doi: 10.22074/cellj.2017.4718
15. Harris MA, Clark J, Ireland A, Lomax J, Ashburner M, Foulger R, et al. Consortium GO. The Gene Ontology (GO) database and informatics resource. *Nucleic acids Res.* 2004;32(suppl_1):D258-D261. doi: 10.1093/nar/gkh036.
16. Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, et al. Gene ontology: tool for the unification of biology. *Nat Genet.* 2000;25(1):25-9. doi: 10.1038/75556.
17. Schlicker A, Lengauer T, Albrecht M. Improving disease gene prioritization using the semantic similarity of Gene Ontology terms. *Bioinformatics*. 2010;26(18):i561-i7. doi: 10.1093/bioinformatics/btq384.
18. Prakash T, Ramachandra NB. Integrated Network and Gene Ontology Analysis Identifies Key Genes and Pathways for Coronary Artery Diseases. *Avicenna J Med Biotechnol.* 2021;13(1):15-23. doi: 10.18502/ajmb.v13i1.4581
19. Ghatge M, Nair J, Sharma A, Vangala RK. Integrative gene ontology and network analysis of coronary artery disease associated genes suggests potential role of ErbB pathway gene EGFR. *Mol Med Rep*. 2018;17(3):4253-64. doi: 10.3892/mmr.2018.8393.
20. Rezaei Tavirani M, Mansouri V, Rezaei Tavirani S, Hesami Tackallou S, Rostami-Nejad M. Gliosarcoma protein-protein interaction network analysis and gene ontology. *Int J Cancer Manag.* 2018;11(5): e65701. doi: 10.5812/ijcm.65701.
21. Li L, Zhang N, Li S. Ranking effects of candidate drugs on biological process by integrating network analysis and Gene Ontology. *Chinese Sci Bull.* 2010;55(26):2974-80. doi: 10.1007/s11434-010-4067-6.
22. Kilik R, Bober P, Ropovik I, Beňačka R, Genči J, Nečas A, et al. Proteomic Analysis of Plasma Proteins after Low-Level Laser Therapy in Rats. *Physiol Res*. 2019;68(Suppl 4):S399-S404. doi: 10.33549/physiolres.934377.
23. Longstaff C. Measuring fibrinolysis: from research to routine diagnostic assays. *J Thromb Haemost.* 2018;16(4):652-62. doi: 10.1111/jth.13957
24. Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. *Blood rev.* 2015;29(1):17-24. doi: 10.1016/j.blre.2014.09.003.
25. Rezaei-Tavirani M, Nejad MR, Arjmand B, Tavirani SR, Razzaghi M, Mansouri V. Fibrinogen Dysregulation is a Prominent Process in Fatal Conditions of COVID-19 Infection; a Proteomic Analysis. *Arch Acad Emerg Med.* 2021;9(1):e26. doi: 10.22037/aaem.v9i1.1128
26. Collen D. The plasminogen (fibrinolytic) system. *Thromb*. Haemost.1999;82(08):259-70.
27. Lucas MA, Fretto L, McKee P. The binding of human plasminogen to fibrin and fibrinogen. *J Biol Chem.* 1983;258(7):4249-56. doi:10.1016/s0021-9258(18)32614-0
28. Bjordal JM, Bensadoun R-J, Tunèr J, Frigo L, Gjerde K, Lopes-Martins RA. A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. *Support Care Cancer.* 2011;19(8):1069-77. doi: 10.1007/s00520-011-1202-0.
29. De Marchi T, Junior ECPL, Bortoli C, Tomazoni SS, Lopes-Martins RÁB, Salvador M. Low-level laser therapy (LLLT) in human progressive-intensity running: effects on exercise performance, skeletal muscle status, and oxidative stress. *Lasers Med Sci.* 2012;27(1):231-6. doi: 10.1007/s10103-011-0955-5.
30. Pinheiro AL, Oliveira MG, Martins PPM, Ramalho LMP, de Oliveira MAM, Júnior AN, et al. Biomodulatory effects of LLLT on bone regeneration. *Laser ther.* 2000;13(1):73-9. doi: 10.5978/islsm.13.73
31. Nussbaum EL, Lilge L, Mazzulli T. Effects of low-level laser therapy (LLLT) of 810 nm upon in vitro growth of bacteria: relevance of irradiance and radiant exposure. *J clin laser med surg.* 2003;21(5):283-90. doi: 10.15171/jlms.2020.15.