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Original Research Article

Danshen, a Traditional Chinese Medicine, mitigates septic shock in patients by regulating the expression of Orosomucoid 1

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Abstract

Purpose: *To analyze the effects of the components of the traditional Chinese medicine (TCM), Danshen, in the treatment of patients with septic shock.*
Methods: *The expression profiles of three experiments on septic shock, two therapeutic experiments, and one experiment associated with TCM treatment were collected to probe into the genes related to septic shock and regulated by TCMs. Function as well as protein-protein interaction (PPI) analysis were performed with the co-regulated genes related with septic shock.*
Results: *Precisely 187 co-regulated genes associated with septic shock were observed, and were enriched in the immune response, defense response to the bacterium, as well as infection and immune pathways. Ten (10) critical genes (RETN, LCN2, ELANE, LTF, MMP8, SLPI, ARG1, HP, PGLYRP1 and ORM1) were obtained. ORM1 expression was statistically stimulated under the treatment of the mixture of four TCM components in Danshen, and an increase of ORM1 expression was shown in septic shock patients being treated with hydrocortisone.*
Conclusion: *The mixture of four TCM components in Danshen has the potential to alleviate the conditions of septic shock patients by upregulating the expression of ORM1.*

Keywords: *Sepsis, Septic shock, Traditional Chinese medicine, Danshen, Orosomucoid 1, Hydrocortisone*

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INTRODUCTION

Sepsis, a systemic inflammation caused by severe infection, injury or endotoxin, causes damage to organs or even leads to death [1,2]. Though great improvements have been made in medical therapy and organ support, and a more in-depth knowledge of the pathophysiology of sepsis has been reached, it is still a cause of mass mortality, especially in hospitals' Intensive Care Unit (ICU) [3,4]. If no special supportive or antibiotic therapy was given, the mortality rate of severe sepsis will exceed 30 % [5].

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Septic shock is a potentially fatal medical condition that occurs along with severe hypotension or hyperlactatemia caused by sepsis, and it is characterized by circulatory, cellular, and metabolic dysfunction. Septic shock has a greater mortality risk compared to sepsis alone [1,2], and the heterogeneity in the causes and clinical features of septic shock impedes the progress of its therapies, causing bad outcomes in children with septic shock [5]. Hence, more attention needs to be paid to the pathophysiology and new therapies of septic shock. With the development of sequencing, new and targeted therapies for septic shock have been explored by researchers by analyzing differentially expressed genes or gene clusters [6].

Traditional Chinese medicines (TCMs) are medicines that have existed in Asia since antiquity. The significance of TCMs in treating diseases has been revealed by recent publications. Kehui Chen (1898–1988), the first TCM pharmacologist, discovered ephedrine from the traditional Chinese herb—Ma Huang—used for treating asthma. Youyou Tu, the Nobel laureate in 2015, found artemisinin (qinghaosu), a precious gift received from the Chinese medicine and which is currently a principal therapeutic drug for treating malaria [6,7]. Compared with western medicines often with a single or major chemical component, TCMs are complex mixtures which usually contain hundreds of different chemical constituents with a large amount of sugars or proteins, making them multi-targets, making it sometimes difficult to ensure quality.

Multiple efficient and selective methods such as chromatography, electromigration and chemical fingerprinting were adopted to explore the principal component of TCMs. Wu *et al* constructed SymMap, an integrative database of traditional Chinese medicine, to help deepen the cognition of symptoms treated by TCMs for modern medicine scientists[8]. Besides, the benefit of using TCMs in treating patients with sepsis was also reported. Oxymatrine affects the prevention and treatment of the myocardial injury of rats with septic shock. Tanshinone II-A (TSN), an ingredient in Danshen, can increase the survival of septic mice by strengthening their immune system. Tanshinone II-A (TSN) ameliorates the sepsis-induced brain damage and boosts the postoperative survival in mice by suppressing the expression of *TNF-α*, *IL-6*, and *Iba-1* in the circumference blood. Liu-Shen-Wan (LSW) was reported as having the potential to reduce TNF-α, MDA and improve macrophage phagocytosis in sepsis [9-11].

Clinical researchers in TCMs divided the treatment process of sepsis into three stages: the initial, advanced and recovery stages [12]. The accessibility of gene expression data associated with sepsis and TCM components from GEO database (https://www.ncbi.nlm.nih.gov/geo/), together with the convenient statistical R package, facilitates the process of integrating results and contributes a lot in finding the potential molecular metabolism of TCMs in regulating immunity under the septic shock condition.

In this study, three datasets - GSE26378, GSE26440 and GSE13904 with data of children with septic shock were downloaded. Differentially expressed genes (DEGs) associated with the septic shock and the co-regulated septic shock genes were analyzed; functional enrichment of co-regulated genes was performed; protein-protein interactions (PPI) of genes with similar expression patterns among different septic shock data were analyzed, and based on the PPI, the hub genes related to septic shock were revealed. GSE85871, a dataset on the experiment of TCM components mixture was used to explore septic shock related genes that were statistically and differently regulated by TCMs. Two therapeutic experiments of septic shock were used to examine the expression status of genes before and after treatment.

METHODS

Download and preprocess data

To identify genes both related to sepsis and the Chinese medicine, the gene expression data associated with septic shock and the Chinese medicine were downloaded from the GEO database (https://www.ncbi.nlm.nih.gov/geo/). There are three datasets related to septic shock (GSE26378 containing 82 samples with septic shock and 21 healthy controls, GSE26440 with 98 children with septic shock and 32 normal controls, and GSE13904 with 106 children with septic shock and 18 healthy controls); two datasets associated with therapy experiments: GSE106878 (including 94 paired samples of 47 septic shock patients treated with placebo or hydrocortisone (HC)), and GSE110487 (including 31 septic shock patients, 17 responders and 14 non- responders to early therapy); and a dataset of Chinese compounds related experiment: GSE85871 with 102 TCM (traditional Chinese medicine) components. Relevant expression matrixes were annotated according to their sequencing platforms: GPL570, Affymetrix Human Genome U133 Plus 2.0 Array for GSE26378, GSE26440 and GSE13904;

GPL10295, Illumina human-6 v2.0 expression beadchip (using nuIDs as an identifier) for GSE106878; GPL10999, Illumina Genome Analyzer IIx (Homo sapiens) and GPL16791, Illumina HiSeq 2500 (Homo sapiens) for GSE110487; and GPL571, Affymetrix Human Genome U133A 2.0 Array for GSE85871. Then, they were normalized based on the quantile method of limma package and transformed by log2, if needed.

DEGs analysis

A contrast matrix containing different groups was constructed and the analysis of differentially expressed genes (DEGs) was calculated using limma package. Genes with $|\log_2 FC| > 1$ were identified as statistically differently expressed genes (DEGs) and *P* value < 0.05 was adjusted. These DEGs were collected and prepared for co-regulated gene analysis. The DEGs were visualized by the volcano plot for each septic shock experiment.

Construction and visualization of co-regulated septic shock genes

Based on the DEGs of septic shock, RobustRankAggreg package was used for the integration analysis of the gene expression of three sets of GEO septic shock data. Statistically significant co-upregulated genes and co-downregulated genes were collected and saved for downstream analysis. The R package and heatmap were applied to visualize the expression of co-regulated genes.

Gene function enrichment analysis of co-regulated septic shock gene modules

To evaluate the function of co-regulated genes, the Gene Ontology (GO) analysis was carried out using co-regulated genes, and based on the DAVID database (https://david.ncifcrf.gov/), a database that provides a systematic and comprehensive knowledge of genes and proteins. The top 5 enriched terms in each class (biological process (BP), molecular function (MF) and cell component (CC)) were visualized through circle plot. The Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis was performed based on the results from the DAVID database and presented using the bubble plot. To analyze the relationships of co-regulated septic genes, protein-protein interaction (PPI) was constructed using STRING (https://string-db.org/), an online tool that provides information on the interactions between proteins. To scan the potential hub genes widely used in cancer projects among co-regulated genes, Cytoscape software (https://cytoscape.org/) was utilized to visualize the interaction network, and MCODE, a plug-in of the Cytoscape, was used to analyze the hub genes with default parameters.

DEGs analysis between septic shock and TCMs

To identify the potential statistically significant and differentially regulated genes related to septic shock under the treatment of TCMs, a gene expression matrix of the Chinese medicine compounds experiment-GSE85871 was downloaded. DEGs was obtained via limma package with parameters mentioned above. The overlap analysis of co-regulated DEGs in septic shock and DEGs under the treatment of TCMs was performed and visualized using R package, VennDiagram. The gene expression levels between normal and treatment conditions were demonstrated by the boxplot. Expression profiles of two therapy experiments in septic shock (GSE106878 and GSE110487) were downloaded for analyzing the expression status of genes overlapped before and after the therapy.

RESULTS

Identifications of DEGs related to septic shock and TCMs

Under the treatment of the mixture of four TCM components in Danshen, 62 DEGs (310 up-regulated genes; 252 down-regulated genes) in GSE26378 (Figure 1 A), 510 DEGs (330 up-regulated genes; 180 down-regulated genes) in GSE26440 (Figure 1 B), 492 DEGs (304 up-regulated genes; 188 down-regulated genes) in GSE13904 (Figure 1 C), and 427 DEGs (215 up-regulated genes; 212 down-regulated genes) in GSE85871were obtained through DEGs analysis (Figure 1 D).

Co-regulated genes related to septic shock

A total of 187 co-regulated septic shock genes (125 up-regulated and 62 down-regulated genes) were obtained through co-regulated gene analysis by using RobustRankAggreg package (Figure 2 A). It was indicated by GO enrichment analysis that the differentially regulated genes were related to extracellular exosome, plasma membrane, extracellular space and extracellular region function (Figure 2 B and C). As shown by the KEGG analysis, those co-regulated genes were enriched in infection pathways such as *Staphylococcus aureus* infection, HTLV-I

infection, and Epstein-Barr virus infection; immune system signaling such as TNF signaling pathway, NOD-like receptor signaling pathway, intestinal immune network for IgA production and antigen processing & presentation; and molecular processes including cytokine-cytokine receptor interaction, complement and coagulation cascades (Figure 3).

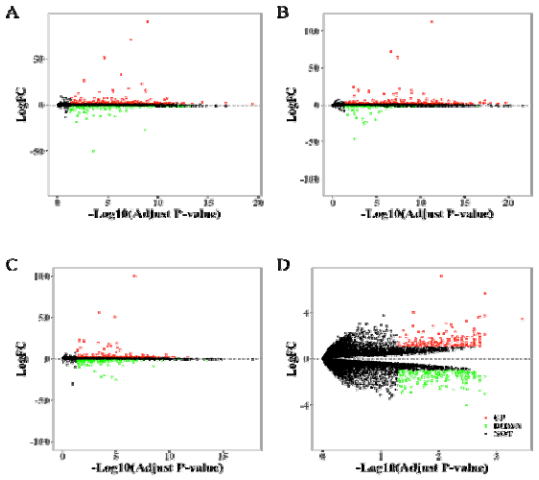

Figure 1: Differentially expressed genes related to septic shock and the mixture of four traditional Chinese medicine components in Danshen. DEGs were visualized using the volcano plot. The upregulated genes and downregulated genes were marked in red and green dots, respectively. A, B, C and D represents the volcano plots of GSE26378, GSE26440, GSE13904 and GSE85871

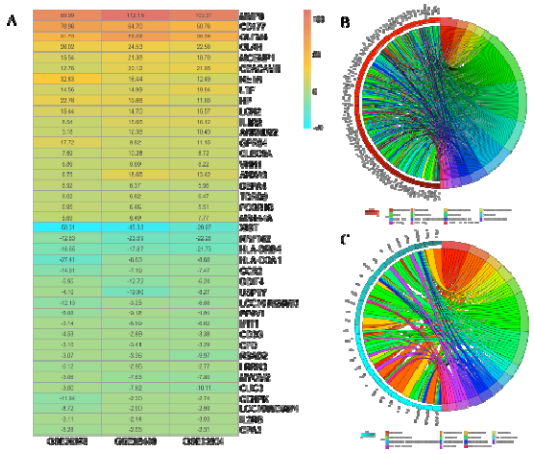

Figure 2: Co-regulated septic shock genes. (A) Visualization of the expression level of co-regulated genes amongst the septic shock data was constructed using the top 20 genes. The circle plot shows the results of GO analysis of up-regulated (B) and down-regulated (C) genes. Fold change was ordered and indicated by red (up-regulated genes) and blue (the down-regulated genes)

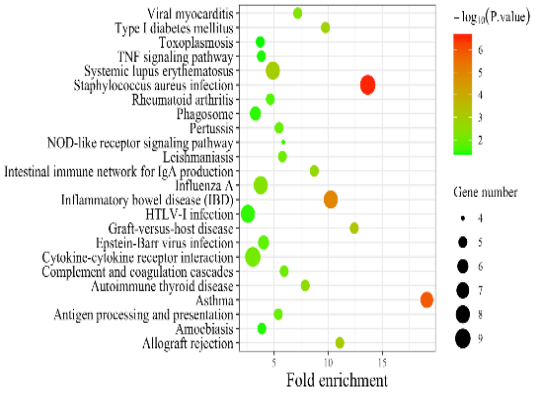

Figure 3: Bubble plot of co-regulated septic shock genes. The significance level, *P*-value, was transformed using -log$_{10}$ (*P* value) and ranked by red-yellow-green. X-axis refers to fold enrichment; Y-axis refers to pathways; and the size of dots indicates the number of genes

PPI of co-regulated genes related to septic shock

PPI analysis of results indicate that co-regulated septic shock genes contains two potential gene modules, or gene clusters (Figure 4 A). 10 hub genes (*RETN*, *LCN2*, *ELANE*, *LTF*, *MMP8*, *SLPI*, *ARG1*, *HP*, *PGLYRP1* and *ORM1*) were revealed by the hub genes analysis *via* MCODE plug-in of Cytoscape (Figure 4 B, Table 1).

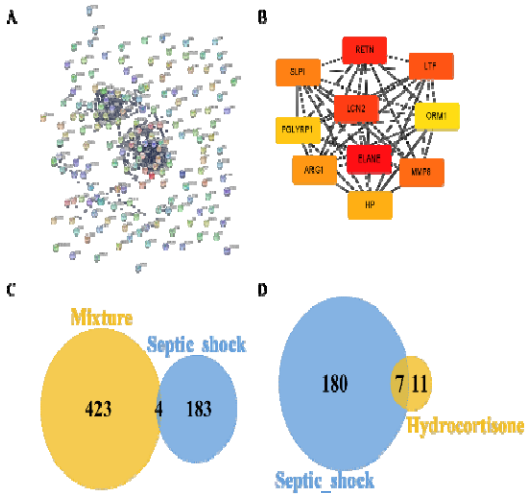

Figure 4: PPI, hub genes of co-regulated genes associated with septic shock, and Venn plots of co-regulated genes and DEGs under the TCMs therapy treatment. (A) shows the protein-protein interaction of co-regulated septic shock genes; and the interactions of the top 10 hub genes were extracted (B). Venn plot of septic shock genes and the mixture of four TCM components in Danshen (C) as well as hydrocortisone treatment (D)

Table 1: The top 10 hub genes ranked using MCC method. ***Note:*** The information of the top 10 hub genes obtained from STRING interactions analysis; the fold changes of the expression level of DEGs was transformed by log method and two decimals were reserved

Rank	Symbol	Gene description	LogFC
1	*ELANE*	Elastase, Neutrophil Expressed	5.15
2	*RETN*	RETN	20.59
3	*LCN2*	Lipocalin 2	15.24
4	*LTF*	Lactotransferrin	16.47
5	*MMP8*	Matrix Metallopeptidase 8	100.82
6	*SLPI*	Secretory Leukocyte Peptidase Inhibitor	2.67
7	*ARG1*	Arginase 1	4.90
8	*HP*	Haptoglobin	1.81
9	*PGLYRP1*	Peptidoglycan Recognition Protein 1	3.70
10	*ORM1*	Orosomucoid 1	2.61

Four co-regulated genes between septic shock and TCMs

Four genes, *GADD45A*, *CYP1B1*, *ORM1* and *ADM* were obtained from the overlap analysis with the data set of co-regulated septic shock genes containing 187 genes and 427 DEGs (Figure 4 C) under the treatment of the four TCM mixture of Danshen (tanshinone IIA, salvianic acid A sodium, protocatechuic aldehyde, salvianolic acid B).

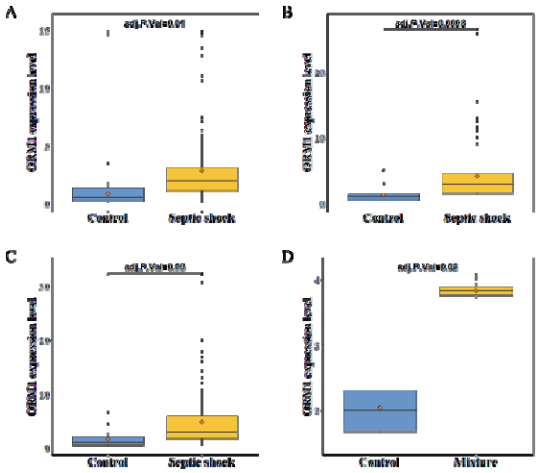

Figure 5: Gene expression levels of *ORM1* under septic shock and under the treatment of TCMs. ***Note:*** *ORM1* expression levels in three septic shock datasets (A: GSE26378; B: GSE26440; C: GSE13904) and a septic shock dataset treated by the mixture of four TCM components in Danshen (D, GSE85871) were visualized via boxplots. The colors of dark blue and yellow were used to indicate ORM1 expression levels in the normal and treatment conditions, respectively

The hub gene, ORM1, with higher expression in patients with septic shock, (Figure 5 A - C), was statistically and significantly upregulated under the treatment with the mixture of the four TCM components of Danshen (Figure 5D). Seven co-regulated septic shock genes (*CCR3*, *DAAM2*, *PRSS33*, *VSIG4*, *CD163*, *FKBP5* and *PI3*) were differentially expressed under hydrocortisone treatment (Figure 4 D), and none of them were significantly regulated under the treatment of TCMs.

DISCUSSION

187 co-regulated genes related to septic shock were found in this study by analyzing the three experiments performed on children with septic shock from the GEO database. Four genes, *GADD45A*, *CYP1B1*, *ORM1* and *ADM* of them were statistically and differentially regulated in the experimental treatment under TCMs. Ten hub genes, *RETN*, *LCN2*, *ELANE*, *LTF*, *MMP8*, *SLPI*, *ARG1*, *HP*, *PGLYRP1* and *ORM1* were obtained through PPI analysis based on STRING, followed by the analysis of the hub genes via the Cytoscape software. The hub gene, *ORM1*, was significantly increased under the treatment of TCMs, which indicated that TCMs potentially modulate the inflammation of organs or tissues in response to septic shock, and by regulating the expression of *ORM1*.

It was revealed by previous studies that the expression of two gene sets have the potential to be septic diagnostic tools [13]. However, only one gene of the gene sets, *ORM1*, was observed in this study. Lu focused in detail on the common expression patterns of genes across three sepsis data. In this study, the protein-protein interactions between the co-regulated genes were predicted with STRING database, instead of the expression patterns. It was employed to explore relevant hub genes. In addition, three experiments associated with septic shock were collected for this study. Ten co-regulated genes associated with the septic shock (including nine up-regulated genes (*OLFM4*, *ORM1*, *CEP55*, *S100A12*, *LRG1*, *CEACAM8*, *MS4A4A*, *PLSCR1*, *IL1R2*) and one down-regulated gene, *IL2RB*), previously considered as sepsis-related genes, were observed in this study, and their potential as diagnostic agents for children with septic shock was validated.

Orosomucoid 1 (alpha-1-acid glycoprotein 1, *ORM1*), is a primary acute-phase plasma protein, and was enhanced under physical trauma conditions, bacterial infection and inflammation [14]. The potential role of *ORM1* in sepsis was revealed by previous studies. Barroso-Sousa

reported the independent association of the down-regulation of *ORM1* and 96 h mortality of patients, with severe sepsis [15]. Gemelli and his colleagues found that Vitamin D could enhance the expression of *ORM1*, which inhibits the expression of pro-inflammatory factor-cytokines (TNF-α, and IL-6), and promotes the expression of *CD163* [16]. *ORM1* also protects against oxidative stress caused by hemolysis in monocytes THP-1 cells and peripheral blood mononuclear cells, by up-regulating the expression of *CD163* via *TLR4*/*CD14* pathway. In this analysis, the treatment of the mixture of four TCM components in Danshen (tanshinone IIA, salvianic acid A sodium, protocatechuic aldehyde and salvianolic acid B) enhanced the expression of *ORM1*.

No significant changes of the expression of *TLR4* or *CD14* was shown under the treatment of TCMs. *ORM1* expression was not significantly increased under the treatments of other TCM components in GSE85871, including the treatments of tanshinone IIA, salvianic acid A sodium, protocatechuic aldehyde and salvianolic acid B, respectively, which indicates that it is the complicated interaction among the four components in Danshen (tanshinone IIA, salvianic acid A sodium, protocatechuic aldehyde and salvianolic acid B), and not just the individual or single ingredient of Danshen, that stimulates the expression of *ORM1*.

To explore the effects of *ORM1* and *CD163* in the therapy of sepsis, the expression of *ORM1* and *CD163* were analyzed with two experiments on the treatment of sepsis (GSE106878, septic shock patients treated by hydrocortisone, an effective therapeutic drug used in severe sepsis and GSE110487, septic shock patients treated by early supportive hemodynamic therapy) based on the GEO database. *CD163* was statistically as well as significantly up-regulated in patients with septic shock treated by hydrocortisone. This indicates that *CD163* was involved in the treatment process of septic shock by hydrocortisone, and an increased trend was shown in *ORM1* expression (not statistically significant) under the treatment with hydrocortisone.

However, *CD163* was not statistically and differentially regulated under the treatment by the mixture of the four components of Danshen (tanshinone IIA, salvianic acid A sodium, protocatechuic aldehyde and salvianolic acid B). Given the fact that the absence of the expression matrix of sepsis treated by TCMs, and the limited information gained from the current studies, more experiments are needed to be constructed to explore the relationships between *CD163* and *ORM1*, and the roles of TCMs in treating septic shock patients.

Nevertheless, this study revealed the potential of the mixture of four components of Danshen (tanshinone IIA, salvianic acid A sodium, protocatechuic aldehyde and salvianolic acid B) in regulating septic shock by influencing the expression of *ORM1*.

CONCLUSION

The mixture of four TCMs in Danshen, *viz*, tanshinone IIA, salvianic acid A sodium, protocatechuic aldehyde, salvianolic acid B, have the potential to ameliorate the conditions of patients with septic shock by improving the expression of *ORM1*.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Guangjun Jin conducted most of the analysis of data. Weizhang Zhong wrote the manuscript and Li Yu revised the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. *Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama-Journal of the American Medical Association. 2016; 315(8): 801-810.*

2. Bone RC, Sibbald WJ, Sprung CL. The Accp-Sccm Consensus Conference on Sepsis and Organ Failure. Chest. 1992; 101(6): 1481-1482.
3. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, Angus DC, Reinhart K, International Forum of Acute Care T. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. Am J Respir Crit Care Med. 2016; 193(3): 259-272.
4. Cohen J. The immunopathogenesis of sepsis. Nature. 2002; 420(6917): 885-891.
5. Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkey AJ. Two Decades of Mortality Trends Among Patients With Severe Sepsis: A Comparative Meta-Analysis. Critical Care Medicine. 2014; 42(3): 625-631.
6. Chen KK. A pharmacognostic and chemical study of ma huang (Ephedra vulgaris var. helvetica). 1925. J Am Pharm Assoc (2003). 2012; 52(3): 406-412.
7. Tu Y. The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine. Nat Med. 2011; 17(10): 1217-1220.
8. Wu Y, Zhang F, Yang K, Fang S, Bu D, Li H, Sun L, Hu H, Gao K, Wang W, et al. SymMap: an integrative database of traditional Chinese medicine enhanced by symptom mapping. Nucleic Acids Res. 2019; 47(D1): D1110-D1117.
9. Gao M, Ou H, Jiang Y, Wang K, Peng Y, Zhang H, Yang M, Xiao X. Tanshinone IIA attenuates sepsis-induced immunosuppression and improves survival rate in a mice peritonitis model. Biomed Pharmacother. 2019; 112: 108609.
10. Xiong CQ, Zhou HC, Wu J, Guo NZ. The Protective Effects and the Involved Mechanisms of Tanshinone IIA on Sepsis-Induced Brain Damage in Mice. Inflammation. 2019; 42(1): 354-364.
11. Ma H, Kou J, Zhu D, Yan Y, Yu B. Liu-Shen-Wan, a traditional Chinese medicine, improves survival in sepsis induced by cecal ligation and puncture via reducing TNF-alpha levels, MDA content and enhancing macrophage phagocytosis. Int Immunopharmacol. 2006; 6(8): 1355-1362.
12. Zhao GZ, Chen RB, Li B, Guo YH, Xie YM, Liao X, Yang YF, Chen TF, Di HR, Shao F, et al. Clinical practice guideline on traditional Chinese medicine therapy alone or combined with antibiotics for sepsis. Annals of Translational Medicine. 2019; 7(6).
13. Lu J, Li Q, Wu Z, Zhong Z, Ji P, Li H, He C, Feng J, Zhang J. Two gene set variation indexes as potential diagnostic tool for sepsis. Am J Transl Res. 2020; 12(6): 2749-2759.
14. Luo Z, Lei H, Sun Y, Liu X, Su DF. Orosomucoid, an acute response protein with multiple modulating activities. J Physiol Biochem. 2015; 71(2): 329-340.
15. Barroso-Sousa R, Lobo RR, Mendonca PR, Memoria RR, Spiller F, Cunha FQ, Pazin-Filho A. Decreased levels of alpha-1-acid glycoprotein are related to the mortality of septic patients in the emergency department. Clinics (Sao Paulo). 2013; 68(8): 1134-1139.
16. Gemelli C, Martello A, Montanari M, Zanocco Marani T, Salsi V, Zappavigna V, Parenti S, Vignudelli T, Selmi T, Ferrari S, et al. The Orosomucoid 1 protein is involved in the vitamin D - mediated macrophage de-activation process. Exp Cell Res. 2013; 319(20): 3201-3213.