Study on the mechanism of Jiawei Linggui Zhugan Decoction in the treatment of myelodysplastic syndrome based on network pharmacological analysis

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Article History Received 5 June 2021 Accepted 25 July 2021 Published 30 September 2021

Cite this Article MO Binyan. Study on the mechanism of Jiawei Linggui Zhugan Decoction in the treatment of myelodysplastic syndrome based on network pharmacological analysis [J]. Medical Research, 2021.3(3):50-64, [http://dx.doi.org/mrhc/10.6913/MRHC.202109_3\(3\).0006](http://dx.doi.org/mrhc/10.6913/MRHC.202109_3(3).0006)

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Abstract the research method of network pharmacology is used to explore the material basis and mechanism of modified Linggui Zhugan Decoction in the treatment of myelodysplastic syndrome. Methods: the main active components of 8 traditional Chinese medicines of Jiawei Linggui Zhugan Decoction were searched through tcmsp database, and the target was predicted. The relevant targets of myelodysplastic syndrome were searched through geo database, and the common action targets were obtained by intersection of traditional Chinese medicine targets and disease targets. The core targets were selected by topological analysis with Cytoscape software. Finally, go-bp biological function enrichment and KEGG pathway analysis were carried out based on R software. Results: according to the database analysis, there were 248 active compounds and 3695 targets in the modified Linggui Zhugan decoction, of which 34 were common targets with metabolic syndrome; Through the topological analysis of common targets, 9 core targets were selected. Go-bp biological function enrichment and KEGG pathway analysis found that it can play its therapeutic role through p53, AGE-RAGE, cellular sensitivity, NF KB and other signal pathways. Conclusion: modified Linggui Zhugan decoction may play a therapeutic role through p53 signaling pathway, AGE-RAGE signaling pathway, cellular sensitivity, NF kappa B signaling pathway and cell cycle, so as to provide a new scientific basis for its clinical and basic research.

Key Words Jiawei Linggui Zhugan Decoction; myelodysplastic syndrome; network pharmacological analysis

Myelodysplastic syndromes (MDS) are a group of heterogeneous myeloid tumors originated from hematopoietic stem cells. Its basic pathological changes are clonal hematopoietic stem and progenitor cell dysplasia (dysplasia), resulting in ineffective hematopoiesis and increased risk of malignant transformation [1]. It has a high risk of transformation to acute myeloid leukemia (AML). MDS is defined as "marrow toxin labor" in traditional Chinese medicine. Its pathogenesis is characterized by evil excess and positive deficiency, mixed deficiency and excess, toxin and blood stasis as evil excess, and deficiency of Qi, blood and Yin and Yang as positive deficiency [2]. At present, there is no standard treatment scheme for MDS in traditional Chinese and Western medicine, and it is not clear whether there is correlation between TCM syndrome changes and disease genetics and gene changes in different risk stratification. Some scholars [3] analyzed the medication law and medication of traditional Chinese medicine in the treatment of myelodysplastic syndrome in recent 20 years, and found that the basic treatment methods in the treatment of myelotoxic labor are mainly strengthening spleen and Qi, tonifying kidney and filling marrow, detoxifying and removing blood stasis Linggui Zhugan Decoction in Treatise on febrile diseases mainly treats the syndrome of deficiency of Yang Qi in middle Jiao, loss of healthy movement of spleen and accumulation of dampness. The adverse reactions of MDS can be attributed to the deficiency of Yang Qi and the internal flooding of phlegm. On the basis of Linggui Zhugan decoction, add the products of Tonifying Qi and strengthening the spleen, warming yang and removing turbidity to form the modified Linggui Zhugan Decoction of Warming Yang and Tonifying Qi, removing turbidity and removing phlegm. The prescription consists of 12 traditional Chinese medicines such as Poria cocos, Cinnamon Twig, Atractylodes macrocephala, roasted licorice, Codonopsis pilosula, astragalus, yam, epimedium, Morinda officinalis, tangerine peel, ginger Pinellia ternata and coix seed. Clinically, it is mainly used to treat the syndrome of deficiency of spleen and kidney yang [4-7]. Traditional Chinese medicine compound has the coordinated role of multi-component, multi-target and multi link in the treatment of diseases. Network pharmacology is through the cross application of multi disciplines and the analysis and re integration of the overall biological network, from predicting and identifying the action target of traditional Chinese medicine compound, clarifying the action mechanism, scientifically explaining the formula law Discover new indications and apply it in combination with omics technology, build a multi-level network model to explain the multi-component and multi-target drug treatment mechanism from the aspects of gene distribution, molecular function and signal

pathway, which is suitable for the study of traditional Chinese medicine compounds 8]. This study applied network pharmacology technology to explore the target and mechanism of Jiawei Linggui Zhugan Decoction in the treatment of MDS, so as to provide a new scientific basis for its clinical and basic research in the future.

1. Materials and methods

1.1 screening of active components and target genes.

The tcmsp platform was used under the conditions of drug like characteristics $DL \geq 0.18$ and oral bioavailability $ob \geq 30\%$ (<https://tcmsp-e.com/>) Screen the effective components of Poria cocos, Cinnamon Twig, Atractylodes macrocephala, licorice, Codonopsis pilosula, astragalus, yam, epimedium, Morinda officinalis, tangerine peel, Pinellia ternata, coix seed and other traditional Chinese medicine. The predicted targets of screened compounds come from the drug library (<https://www.drugbank.ca/>) database and validated literature.

1.2 acquisition of differential genes.

Gene sample series of patients with myelodysplastic syndrome and healthy people: gse16236 is from the geosynchronous orbit database (<https://www.ncbi.nlm.nih.gov/geo/>) Obtained. The script runs in perl-5.30.2.1 (Perl) software, and the gene probe names are annotated as gene symbols and grouped. The "limma" package is installed in Perl software, and the sample values are corrected and $\log_2(\log_{fc})$ converted. The samples with $P \text{ value} < 0.005$ and $|\log_2\text{fold change}| > 1$ were screened and considered to have statistically significant gene differences. The gene volcano map of the sample was generated by r3.6.3 software, and the top 20 genes with the most significant up-regulation and down-regulation were selected to draw the heat map.

1.3 traditional Chinese medicine compound - disease control network.

The intersection genes of disease difference genes and target genes of traditional Chinese medicine and the effective components of traditional Chinese medicine were obtained by Perl software. Then, the traditional Chinese medicine compound disease regulation network was generated by using Cytoscape 3.7.2 software.

1.4 protein interaction network and topology analysis.

The "bisogenet, cytonac" package is installed in Cytoscape 3.7.2 software, the intersection gene is input, and the parameter "Homo sapiens" is selected. The data for constructing protein-protein interaction network comes from six main experimental research databases: human protein reference database, interaction protein database, interaction dataset biological database, human protein reference database, complete molecular interaction database, molecular interaction database and biomolecular interaction network database. The method of "input node and its neighbors" is selected to obtain the producer price index network, and the topology

analysis is carried out according to its network centrality.

1.5GO and KEGG concentration analysis.

R packages including "colorspace", "stringi" and "ggplot2" are installed in software R 3.6.3. A Bioconductor package including "dose", "clusterprofiler" and "enrichplot" is used for go and genome Encyclopedia (KEGG) enrichment analysis. The function "enrichgo" is used for go enrichment analysis. The database is org.hs.eg.db (DOI: 10.18129/http://B9.bioc.org.Hs.eg.db); “ Enrich KEGG "function is applied to KEGG enrichment analysis, and the database is KEGG database (https://www.kegg.jp/). As for the parameters of the two functions, the species is set to "yes" and the filter value (i.e. p value and Q value) is set to 0.05. The first 20 enrichment results were visualized as bar graphs, and the KEGG regulatory network was generated by cystocape 3.7.2 software.

2. Results

2.1. Screening of active ingredients and target genes. In the database of traditional Chinese medicine decoction pieces, ob $\geq$ 30% and DL $\geq$ 0.18 were selected. Results 248 active ingredients were obtained, including Poria cocos 15, Cinnamon Twig 7, Atractylodes macrocephala 7, licorice 92, Codonopsis pilosula 21, Astragalus 20, yam 16, Epimedium 23, Morinda officinalis 20, tangerine peel 5, Pinellia ternata 13 and coix seed 9 (Table 1). The target was predicted in the drug library database. Finally, 3695 targets were obtained, including 23 Atractylodes macrocephala, 146 Morinda officinalis, 173 Pinellia ternata, 96 tangerine peel, 215 Codonopsis pilosula, 30 Poria cocos, 1769 licorice, 74 Cinnamon Twig, 463 Astragalus, 145 yam, 512 epimedium and 49 coix seed.

Table 1 total effective components of modified Linggui Zhugan
Decoction

traditional Chinese medicine	OB (median)	DL (median)	Drug fraction
Atractylodes macrocephala	54.07	0.30	7
Tangerine peel	59.29	0.51	5
Coix seed	36.91	0.55	9
Morinda officinalis	46.09	0.38	20
Epimedium	41.88	0.48	23
Yam	43.80	0.61	16
Astragalus	49.44	0.78	20
Cinnamon Twig	48.96	0.27	7
Poria cocos	37.96	0.81	15

Codonopsis			
pilosula	42.56	0.58	21
Ginger			
Pinellia			
ternata	38.69	0.32	13
roasted			
licorice	49.01	0.42	92

2.2 differential gene screening. By comparing 7 normal samples and 7 disease samples in geo database, a total of 21654 differential genes were obtained, including 10876 up-regulated genes and 10778 down-regulated genes. After screening with P value < 0.005 and $|\log_2\text{chang}| > 1$, a total of 40 up-regulated genes and 890 down-regulated genes were obtained. As shown in the gene volcano map (Figure 1), the differential genes in the disease samples are normally distributed, and the number of significantly up-regulated genes is more than that of significantly down-regulated genes. Figure 2 and table 2 list the top 20 genes with the most significant up-regulation and down-regulation.

Figure 1: Gene volcano map shows the gene distribution in disease samples. Red and green represent upregulated genes ($\log_{FC} > 0$) and downregulated genes ($\log_{FC} < 0$), respectively, whereas black indicates no significant difference.

Figure 2: Gene heat map. In the gene heat map, red and green represent upregulated ($\log_{2}FC > 0$) and downregulated ($\log_{2}FC < 0$) genes in the sample, respectively, whereas black represents no significant difference. The first seven samples were from healthy people and the last seven samples were from MDS patients.

Table 2: The first 20 genes that are upregulated and downregulated.

Gene ID	logFC	P.Value	Regulation direction
PXMP2	2.784180724	5.11E-10	Up
MGST2	2.756580633	3.08E-08	Up
MYB	3.159585372	3.67E-08	Up
FAH	1.797944821	3.70E-08	Up
IL18	4.306462429	5.75E-08	Up
TTK	3.200052102	7.72E-08	Up
KIAA0101	3.053387133	1.29E-07	Up
LOC81691	3.139047393	1.32E-07	Up
DTL	3.390996827	1.41E-07	Up
TUBB	1.837370969	1.46E-07	Up
TYMS	2.439412418	2.44E-07	Up
RUVBL2	1.576639153	3.05E-07	Up
C11orf74	3.262040204	3.13E-07	Up
BTK	2.650664556	3.15E-07	Up
RAB13	4.866134204	3.23E-07	Up
RNASEH2A	2.420562765	3.51E-07	Up
CREG1	2.792324362	5.38E-07	Up
FES	2.524576148	5.46E-07	Up
MAP7	2.147176276	6.16E-07	Up

DHFR	2.493117429	6.71E-07	Up
BCL11B	-4.617963546	7.49E-14	Down
KLRB1	-6.633700429	4.41E-13	Down
CD3D	-5.514226704	2.85E-12	Down
GZMK	-6.774806985	3.21E-12	Down
RORA	-3.8416655	4.32E-12	Down
TRAC	-4.207992816	4.79E-12	Down
GATA3	-4.902423245	6.67E-12	Down
IL7R	-6.125276663	1.17E-11	Down
LY9	-3.438171602	1.91E-11	Down
CAMK4	-3.739913633	2.83E-11	Down
NELL2	-5.536562735	9.12E-11	Down
CD247	-4.958245995	2.98E-10	Down
CD3G	-4.912847939	3.29E-10	Down
LEF1	-2.816476398	4.40E-10	Down
CD28	-2.435598765	4.81E-10	Down
CD2	-5.687842694	5.75E-10	Down
IL2RB	-4.834820138	6.72E-10	Down
CD8A	-6.252293245	8.31E-10	Down
RASGRP1	-6.223615255	8.60E-10	Down
LCK	-5.296255704	1.01E-09	Down

Figure 3: TCM compound-disease regulatory network. This network shows the targeted relationship between the active components of TCM and the intersection genes.

2.3. Construct the disease control network of traditional Chinese medicine compound. As listed in Table 3, there are 34 cross genes (sorted by logfc). The targeting relationship between active components of traditional Chinese medicine and cross genes is presented by traditional Chinese medicine compound disease regulation network (Fig. 3). Glycyrrhiza uralensis and

epimedium have the most effective components and the most related target genes, indicating that Glycyrrhiza uralensis and epimedium are the most effective components in flavoring. Quercetin, luteolin, baicalein, kaempferol and kaempferol were associated with 27, 12, 12, 9 and 9 target genes, respectively. Therefore, they are divided into multi-target and multi effect compounds. The gene PTGS2 is related to the highest number of active components, followed by ptgs1, ccna2, chek1, DPP4, NCOA1 and nr3c2.

Table3 The 34 intersection genes sorted by logFC

Intersection gene	logFC	P.Value
PTGS2	3.195516612	0.002724576
DPP4	-2.042879806	3.94E-05
NCOA1	-1.555467735	0.000955443
PTGS1	1.925801449	0.000127688
BCL2	-1.106435112	0.001414351
BAX	1.081456867	0.0015569
NR3C2	-1.792729612	0.000205379
CCNA2	1.412411668	0.000929308
RELA	-1.024765102	0.002945479
VEGFA	1.299069276	0.005458024
CDK1	-1.976943408	2.56E-05
CCNB1	2.786600378	0.000766121
MPO	5.207174429	0.000302505
FABP5	2.33885498	0.00212477
PLAU	1.503381949	0.000138631
CA2	3.747894796	0.004538287
CAT	2.445206878	6.94E-07
GSTP1	1.64419627	5.46E-05
AKR1C1	1.033521184	0.002917142
CHEK1	1.759436347	2.92E-06
PLA2G4A	2.063746776	0.000151476
CDK4	2.420762367	2.31E-05
PCNA	1.316517949	0.004171207
BIRC5	2.178626969	5.53E-06
TOP2A	1.545251296	2.54E-05
NUF2	2.213336413	0.000276736
NR3C1	-2.047429276	6.75E-05
VCAM1	-2.648208311	6.84E-06
EIF6	1.007453495	9.25E-05
IL1B	2.371850622	0.00197242
CXCL2	1.256305765	0.000555994
CHEK2	1.46428626	0.000738435
ACPP	1.350374531	0.002174196
IGFBP3	-1.645689128	1.03E-06

2.4. Protein interaction network and topology analysis. In PPI networks, the degree centrality (DC) of a node is only its number of edges. The higher the degree, the more central the node is. Centrality (BC) captures the location of points between other nodes. Specifically, it is the ratio of the number of shortest paths through the node to the total number of shortest paths in the network. DC and BC reflect the influence of corresponding nodes in the whole network. They describe topological centrality based on the connectivity and controllability of the network. The combination of DC value and BC value has been proved to be effective for screening reliable important proteins. As shown in Figure 4, 2153 protein nodes and 54285 edges were obtained. After screening in the case of $DC > 61$ and BC range 300 – 8669, table 4 shows 30 proteins (in descending order of degree), with a total of 208 edges. Among the 30 proteins, 9 proteins are the predicted targets of active components, including obsl1, MCM2, FN1, YWHAZ, Rnf2, Myc, VCAM1, VCP, APP and EP300.

Figure 4: Topological analysis of the protein-protein interaction network. Herein, 2153 protein nodes were obtained according to the intersection genes. After screening by $DC > 61$, and the first 30 proteins were extracted according to BC for the second time.

Table4 Topological analysis results by degree—the first 30 proteins

Gene name	Annotation	Degree	Betweenness
OBSL1	obscurin like 1	313	1773.209931
MCM2	minichromosome maintenance complex component 2	443	5673.5801
FN1	fibronectin 1	478	4221.359247
YWHAZ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta	294	2547.354854
RNF2	ring finger protein 2	319	3504.341521
MYC	v-myc avian myelocytomatosis viral oncogene homolog	259	2369.390721
VCAM1	vascular cell adhesion molecule 1	451	3065.501965
VCP	valosin containing protein	269	1929.993847
APP	amyloid beta precursor protein	435	2137.885425
EP300	E1A binding protein p300	296	2339.558054
CAND1	cullin associated and neddylation dissociated 1	309	2394.916976

BRCA1	BRCA1, DNA repair associated	274	2498.175263
VHL	von Hippel-Lindau tumor suppressor	252	1906.607102
COPS5	COP9 signalosome subunit 5	359	3308.766663
ITGA4	integrin subunit alpha 4	425	3759.3985
NPM1	nucleophosmin	322	2947.713038
HSP90AA1	heat shock protein 90 alpha family class A member 1	311	2298.425613
HUWE1	HECT, UBA and WWE domain containing 1, E3 ubiquitin protein ligase	262	2131.329855
NTRK1	neurotrophic receptor tyrosine kinase 1	675	8046.181383
UBC	ubiquitin C	354	2804.304879
CUL1	cullin 1	341	3049.906746
CUL3	cullin 3	476	6074.895528
EGFR	epidermal growth factor receptor	305	1761.559249
SNW1	SNW domain containing 1	243	2036.189283
ESR1	estrogen receptor 1	425	6371.73401
XPO1	exportin 1	362	2273.249802
HDAC5	histone deacetylase 5	255	2111.011323
CUL7	cullin 7	368	2848.281378
TP53	tumor protein p53	480	7848.577396
CDK2	cyclin dependent kinase 2	442	5318.742428

2.5. Go function analysis and KEGG enrichment of related targets. Go enrichment analysis elucidates gene function from three aspects: biological process, cell composition and molecular function. BP is mainly involved in response to acid chemical, cellular response to drug, response to oxygen levels, etc; CC is mainly involved in cyclin dependent protein kinase holoenzyme complex, serine / threonine protein kinase complex, protein kinase complex, etc., while MF is mainly involved in peroxidase activity, oxidant activity, acting on peroxide as acceptor, antioxidant activity, etc (Figure 5). According to the KEGG enrichment results, the mechanism of modified Linggui Zhugan Decoction in the treatment of myelodysplastic syndrome is mainly concentrated in p53 signaling pathway, AGE-RAGE signaling pathway, cellular sensitivity, NF kappa B signaling pathway, cell cycle and other pathways (Fig. 6). The genes associated with the most pathways were BCL2, RELA, Bax, CDK4, VCAM1, IL1B, CDK1, CCNB1, CHEK1, CHEK2 (Fig. 7 and table 5).

Figure 5: GO enrichment analysis of GGQL targets in treating UC. The horizontal axis of the BP and MF column represents the number of genes enriched in each item, and the color represents the enrichment significance based on the corrected P value.

Figure 7: KEGG relational regulatory network. This network shows the relationship between the enriched 12 pathways and 9 genes, and the size of the graph shows the number of pathways or genes connected.

Table5 The enrichment pathways corresponding to intersection genes

ID	Description	geneID	GeneRatio	Count
hsa0415	p53 signaling pathway	BCL2/BAX/CDK1/CCNB1/CHEK1/CDK4/CHEK2/IGFBP3	8/32	8
hsa04933	AGE-RAGE signaling pathway in diabetic complications	BCL2/BAX/RELA/VEGFA/CDK4/VCAM1/IL1B	7/32	7
hsa04218	Cellular senescence	CCNA2/RELA/CDK1/CCNB1/CHEK1/CDK4/CHEK2/IGFBP3	8/32	8
hsa04064	NF-kappa B signaling pathway	PTGS2/BCL2/RELA/PLAU/VCAM1/IL1B/CXCL2	7/32	7
hsa04110	Cell cycle	CCNA2/CDK1/CCNB1/CHEK1/CDK4/PCNA/CHEK2	7/32	7
hsa01524	Platinum drug resistance	BCL2/BAX/GSTP1/BIRC5/TOP2A	5/32	5
hsa05418	Fluid shear stress and atherosclerosis	BCL2/RELA/VEGFA/GSTP1/VCAM1/IL1B	6/32	6
hsa05222	Small cell lung cancer	PTGS2/BCL2/BAX/RELA/CDK4	5/32	5

hsa051 61	Hepatitis B	BCL2/BAX/CCNA2/RELA/PCNA/BIRC5	6/32	6
hsa046 68	TNF signaling pathway	PTGS2/RELA/VCAM1/IL1B/CXCL2	5/32	5

3. Discussion

In this study, the drug components of 12 traditional Chinese medicines in Jiawei Linggui Zhugan Decoction and obesity disease targets were analyzed by network pharmacology. The results showed that the traditional Chinese medicine compound Jiawei Linggui Zhugan Decoction contained 248 chemical components, 3695 action targets and 34 common targets with MS. Through PPI network analysis, 9 core targets were obtained. The results show that the modified Lingguizhugan decoction can act on OBSL1, MCM2, FN1, YWHAZ, RNF2, MYC, VCAM1, VCP, APP, EP300 and other targets through the active components such as quercetin, luteolin, baicalein, kaempferol, kaempferol and so on. Thus, VEGF is activated and induced through biological functions such as response to acid chemical, cyclin dependent protein kinase holoenzyme complex and peroxidase activity, as well as p53 signal pathway and AGE-RAGE signal pathway.

At present, the active components of modified Linggui Zhugan decoction have also been studied in anti-inflammatory, anti-oxidation, anti-tumor and so on. Kaempferol comes from the rhizome of ginger plant kaempferol galanga L. as the most common flavonoids, long-term diet will reduce the risk of cancer. Liu et al. [9] found that kaempferol may reduce the relative expression of P-gp and MRP1 in K562 / ADM cells by inhibiting p38 MAPK pathway, increase the accumulation of ADM in cells, and reverse the drug resistance of K562 / ADM cells in chronic myeloid leukemia. Quercetin, a flavonol compound with a variety of biological activities, is widely distributed in herbs. Modern research shows that quercetin can resist free radicals, complex or capture free radicals and prevent lipid peroxidation; It can directly inhibit tumor and effectively play the role of cancer prevention and anticancer [10]; Shi et al. [11] found that quercetin inhibited the proliferation of primary leukemia cells in a time-dependent manner; Quercetin combined with adriamycin significantly inhibited the proliferation of primary leukemia cells, and had synergistic and additive effects on the proliferation of primary leukemia cells, and its inhibitory effect on cell proliferation was concentration and time-dependent. Luteolin, which also exists in a variety of plants, is a natural flavonoid with antitumor and other pharmacological effects; It can be used in multi-target, multi-channel and multi loop anti-tumor. Its mechanisms include preventing tumor formation, inhibiting tumor cell proliferation, inducing tumor cell apoptosis, inhibiting tumor metastasis, inhibiting tumor angiogenesis and sensitizing anticancer drug activity [12]. Horinaka m [13] found that luteolin

may continuously activate JNK and promote apoptosis by regulating the activities of bad and p53. JNK regulates the expression of Pro apoptotic protein Bax induced by p53. The activation of JNK causes the increase of Bax / bak ratio and induces endogenous apoptosis pathway [14]. Scutellarin is a flavonoid extracted from *Scutellaria baicalensis*, which has a proliferation inhibition effect on leukemia, breast cancer, lung cancer and other tumor cells [15]; Baicalein inhibits HL-60 cell proliferation and reverses drug resistance. Its mechanism may be related to inhibiting the expression of PI3K-Akt signaling pathway protein and down regulating ERK phosphorylation level in Raf / MEK / ERK signaling pathway [16]. Huang et al. Confirmed that baicalein can inhibit the proliferation of leukemia HL-60 cells by inhibiting telomerase activity [17]. Qian et al. [18] treated a variety of leukemia with different concentrations of baicalein. The experiment found that baicalein can inhibit the proliferation of all leukemia cells in the experiment, mainly by inducing leukemia cell apoptosis and cell cycle arrest, so as to inhibit their proliferation. It may be an effective candidate drug for anti leukemia.

In conclusion, based on the network pharmacology technology, this study explores the mechanism of Jiawei Linggui Zhugan Decoction in the treatment of MDS from the aspects of its composition, action target, biological function and metabolic pathway, which can provide a reference for the study of its pharmacological mechanism in the future.

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