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Supplementary Material

Therapeutic Efficacy Evaluation and Underlying Mechanisms Prediction of Jianpi Liqi Decoction for Hepatocellular Carcinoma

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ARTICLE INFO

Article history:

Received: 24 August, 2021

Accepted: 9 September, 2021

Published: 22 September, 2021

Keywords:

Jianpi Liqi decoction
 hepatocellular carcinoma
 mechanisms
 IGFBP3
 CA2

ABSTRACT

Objective: The aim of this study was to assess the therapeutic effects of Jianpi Liqi decoction (JPLQD) in hepatocellular carcinoma (HCC) and explore its underlying mechanisms.

Methods: The characteristics and outcomes of HCC patients with intermediate stage B who underwent sequential conventional transcatheter arterial chemoembolization (cTACE) and radiofrequency ablation (RFA) only or in conjunction with JPLQD were analysed retrospectively. The plasma proteins were screened using label-free quantitative proteomics analysis. The effective mechanisms of JPLQD were predicted through network pharmacology approach and partially verified by ELISA.

Results: Clinical research demonstrated that the Karnofsky Performance Status (KPS), traditional Chinese medicine (TCM) syndrome scores, neutropenia and bilirubin, median progression-free survival (PFS), and median overall survival (OS) in HCC patients treated with JPLQD were superior to those in patients not treated with JPLQD (all $P < 0.05$). The analysis of network pharmacology, combined with proteomics, suggested that 52 compounds targeted 80 potential targets, which were involved in the regulation of multiple signaling pathways, especially affecting the apoptosis-related pathways including TNF, p53, PI3K-AKT, and MAPK. Plasma *IGFBP3* and *CA2* were significantly up-regulated in HCC patients with sequential cTACE and RFA therapy treated with JPLQD than those in patients not treated with JPLQD ($P < 0.001$). The AUC of the *IGFBP3* and *CA2* panel, estimated using ROC analysis for JPLQD efficacy evaluation, was 0.867.

Conclusion: These data suggested that JPLQD improves the quality of life, prolongs the overall survival, protects liver function in HCC patients, and exhibits an anticancer activity against HCC. *IGFBP3* and *CA2* panels may be potential therapeutic targets and indicators in the efficacy evaluation for JPLQD treatment, and the effective mechanisms involved in the regulation of multiple signaling pathways, possibly affected the regulation of apoptosis.

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Supplementary Table 1: All pathways of the putative targets.

Pathway ID	Pathway Names	Classes	P values	Genes	Counts
hsa00140	Steroid hormone biosynthesis	Metabolism	2.14E-03	<i>CYP11A1, CYP17A1, AKR1C2, COMT</i>	4
hsa00061	Fatty acid biosynthesis	Metabolism	6.47E-03	<i>ACACA, ACSL4</i>	2
hsa01212	Fatty acid metabolism	Metabolism	1.04E-02	<i>ACACA, SCD, ACSL4</i>	3
hsa00480	Glutathione metabolism	Metabolism	1.30E-02	<i>GSTM1, GSTP1, PGD</i>	3
hsa00030	Pentose phosphate pathway	Metabolism	3.06E-02	<i>PGD, TALDO1</i>	2
hsa00980	Metabolism of xenobiotics by cytochrome P450	Metabolism	3.17E-02	<i>CYP11A1, GSTM1, GSTP1</i>	3
hsa04151	PI3K-Akt signaling pathway	Environmental Information Processing	1.11E-08	<i>HSP90AA1, KDR, MET, CDK2, NOS3, CCND1, IL6, CDK4, EGF, PTEN, MTOR, RAC1, PDGFB, PIK3CA, FGF4, TP53, BCL2L1</i>	17
hsa04668	TNF signaling pathway	Environmental Information Processing	6.61E-08	<i>ICAM1, TNF, CASP8, JUN, IL6, PTGS2, VCAM1, FOS, MMP9, PIK3CA</i>	10
hsa04370	VEGF signaling pathway	Environmental Information Processing	2.15E-05	<i>KDR, NOS3, PTGS2, HSPB1, RAC1, PIK3CA</i>	6
hsa04068	FoxO signaling pathway	Environmental Information Processing	3.48E-05	<i>CDK2, CCND1, IL6, TGFB1, EGF, PTEN, ATM, PIK3CA</i>	8
hsa04010	MAPK signaling pathway	Environmental Information Processing	1.28E-04	<i>TNF, JUN, TGFB1, HSPB1, FOS, EGF, RAC1, PDGFB, FGF4, TP53</i>	10
hsa04071	Sphingolipid signaling pathway	Environmental Information Processing	1.36E-04	<i>TNF, NOS3, PTEN, CTSD, RAC1, PIK3CA, TP53</i>	7
hsa04152	AMPK signaling pathway	Environmental Information Processing	1.66E-04	<i>CCND1, SREBF1, ACACA, HMGCR, MTOR, SCD, PIK3CA</i>	7
hsa04064	NF-kappa B signaling pathway	Environmental Information Processing	2.33E-04	<i>ICAM1, TNF, PTGS2, VCAM1, ATM, BCL2L1</i>	6
hsa04066	HIF-1 signaling pathway	Environmental Information Processing	4.06E-04	<i>NOS3, ERBB2, IL6, EGF, MTOR, PIK3CA</i>	6
hsa04015	Rap1 signaling pathway	Environmental Information Processing	8.00E-04	<i>KDR, MET, CTNNB1, EGF, RAC1, PDGFB, PIK3CA, FGF4</i>	8
hsa04014	Ras signaling pathway	Environmental Information Processing	1.32E-03	<i>KDR, MET, EGF, RAC1, PDGFB, PIK3CA, FGF4, BCL2L1</i>	8
hsa04012	ErbB signaling pathway	Environmental Information Processing	1.41E-03	<i>ERBB2, JUN, EGF, MTOR, PIK3CA</i>	5
hsa04150	mTOR signaling pathway	Environmental Information Processing	2.43E-03	<i>TNF, PTEN, MTOR, PIK3CA</i>	4
hsa04310	Wnt signaling pathway	Environmental Information Processing	1.12E-02	<i>CCND1, JUN, CTNNB1, RAC1, TP53</i>	5
hsa04060	Cytokine-cytokine receptor interaction	Environmental Information Processing	1.24E-02	<i>KDR, MET, TNF, IL6, TGFB1, EGF, PDGFB</i>	7
hsa04630	Jak-STAT signaling pathway	Environmental Information Processing	1.67E-02	<i>CCND1, IL6, MTOR, PIK3CA, BCL2L1</i>	5
hsa04115	p53 signaling pathway	Cellular Processes	1.30E-08	<i>IGFBP3, CDK2, CCND1, CASP8, CDK4, PTEN, CDKN2A, ATM, TP53</i>	9
hsa04210	Apoptosis	Cellular Processes	6.47E-07	<i>TNF, CASP8, JUN, FOS, CTSD, ATM, PIK3CA, TP53, BIRC5, BCL2L1</i>	10
hsa04110	Cell cycle	Cellular Processes	2.16E-06	<i>HDAC1, CDK2, CCND1, TGFB1, CDK4, E2F1, CDKN2A, ATM, TP53</i>	9
hsa04510	Focal adhesion	Cellular Processes	2.67E-06	<i>KDR, MET, ERBB2, CCND1, JUN, CTNNB1, EGF, PTEN, RAC1, PDGFB, PIK3CA</i>	11
hsa04520	Adherens junction	Cellular Processes	5.19E-03	<i>MET, ERBB2, CTNNB1, RAC1</i>	4
hsa04810	Regulation of actin cytoskeleton	Cellular Processes	1.59E-02	<i>EGF, F2, RAC1, PDGFB, PIK3CA, FGF4</i>	6
hsa04919	Thyroid hormone signaling pathway	Organismal Systems	1.38E-05	<i>NCOA1, HDAC1, CCND1, CTNNB1, MTOR, PIK3CA, MED1, TP53</i>	8
hsa04915	Estrogen signaling pathway	Organismal Systems	3.77E-05	<i>HSP90AA1, NOS3, JUN, MMP2, FOS, MMP9, PIK3CA</i>	7
hsa04620	Toll-like receptor signaling pathway	Organismal Systems	5.86E-05	<i>TNF, CASP8, JUN, IL6, FOS, RAC1, PIK3CA</i>	7
hsa04670	Leukocyte transendothelial migration	Organismal Systems	1.16E-04	<i>ICAM1, VCAM1, MMP2, CTNNB1, MMP9, RAC1, PIK3CA</i>	7
hsa04380	Osteoclast differentiation	Organismal Systems	1.50E-03	<i>TNF, JUN, TGFB1, FOS, RAC1, PIK3CA</i>	6
hsa04621	NOD-like receptor signaling pathway	Organismal Systems	2.01E-03	<i>HSP90AA1, TNF, CASP8, IL6</i>	4
hsa04660	T cell receptor signaling pathway	Organismal Systems	3.08E-03	<i>TNF, JUN, FOS, CDK4, PIK3CA</i>	5
hsa04921	Oxytocin signaling pathway	Organismal Systems	3.71E-03	<i>NOS3, CCND1, JUN, PTGS2, FOS, PIK3CA</i>	6

hsa04976	Bile secretion	Organismal Systems	4.47E-03	<i>CA2, ABCB1, HMGCR, NRIH4</i>	4
hsa04917	Prolactin signaling pathway	Organismal Systems	4.70E-03	<i>CCND1, FOS, CYP17A1, PIK3CA</i>	4
hsa04662	B cell receptor signaling pathway	Organismal Systems	4.94E-03	<i>JUN, FOS, RAC1, PIK3CA</i>	4
hsa04913	Ovarian steroidogenesis	Organismal Systems	1.17E-02	<i>CYP11A1, PTGS2, CYP17A1</i>	3
hsa04664	Fc epsilon RI signaling pathway	Organismal Systems	2.64E-02	<i>TNF, RAC1, PIK3CA</i>	3
hsa04722	Neurotrophin signaling pathway	Organismal Systems	2.68E-02	<i>JUN, RAC1, PIK3CA, TP53</i>	4
hsa04920	Adipocytokine signaling pathway	Organismal Systems	2.85E-02	<i>TNF, MTOR, ACSL4</i>	3
hsa04612	Antigen processing and presentation	Organismal Systems	3.76E-02	<i>HSP90AA1, TNF, HSPA5</i>	3
hsa04650	Natural killer cell mediated cytotoxicity	Organismal Systems	3.89E-02	<i>ICAM1, TNF, RAC1, PIK3CA</i>	4
hsa04910	Insulin signaling pathway	Organismal Systems	4.26E-02	<i>SREBF1, ACACA, MTOR, PIK3CA</i>	4

Supplementary Table 2: Gene Ontology(GO) analysis of the putative targets (top 10).

Category	GO_ID	GO_Names	P values
biological process	GO:0070887	cellular response to chemical stimulus	1.67E-60
biological process	GO:0042221	response to chemical	5.96E-55
biological process	GO:0010033	response to organic substance	2.80E-54
biological process	GO:0071310	cellular response to organic substance	4.07E-53
biological process	GO:0048522	positive regulation of cellular process	1.31E-52
biological process	GO:0031325	positive regulation of cellular metabolic process	1.15E-51
biological process	GO:0048583	regulation of response to stimulus	1.37E-48
biological process	GO:0048518	positive regulation of biological process	2.60E-48
biological process	GO:0010604	positive regulation of macromolecule metabolic process	6.04E-48
biological process	GO:1901700	response to oxygen-containing compound	7.93E-47
cellular component	GO:0031982	vesicle	3.31E-27
cellular component	GO:0031988	membrane-bounded vesicle	1.39E-25
cellular component	GO:0005576	extracellular region	4.00E-23
cellular component	GO:0031974	membrane-enclosed lumen	5.38E-23
cellular component	GO:0044421	extracellular region part	1.89E-22
cellular component	GO:0043233	organelle lumen	5.11E-22
cellular component	GO:0065010	extracellular membrane-bounded organelle	3.69E-21
cellular component	GO:0070062	extracellular exosome	5.42E-21
cellular component	GO:1903561	extracellular vesicle	6.49E-21
cellular component	GO:0043230	extracellular organelle	6.66E-21
molecular function	GO:0005515	protein binding	2.29E-32
molecular function	GO:0019899	enzyme binding	1.20E-25
molecular function	GO:0044877	macromolecular complex binding	1.57E-23
molecular function	GO:0005102	receptor binding	1.39E-19
molecular function	GO:0046983	protein dimerization activity	6.63E-18
molecular function	GO:0042802	identical protein binding	6.38E-17

molecular function	GO:0008134	transcription factor binding	6.97E-15
molecular function	GO:0044212	transcription regulatory region DNA binding	1.34E-14
molecular function	GO:0000975	regulatory region DNA binding	1.34E-14
molecular function	GO:0001067	regulatory region nucleic acid binding	1.35E-14
