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Potential Anti-Oral Cancer Activity of Babao Dan: A Network Pharmacology and Molecular Docking Study

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Abstract: Babao Dan (BBD), a traditional Chinese patent medicine, has shown antitumour activity against gastric, liver and breast cancers through multi-target kinase signalling. However, oral cancer differs from these tumours in its chronically inflamed and immunosuppressive microenvironment, so whether BBD remains effective is unclear. Therefore, in this study, we performed a network pharmacological analysis and molecular docking to identify and profile the anti-cancerous mechanisms of this plant on oral cancer. Upon the analysis, we identified fifty-three active compounds acting on 717 predicted targets, 247 of which were associated with oral cancer. The hub genes AKT1, MAPK3, JUN, PIK3CA and IL6 are core components of the PI3K-Akt and MAPK pathways. In molecular docking, the five lead compounds formed stable complexes with these targets, the strongest pairs being morin–MAPK3 (−9.1 kcal/mol) and androstenedione–AKT1 (−8.1 kcal/mol). These results suggest that Babao Dan may act against oral cancer by modulating kinase-dependent signalling at multiple targets, and provide a basis for further experimental validation.

1. Introduction

Oral cancer, predominantly oral squamous cell carcinoma (OSCC), is one of the most common head and neck malignancies and remains a major cause of cancer-related mortality worldwide[1]. The 5-year overall survival rate remains around 60% and has improved little over the past decades, mainly because of high recurrence, metastasis and drug resistance[1, 2]. Surgery combined with radiotherapy and chemotherapy remains the mainstay of treatment, but its efficacy is limited by toxicity and acquired resistance, which has renewed interest in traditional Chinese medicine (TCM) as a source of multi-target anticancer agents[3].

Babao Dan (BBD) is a well-known traditional Chinese patent medicine composed of Niuhuang, Lingyangjiao, Sanqi, Zhenzhu, Shexiang and Shedan. It has long been used to clear heat and remove toxins, and has been reported to inhibit proliferation, induce apoptosis, suppress metastasis and reverse drug resistance in gastric, liver and breast cancers[4-7]. For example, BBD reverses multi-drug resistance in gastric cancer cells via PI3K/AKT/mTOR-mediated apoptosis and

autophagy[4], enhances the anti-tumour efficacy of the PD-1 antibody camrelizumab by remodelling M2 macrophages in hepatocellular carcinoma[5], and suppresses the inflammatory and vascular microenvironment of triple-negative breast cancer through cGAS-STING/NF-κB signalling[6].

The relevance of these findings to oral cancer, however, is not self-evident. OSCC arises in a chronically inflamed microenvironment and is characterised by pronounced immunosuppression with elevated PD-L1 expression[8], features that distinguish it from the tumours in which BBD has been studied. The inflammatory and immunosuppressive milieu may either attenuate the efficacy of BBD or provide the context in which its multi-target action is most relevant; because the hypothesis can be argued in either direction, whether BBD acts on oral cancer warrants investigation.

Given this context, Network pharmacology is particularly suitable for dissecting the multi-component and multi-target actions of TCM formulas[9, 10], and molecular docking predicts the binding affinity between candidate compounds and their putative targets[11]. In this study, we combined the two approaches to explore the anti-oral cancer potential of BBD. Active constituents were screened from public databases, oral cancer-related targets were predicted, and the key compounds were docked into the top-ranked hub proteins to evaluate their binding affinities. Our findings may provide a scientific basis for the further development of BBD as a therapeutic agent for oral cancer.

2. Materials and Methods

2.1. Network Pharmacology

The chemical constituents of the six medicinal materials in BBD were retrieved from TCMSP (https://www.tcmsp-e.com/) and HERB (http://herb.ac.cn/), and compounds with oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18 were retained as potentially active. Compound names were standardized against PubChem (https://pubchem.ncbi.nlm.nih.gov/), and duplicates occurring in more than one medicinal material were merged before screening. The retained compounds were further assessed in SwissADME (http://www.swissadme.ch/), and only those with high gastrointestinal absorption and at least two positive drug-likeness criteria (Lipinski, Ghose, Veber, Egan and Muegge) were kept. Their targets were predicted using SwissTargetPrediction (http://www.swisstargetprediction.ch/) restricted to Homo sapiens, and only targets with a probability score > 0.1 were retained to minimize false positives. Oral cancer-related targets were collected from GeneCards (https://www.genecards.org/) using “oral cancer” as the search keyword, and the two target sets were intersected on the Weishengxin platform (https://www.bioinformatics.com.cn/) to obtain common targets. The common targets were uploaded to STRING (https://string-db.org/) for PPI network construction with a minimum interaction score of 0.7 (high confidence), and the network was visualized in Cytoscape 3.10.2. The top 10 hub genes were identified using the maximal clique centrality (MCC) algorithm of cytoHubba, a compound–target–disease network was constructed in Cytoscape, and the degree of each node was calculated to evaluate the relative contribution of each compound. Finally, GO and KEGG enrichment analyses were performed with Metascape (https://metascape.org/) using an adjusted P value < 0.05 as the significance threshold, and the results were visualized as bubble plots on the Weishengxin platform.

2.2. Molecular Docking

Five lead compounds (quercetin, morin, liquiritigenin, 3,5-dihydroxybenzoic acid and androstenedione) were selected for molecular docking against the five top-ranked hub proteins (AKT1, JUN, MAPK3, IL6 and PIK3CA). The receptor structures were downloaded from the

RCSB Protein Data Bank (https://www.rcsb.org/), and water molecules, co-crystallised ligands and heteroatoms were removed. Docking was performed using the CB-Dock2 web server (https://cadd.labshare.cn/cb-dock2/)[11], and the binding energies were recorded.

3. Results

3.1. Active Compounds and Potential Targets of BBD

A total of 53 active compounds were obtained from BBD, including flavonoids, saponins, bile acids and steroid hormones; compounds detected in more than one medicinal material are listed once with all sources indicated in Table 1. Of these, 12 were nutrient-type molecules (11 amino acids and one monosaccharide) that also passed the OB ≥ 30% and DL ≥ 0.18 criteria; they were retained to preserve the complete chemical profile of the animal-derived materials and are identified by category in Table 1. These compounds corresponded to 717 unique targets, while 2,221 oral cancer-related targets were collected from GeneCards. The intersection of the two target sets yielded 247 common targets (Figure 1), which were considered candidate targets through which BBD may act against oral cancer.

Table 1: Active compounds of BBD and their source medicinal materials.

ID	Name	Category	ID	Name	Category
ZZ1, LYJ9	alanine	Amino acid	NH5	desoxycortone	Steroid hormone
ZZ2, LYJ1	aspartic acid	Amino acid	NH6	ergosterol	Sterol
ZZ3	methionine	Amino acid	LYJ2	serine	Amino acid
ZZ4	L-fucose	Monosaccharide	LYJ3, SX1	glutamic acid	Amino acid
SQ1	ginsenoside Rh2	Saponin	LYJ4	phenylalanine	Amino acid
SQ2	diisooctyl phthalate	Plasticiser	LYJ5	leucine	Amino acid
SQ3	liquiritigenin	Flavonoid	LYJ6	lysine	Amino acid
SQ4	ethyl linoleate	Fatty acid ester	LYJ7	tyrosine	Amino acid
SQ5	stigmasterol	Sterol	LYJ8	phosphatidylinositol	Phospholipid
SQ6	β-sitosterol	Sterol	LYJ10	arginine	Amino acid
SQ7	sitogluside	Sterol glycoside	LYJ11	cysteine	Amino acid
SQ8	oleanolic acid	Triterpenoid	SX2	epiandrosterone	Steroid
SQ9	quercetin	Flavonoid	SX4	androstenedione	Steroid
SQ10	myristic acid	Fatty acid	SX5	5α-androstane-3,17-dione	Steroid
SQ11	2-phenyl-2-propanol	Other	SX6	5α-androstane-3β,17β-diol	Steroid
SD1	taurodeoxycholic acid	Bile acid	SX7	3-ethynyl-3-hydroxyandrostan-17-one	Steroid
SD2	taurocholic acid	Bile acid	SX8	androstane-3,17-diol	Steroid
SD3	taurochenodeoxycholic acid	Bile acid	SX9	5β-androstane-3α,17α-diol	Steroid
SD4	lithocholic acid	Bile acid	SX10	estradiol	Steroid
SD5, NH7	cholesterol	Sterol	SX11	3,5-dihydroxybenzoic acid	Phenolic acid
SD6, SX3	cholic acid	Bile acid	SX12	iso-androsterone	Steroid
SD7	α-phocaecholic acid	Bile acid	SX13	3α,17β-dihydroxy-5α-androstane	Steroid
SD8	bile acid	Bile acid	SX14	13-methyl-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthrene-3,17-diol	Steroid
NH1	3α,7β,12α-trihydroxy-5β-cholan-24-oic acid methyl ester	Bile acid	SX15	morin	Flavonoid
NH2	chenodeoxycholic acid	Bile acid	SX16	N-nornuciferine	Alkaloid
NH3	methyl chenodeoxycholate	Bile acid	SX17	17-hydroxyandrost-4-en-3-one	Steroid
NH4	deoxycholic acid	Bile acid			

Note: ZZ, Zhenzhu; LYJ, Lingyangjiao; SD, Shedan; NH, Niuhuang; SX, Shexiang; SQ, Sanqi. The letters indicate the medicinal material of origin and the digits the compound number within that material.

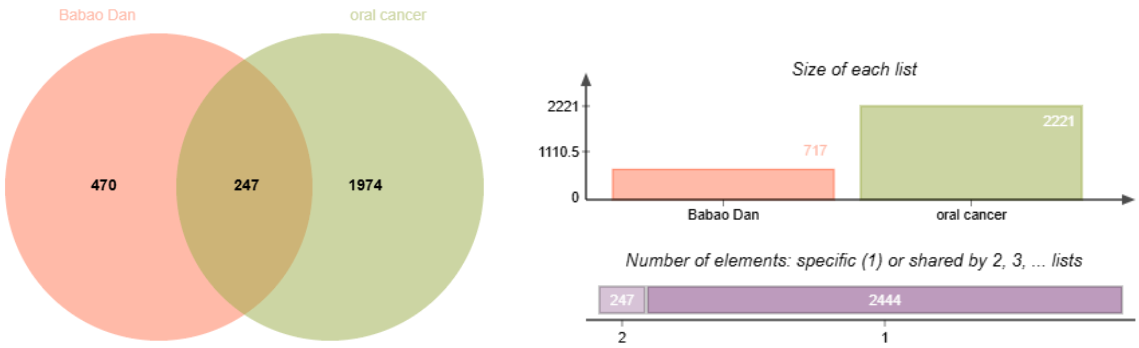


Figure 1: Venn diagram of the predicted targets of BBD active compounds and oral cancer-related targets.

3.2. Construction of the PPI Network and Identification of Hub Genes

The PPI network of the 247 common targets was visualized in Cytoscape (Figure 2A). The network showed a highly connected interaction pattern. The top 10 hub genes identified by the MCC algorithm were AKT1, MAPK3, JUN, PIK3CA, IL6, STAT3, MMP9, TNF, CTNNB1 and HIF1A (Figure 2B). These genes are predominantly protein kinases, inflammatory cytokines and signal transducers, including components of the PI3K-Akt axis (AKT1 and PIK3CA), MAPK signalling (MAPK3 and JUN), inflammatory and immune regulators (IL6, TNF and STAT3), and regulators of invasion and hypoxia (MMP9, CTNNB1 and HIF1A). The five top-ranked proteins, AKT1, MAPK3, JUN, PIK3CA and IL6, were subsequently used as receptors for molecular docking.

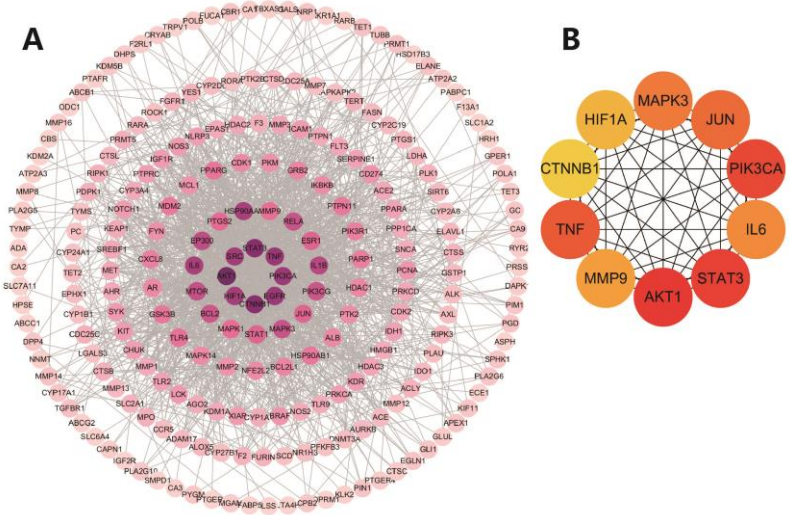


Figure 2: (A) PPI network of the common targets constructed using STRING and visualized in Cytoscape. (B) The top 10 hub genes identified by the MCC algorithm in cytoHubba.

3.3. Compound–Target–Disease Network Analysis

To explore the multi-component and multi-target characteristics of BBD, a compound–target–disease network was constructed in Cytoscape, in which the 53 active compounds, the 247 common targets and oral cancer were represented as nodes (Figure 3). The degree of each compound node was used to estimate its relative contribution to the network. The five compounds with the highest

degrees were quercetin, morin, liquiritigenin, 3,5-dihydroxybenzoic acid and androstenedione. As these compounds connect to the largest number of oral cancer-related targets, they were taken as the lead compounds for the docking analysis.

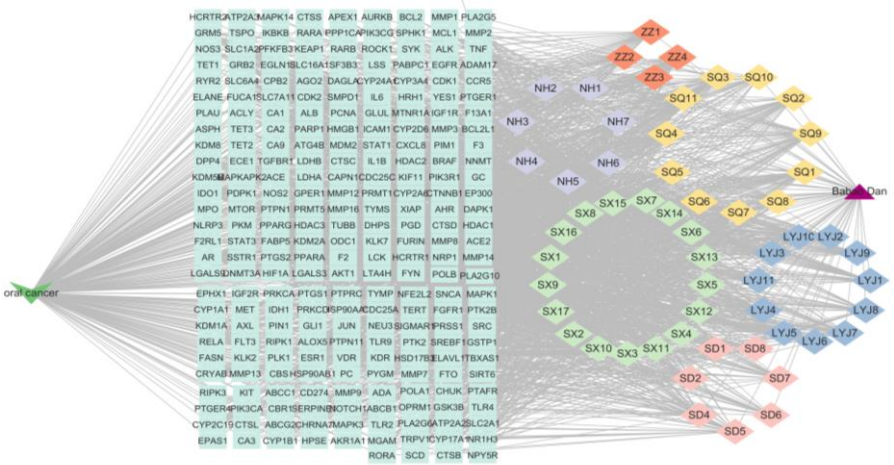


Figure 3: Compound–target–disease network of BBD against oral cancer. The purple triangle represents BBD, coloured diamonds represent active compounds, rectangles represent common targets, and the green triangle represents oral cancer.

3.4. GO and KEGG Enrichment Analysis

GO (Figure 4) and KEGG enrichment (Figure 5) analyses of the 247 common targets were performed using Metascape. For biological process, the most significantly enriched terms were mainly associated with hormone response, regulation of apoptosis and cellular responses to external stimuli; for cellular component, the terms were dominated by membrane rafts and vesicle lumen; and for molecular function, kinase-related activities (protein kinase activity, kinase binding and phosphotransferase activity) prevailed. KEGG pathway enrichment identified “Pathways in cancer”, “Lipid and atherosclerosis”, “Prostate cancer”, “Proteoglycans in cancer” and “HIF-1 signalling pathway” as the most enriched pathways, with the “PI3K-Akt signalling pathway”, “PD-L1 expression and PD-1 checkpoint pathway in cancer” and “Endocrine resistance” also significantly enriched.

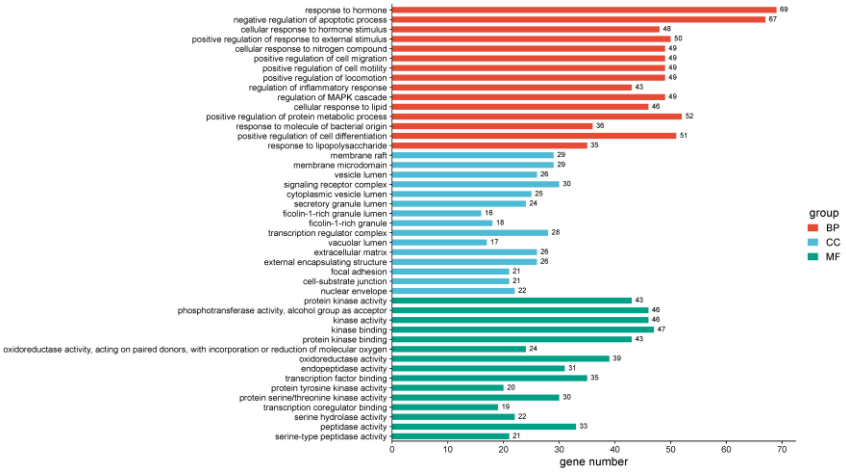


Figure 4: GO enrichment analysis of the common targets. Top 15 terms in biological process (BP; red), cellular component (CC; blue) and molecular function (MF; green). The x-axis indicates gene count.

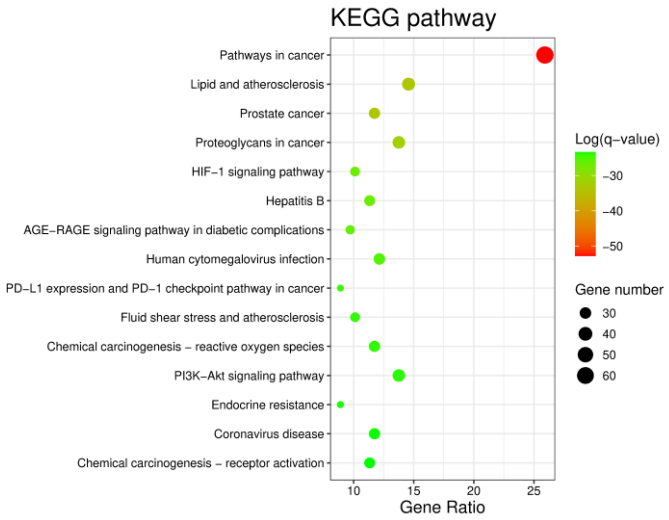


Figure 5: KEGG pathway enrichment analysis of the common targets. Top 15 enriched pathways. Dot size represents gene count, dot colour represents the adjusted P value, and the x-axis indicates the gene ratio.

3.5. Molecular Docking of the Five Compounds with the Hub Proteins

The five compounds were docked against the five top-ranked hub proteins (AKT1, JUN, MAPK3, IL6 and PIK3CA). Binding energies ranged from −9.1 to −4.6 kcal/mol, with 24 of the 25 pairs showing favourable binding (< −5.0 kcal/mol). Morin exhibited the strongest affinity for MAPK3 (−9.1 kcal/mol), followed by androstenedione–AKT1 (−8.1 kcal/mol) and morin–AKT1 (−7.8 kcal/mol). Quercetin, liquiritigenin, and 3,5-dihydroxybenzoic acid also bound well to MAPK3 (−7.8 kcal/mol), IL6 (−7.0 kcal/mol), and MAPK3 (−5.8 kcal/mol), respectively (Table 2). The only pair above the threshold was 3,5-dihydroxybenzoic acid–JUN (−4.6 kcal/mol). Overall, the docking supports the core targets as plausible binding partners for the lead compounds..

Table 2: Binding energies (kcal/mol) of the five lead compounds with the five top-ranked hub proteins.

Target	Quercetin	morin	liquiritigenin	3,5-dihydroxybenzoic acid	androstenedione
AKT1	−7.7	−7.8	−6.9	−5.7	−8.1
JUN	−6.3	−6.4	−6.7	−4.6	−6.7
MAPK3	−7.8	−9.1	−6.6	−5.8	−6.9
IL6	−6.5	−6.5	−7.0	−5.3	−6.7
PIK3CA	−6.3	−6.3	−6.3	−5.2	−6.7

Note: All binding energies are expressed in kcal/mol

4. Discussion

Oral squamous cell carcinoma remains difficult to treat because of its high recurrence rate and limited therapeutic options [1, 2]. In this study, network pharmacology and molecular docking were combined to profile the potential anti-oral cancer mechanism of BBD, which yielded 53 active compounds, 247 common targets and a kinase-centred hub module, and the five lead compounds all docked stably to the hub proteins.

The antitumour activity of BBD has been reported in hepatocellular carcinoma, gastric cancer and triple-negative breast cancer, where it acts through PI3K/AKT/mTOR and other kinase pathways [4-7]. Our analysis extends these findings to oral cancer and identifies a kinase-centred

module: AKT1 and PIK3CA form the core of the PI3K-Akt axis, while MAPK3 and JUN mediate MAPK signalling. Constitutive activation of PI3K-Akt is frequent in OSCC and associated with poor prognosis and cisplatin resistance[12, 13], whereas MAPK signalling drives proliferation and survival in head and neck cancer[14]. This convergence supports the hypothesis that BBD may act as a multi-kinase modulator.

Among the 53 compounds, quercetin, morin, liquiritigenin, 3,5-dihydroxybenzoic acid and androstenedione had the highest node degrees, consistent with the multi-target nature of flavonoids and steroids[15-19]. Of these, quercetin is known to inhibit PI3K-Akt signalling and induce apoptosis in head and neck cancer cells[16, 17], morin suppresses tumour growth through the PI3K/Akt and MAPK pathways[18, 19], and liquiritigenin triggers apoptosis and autophagy in oral cancer cells by blocking PI3K/AKT/mTOR signalling[20]. Androstenedione, a steroid hormone precursor, has been implicated in hormone-dependent tumour progression [21]. These reports agree with our observation that the five compounds connect to the largest number of oral cancer-related targets.

A key question is whether BBD also acts through mechanisms unique to oral cancer. Our enrichment analysis suggests that it does: the PD-L1/PD-1 checkpoint pathway, inflammatory response terms and the HIF-1 signalling pathway were significantly enriched, with IL6, TNF, STAT3 and HIF1A among the top-ranked hub genes, whereas existing studies of BBD in hepatocellular, gastric and breast cancer have mainly implicated macrophage-mediated immune modulation[5], PI3K/AKT/mTOR signalling[4] and cGAS-STING/NF-κB signalling[6]. Thus, in addition to the shared PI3K-Akt/MAPK axis, BBD may act on oral cancer through modulation of the inflammatory and immune microenvironment.

The docking results corroborate the network analysis: morin and androstenedione showed the strongest affinities for MAPK3 and AKT1, respectively, consistent with their known roles in modulating PI3K-Akt and MAPK signalling [18, 19, 21], while the affinity of liquiritigenin for IL6 (−7.0 kcal/mol) suggests a possible effect on the inflammatory microenvironment[20]. The enrichment results echo this picture: IL6, TNF and STAT3 point to the inflammatory milieu of oral tumours[22, 23], and the PD-L1/PD-1 checkpoint pathway suggests that immune-checkpoint-related signalling may be involved in the response to BBD[24].

This study has several limitations. The docking results were not confirmed by molecular dynamics simulation or kinase assays, and no visualisation of binding modes was performed. Twelve nutrient-type molecules passed the OB/DL filter but were included in target prediction to preserve the complete chemical profile; their predicted targets may be non-specific, and the core mechanism was interpreted based on the remaining active compounds. Future studies should validate the predicted targets by Western blotting and kinase activity assays and evaluate the efficacy of the lead compounds in oral cancer models.

5. Conclusion

This study combined network pharmacology and molecular docking to characterize the anti-oral cancer mechanism of BBD. Among 53 active compounds and 717 predicted targets, 247 were linked to oral cancer, with hub genes centred on the PI3K-Akt and MAPK pathways. Morin and androstenedione formed the most stable complexes with MAPK3 (−9.1 kcal/mol) and AKT1 (−8.1 kcal/mol), respectively. Notably, the enrichment of the PD-L1/PD-1 checkpoint pathway and inflammatory response terms, together with the hub genes IL6, TNF and STAT3, suggests that BBD also acts by modulating the inflammatory and immunosuppressive tumour microenvironment, a feature distinguishing oral cancer from previously studied tumours. These findings provide a shortlist of lead compounds and targets for future experimental validation.

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