Research Article

Effective Herbal Cocktail Strategies and Mechanisms in Cancer Treatment

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Abstract

Systematic treatment and cocktailed drug applications have become a paradigm shift for cancer therapy. This study aims to explore the highly potent herbal cocktail strategies and pharmacological mechanisms, by which herbal medicines are effective in cancer treatment. A total of 397 cases of clinically reported cancer treatments with pure herbs were scrutinized, and the herbal prescription rules were systematically analyzed. The core prescriptions and their pharmacological mechanisms were revealed. The results unveiled specific rules for effective herbal treatment of cancer, including boosting energy metabolism, inhibiting tumor proliferation, improving digestion and defecation, enhancing blood circulation, promoting gas exchange, and facilitating water and toxic substance metabolism. Pharmacologically, anti-cancer effects are achieved through the manipulation of PI3K-Akt, IL-17, HIF-1, VEGF, TNF, Wnt, and other pathways. Following this unfolded integrative prescription rule, herbal therapy demonstrated remarkable effects in clinical practices, from which a few representative cases are presented herein.

Keywords

traditional herbal medicine, malignant tumor, pattern of drug administration, medication regularity, clinical exploration

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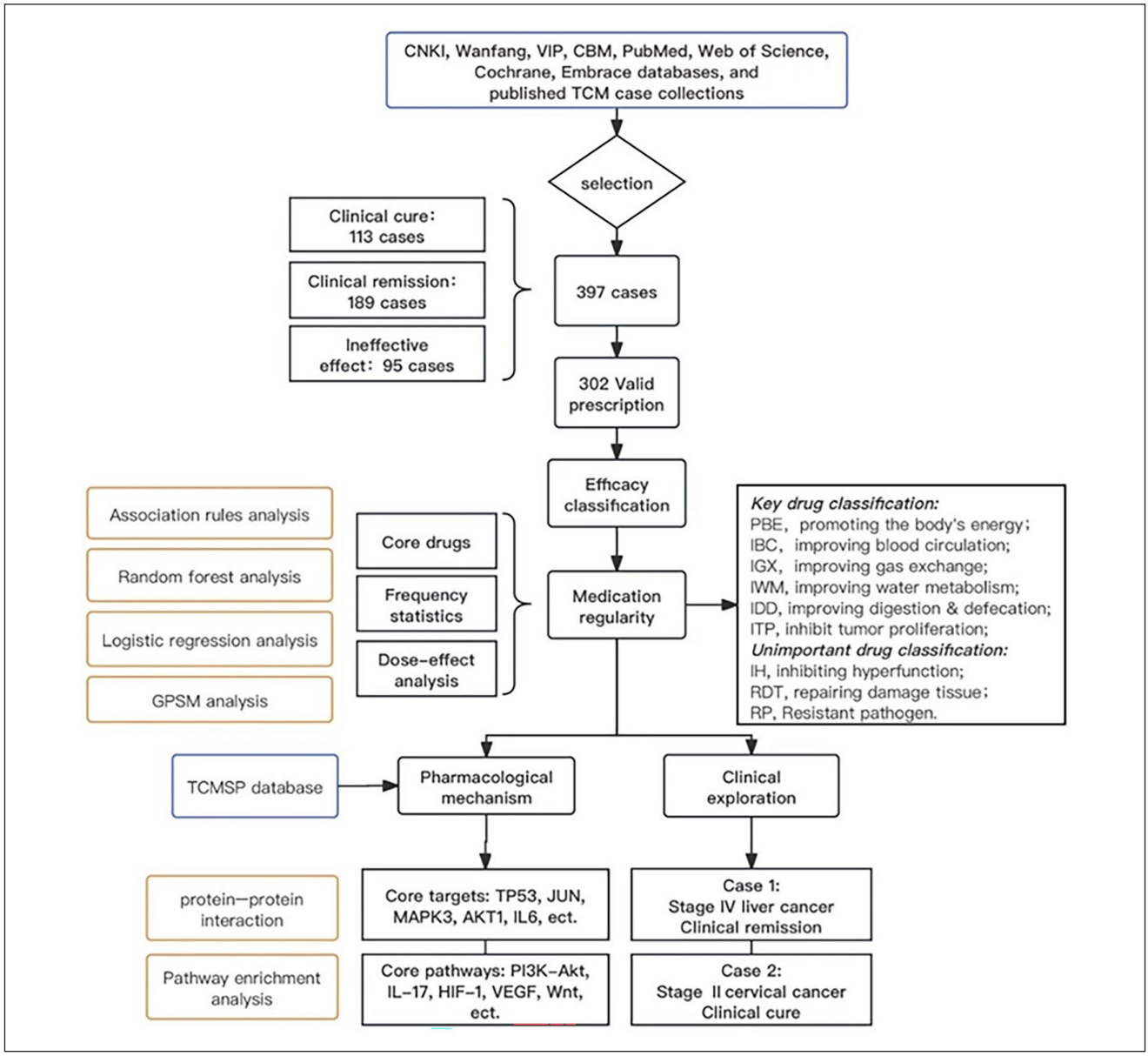
Graphical Abstract



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Introduction

Cancer poses a significant challenge to human health. The global cancer burden is projected to reach 28.4 million cases by 2040, representing a 47% increase compared to 2020.[1] The presence of the cancer microenvironment, hinders the efficacy of approaches for direct cancer elimination, such as radiotherapy, chemotherapy, and targeted therapy.[2,3] More troublingly, the surviving cancer cells may become more malignant.[4] Therefore, better solutions are urgently needed.

The results of IMpower150 suggest that the efficacy of new drug combinations is superior to traditional treatment modes. The mechanisms involved include relieving immunosuppression, anti-angiogenesis, regulating the cancer microenvironment, and directly inhibiting tumor proliferation.[5] This represents a paradigm shift for drug cocktail application in the treatment of complicated diseases like cancer, albeit the cross interactions of drugs still need to be addressed.

Traditional Chinese medicine (TCM) is often used in the form of compound combinations, with a history of more than 2000 years of valuable experience in the clinical treatment of tumors.[6] Recent research has found that herbal medicine can regulate the tumor microenvironment by alleviating hypoxia, retarding tumor angiogenesis, and relieving immunosuppression.[7] Additionally, it can directly inhibit tumors by inducing apoptosis and restraining metastasis.[8] Therefore, the application of herbal medicine in cancer treatment holds intriguing potential.

However, in clinical practice, herbal medicine has not yet received the attention it deserves. Clinical studies on the treatment of cancer with herbal medicine mostly aim to improve symptoms, and reduce the toxicity of radiotherapy and chemotherapy.[9] There is still a lack of clinical studies targeting the suppression of tumor growth. Furthermore, the use of medicine for tumors is mainly based on the experience of experts and schools of thought, and a consensus has not yet been reached.

In recent decades, an increasing number of cases have been reported in which pure herbal medicine treatment has led to the shrinkage or disappearance of tumors. These cases have become an unignorable clinical reference, yet the prescription rules and mechanisms remain unclear. In a preliminary study of the modernization of the herbal medicine systemic framework,[10] it was found that the pharmacological effects of herbal medicine are mainly distributed in the following nine aspects. The first category is maintaining the steady state of the human body, including inhibiting tumor proliferation (ITP), promoting the body's energy (PBE), inhibiting hyperfunction (IH), repairing damaged tissue (RDT), and resisting pathogens (RP). The second category maintains human material exchange, including improving blood circulation (IBC), improving gas exchange (IGX), improving water metabolism (IWM), and improving digestion and defecation (IDD). On this basis, this study attempts to excavate clinical reports of effective tumor treatment with pure herbal medicine, and further analyze the herbal combination patterns and medication mechanisms, providing preliminary references for the treatment of tumors with herbal medicine.

Methods

Search Strategy

Data sources. A systematic search was conducted in CNKI, Wanfang, VIP, CBM, PubMed, Web of Science, Cochrane, and Embrace databases, as well as published TCM medical case collections, to identify relevant studies up to January 2023. The primary search terms included "tumor" or "cancer," while the secondary search terms encompassed "Traditional Chinese Medicine," "Traditional Herbal Medicine," "Chinese Medicine," "case report," or "case series."

Literature selection criteria

(a) Patients diagnosed with malignant tumors were included in the study.
(b) Studies involving purely the use of herbal medicine for treatment were considered. These were categorized as "untreated" cases. Additionally, studies where patients used pure herbal medicine for treatment without other therapeutic measures following conventional treatments such as surgery, radiotherapy, chemotherapy, targeted therapy, and others, due to drug resistance or economic factors, were also included and categorized as "treated" cases.
(c) To ensure that the effect of herbal medicine treatment was fully reflected in the medical records, studies with a treatment duration of more than 3 months were included.
(d) Studies meeting the following efficacy evaluation criteria were included: (1) *Clinical cure*: Complete disappearance of the tumor upon clinical examination. (2) *Clinical relief*: Shrinkage or reduction of the tumor upon clinical examination, or improvement in bone marrow and hemogram for hematologic cancers, with a follow-up period of more than 3 years. (3) *Insufficient efficacy*: No shrinkage or progression of the tumor upon clinical examination.

Literature exclusion criteria

(a) Studies that did not clearly record the tumor results after treatment were excluded.
(b) Studies involving herbal medicine treatment mixed with other treatments were excluded.
(c) Studies where conventional treatments such as surgery, radiotherapy, and chemotherapy were used before the use of herbal medicine, but the efficacy

was not reported, or the tumor was controlled after conventional treatment, were excluded.

(d) Studies that did not disclose the ingredients of the traditional Chinese medicine prescription or preparation were excluded.

Standardized management and establishment of databases. The *Chinese Pharmacopoeia* (2020 Edition) was used as a reference to standardize the drug names, record the sources and compositions of the prescriptions, and conduct consistent inspections and corrections. Two individuals independently entered information on the literature names, traditional Chinese medicine prescriptions, and other relevant details into Excel software. A third party was responsible for verifying the data to ensure its accuracy before finally establishing the database.

Frequency Analysis of Medication

A statistical analysis was performed on the efficacy and cold-heat attributes of all drugs in the database. Drugs with a frequency of ≥ 15 were screened for further investigation.

Drug Decision-Making Analysis

Three types of prescriptions with varying levels of efficacy were selected as research subjects. Random forest analysis and orderly logistic regression analysis were conducted using Stata to comprehensively assess the importance and correlation of various medicines on efficacy. Generalized propensity score matching (GPSM) was employed in Stata to investigate the dose-response relationship of a specific class of drugs while keeping other variables constant.

Influence of Modern Medical Treatment on Herbal Medicine Use

Prescriptions with therapeutic effects of cure or alleviation were chosen as research subjects. An independent samples *t*-test was performed using SPSS to analyze the correlation between treatment history and the frequency of use of herbal medicines with different efficacy.

Core Prescription Analysis

Representative prescription. R software was utilized to analyze correlation rules for prescriptions administered to patients who had not undergone conventional treatments such as chemotherapy and radiotherapy. This ensured that prescriptions for the adverse effects of radiotherapy and chemotherapy were not included in the analysis. The focus was on prescriptions that had been evaluated as having a "clinical cure" level of efficacy. The APRIORI algorithm was applied to identify herbal medicines with higher associated intensity, and the results were visualized using a network diagram. This approach aimed to explore the representativeness of prescriptions used to treat tumors. The Apriori algorithm a classic association rule mining algorithm is primarily employed to discover frequent item sets in large datasets and generate corresponding rules. A higher associated intensity indicates a greater likelihood of these herbs appearing together, and a stronger correlation between them.

Core mechanism analysis. For the representative prescriptions, all components and target proteins of the herbal medicines were obtained using databases such as TCMSP and Symmap.

Compounds of herbal medicine ingredients with a Drug-Likeness (DL) score greater than 0.15 and an Oral Bioavailability (OB) score greater than 0.3 were screened. The Uniprot database was utilized to convert target protein names to gene names, facilitating the identification of representative action targets.

All intersecting genes were uploaded to the String interaction database for Protein-Protein Interaction Networks (PPI) analysis. The species was set to "Homo sapiens," and the minimum interaction score was set to 0.9 to screen for core targets.

The intersecting genes were then uploaded to the DAVID database, and Gene Ontology (GO) was employed to study the roles of the target proteins of representative herbal medicines in treating tumors from three aspects: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF).

Based on the results of comprehensive ordered logistic regression, random forest, and association rule analyses, the most critical classes of drugs for cancer treatment were determined. To further analyze the mechanism of these classes of herbs KEGG pathway enrichment analysis was performed.

Preliminary clinical exploration. In the outpatient clinic, five cancer patients were diagnosed and treated according to the medication strategy derived from the research results. We have obtained informed consent for publication of personal data from patients whose cases are in the manuscript. The cases were organized and documented for further analysis.

Results

Data Collection

Through the search of databases, 776 Chinese literature articles, 11 English literature articles, and 25 books of medical records were initially obtained. Applying the inclusion and exclusion criteria, 113 cases of "clinical cure" 189 cases of "clinical remission" and 95 cases of "insufficient efficacy" were screened out, resulting in a total of 397 cases.

Table 1. Summary of Effective Cases.

Cancer type	Clinical cure and untreated	Clinical cure and treated	Clinical relief and untreated	Clinical relief and treated	Total
Lung cancer	7	3	30	12	52
Liver cancer	13	2	23	1	39
Gastric cancer	5	2	13	12	32
Esophageal cancer	6	2	13	2	23
Upper respiratory cancer	7	4	4	7	22
Breast cancer	1	2	7	9	19
Intestinal cancer	3	3	9	4	19
Carcinoma of uterus	7	1	7	1	16
Brain tumor	4	0	10	1	15
Carcinoma of bladder	3	3	7	0	13
Ovarian cancer	6	3	0	3	12
Pancreatic cancer	6	1	3	1	11
Hematologic tumor	4	2	3	0	9
Sarcoma	4	2	0	0	6
Oral cancer	2	0	2	0	4
Thyroid cancer	1	1	0	1	3
Renal cancer	0	1	1	1	3
Prostate cancer	1	0	0	1	2
Penile cancer	0	0	1	0	1
Testicular cancer	0	1	0	0	1
Total	80	33	133	56	302

Combining the cases of "clinical cure" and "clinical remission" 302 prescriptions were obtained, which can be considered effective cases. Among them, 213 cases had not undergone conventional treatments such as chemotherapy and radiotherapy (untreated), while 89 cases were converted to herbal medicine after ineffective conventional treatment (treated) (Table 1).

Frequency Analysis of Medication

From the efficacy perspective, drugs promoting the body's energy were used most frequently (21.8%), followed by drugs improving blood circulation (16.5%), and drugs inhibiting tumor proliferation (16.2%; Figure 1).

A total of 306 kinds of herbal medicine were involved in the prescription database, with a total medication frequency of 5,106 times. Among them, the drugs with the highest frequency were Poria cocos (2.7%), Astragali (2.5%), and Atractylodes macrocephala (2.1%) (Table 2).

Analysis of Medication Rules

Random forest an algorithm that constructs multiple decision trees in a random manner to train and predict samples, was employed to determine the importance of drugs for efficacy. The results demonstrated that drugs improving blood circulation, promoting the body's energy, repairing damaged tissue, and inhibiting tumor proliferation were of high importance (Figure 2).

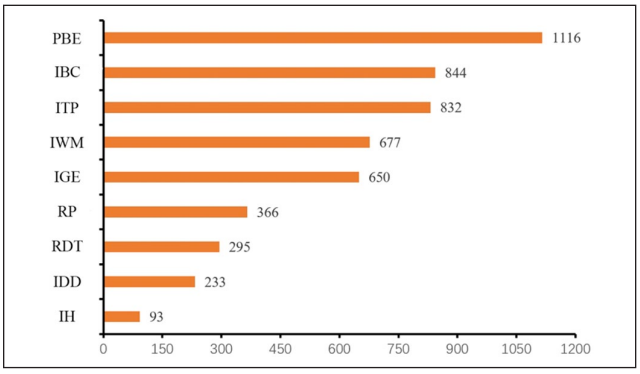

Figure 1. Efficacy statistics. The vertical axis represents the efficacy classification, while the horizontal axis represents the frequency.

Ordinal logistic regression was used to analyze the correlation between influencing factors and results and to determine the degree of positive and negative correlation between drugs and efficacy. The results indicated a significant positive correlation for drugs improving digestion and defecation, while a significant negative correlation was observed for drugs repairing damaged tissue and inhibiting hyperfunction (Table 3).

Table 2. The Top 15 Chinese Medicines by Frequency of Occurrence.

Category	Name	Frequency	Frequency (%)
Improving water metabolism drugs	Poria cocos	138	2.7
Promoting the body's energy drugs	Astragali	129	2.5
Promoting the body's energy drugs	Atractylodes macrocephala	106	2.1
Promoting the body's energy drugs	Codonopsis pilosula	98	1.9
Promoting the body's energy drugs	Glycyrrhiza uralensis	97	1.9
Inhibiting tumor proliferation	Hedyotis diffusa	96	1.9
Improving blood circulation drugs	Angelica sinensis	86	1.7
Improving gas exchange drugs	Citri reticulatae pericarpium	77	1.5
Improving water metabolism drugs	Coicis semen	74	1.4
Inhibiting tumor proliferation	Scutellaria barbata	73	1.4
Inhibiting tumor proliferation	Scolopendra subspinipes mutilans	66	1.3
Improving blood circulation drugs	Curcuma phaeocaulis	65	1.3
Improving blood circulation drugs	Salvia miltiorrhiza	63	1.2
Improving gas exchange drugs	Bupleuri	61	1.2
Inhibiting tumor proliferation	Cremastrae pseudobulbus pleiones pseudobulbus	61	1.2
Improving water metabolism drugs	Pinellia ternate	59	1.1

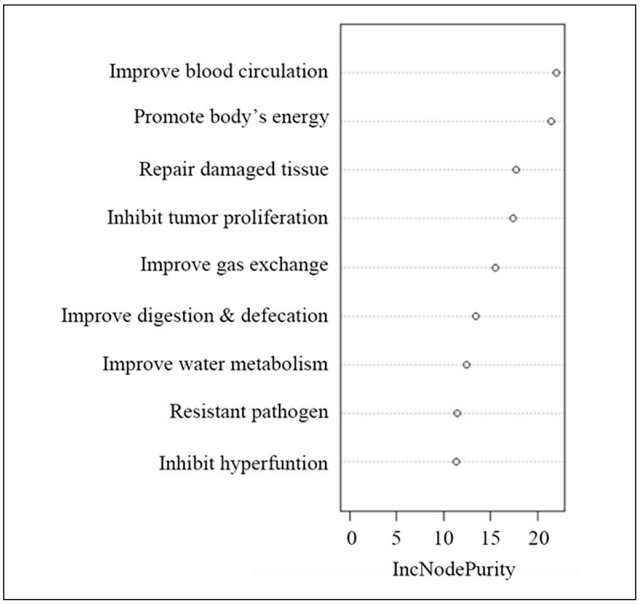

Figure 2. The impact of random forest analysis of different efficacy decisions on efficacy.

Based on the results of random forest analysis and ordered logistic regression analysis, it can be concluded that the efficacy of drugs promoting the body's energy, inhibiting tumor proliferation, improving blood circulation, improving gas exchange, improving water metabolism, and improving digestion and defecation are more pivotal (Figure 3).

The GPSM method establishes a counterfactual analysis framework based on multi-valued processing variables, reducing the multi-dimensional individual characteristics to a single index, and obtaining the dose-effect relationship between various drugs and efficacy. The results indicated that the optimal number of drugs promoting the body's energy was between 6 and 10 in each prescription, while the optimal number for drugs improving blood circulation, improving gas exchange, and improving water metabolism was between 2 and 6. Drugs repairing damaged tissue and inhibiting hyperfunction were optimally prescribed at <2, while drugs improving digestion and defecation and inhibiting tumor proliferation were optimally prescribed at >1; drugs resistant to pathogens were not included due to insufficient significance (Figure 4).

Influence of Modern Medical Treatment on Herbal Medicine Use

Patients who use herbal medicine treatment after the failure of conventional treatment show an increased frequency of using drugs that promote the body's energy, repair damaged tissue, and inhibit hyperfunction. However, there is no significant change in the use of other medicines (Table 4).

Core Prescription Analysis

Core drugs. Association rule analysis is employed to explore the law of simultaneous occurrence of certain elements in a phenomenon, providing insights into the compatibility characteristics of herbal medicine schemes from a holistic perspective. The average number of drugs used in the prescription library was 16; therefore, the top 16 herbal medicines were selected for visual analysis. The results showed that the representative drugs of herbal medicine for the treatment of tumors were Hedyotis diffusa, Pseudostellaria, Codonopsis pilosula, Astragali, Atractylodes macrocephala, Glycyrrhiza

Table 3. Correlation Between Drug Types and Efficacy by Ordinal Logistic Regression Analysis.

Drug classification	Coef.	SE	Z	P > |z|	Odds ratio	[95% conf. interval]	
Inhibiting tumor proliferation	0.011	0.044	0.250	.806	1.011	0.928	1.100
Inhibiting hyperfunction drugs*	−0.787	0.093	−3.850	.000	0.455	0.305	0.679
Improving blood circulation drugs	−0.027	0.045	−0.580	.559	0.974	0.890	1.065
Improving gas exchange drugs	−0.033	0.048	−0.650	.512	0.968	0.878	1.067
Improving water metabolism drugs	0.023	0.065	0.360	.718	1.023	0.904	1.159
Improving digestion and defecation drugs*	0.381	0.145	3.830	.000	1.463	1.204	1.778
Resistant pathogen drugs	0.059	0.087	0.710	.476	1.061	0.902	1.246
Repairing damaged tissue drugs*	−0.328	0.055	−4.300	.000	0.720	0.620	0.837
Promoting the body's energy drugs	−0.019	0.038	−0.490	.626	0.981	0.909	1.059

*$P < .05$.

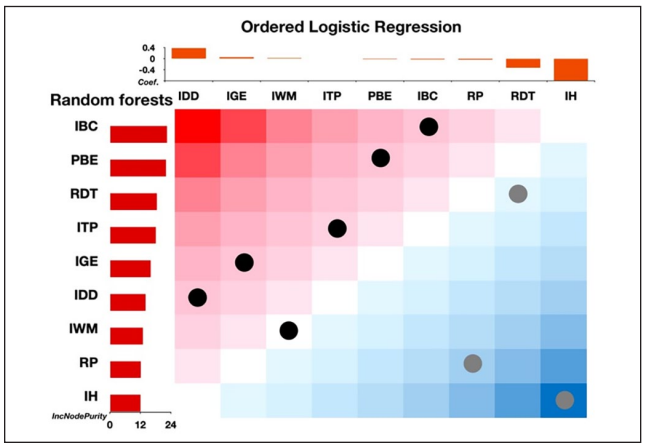

Figure 3. Cross plot of random forest analysis and ordinal logistic regression analysis. The warmer the color temperature, the more positive the correlation with efficacy. The colder the color temperature, the less positive the correlation with efficacy.

uralensis, Cinnamomum cassia, Zingiberaceae, Aconitum carmichaeli, Bupleuri, Citri reticulatae pericarpium, Salvia miltiorrhizae, Angelica sinensis, Pinellia ternate, Poria cocos, and Rheum palmatum (Figure 5).

Core target mechanism. A total of 111 overlapping genes were obtained by mapping representative drug targets with tumor targets. The topological analysis of the target interaction network (degree value reflects the size and color of the target, combined score value reflects the thickness of the edge was performed), and the protein-protein interaction (PPI) network was constructed. The results suggest that TP53, JUN, MAPK3, AKT1, IL6, TNF, MYC, EGFR, and HIF1A are the core targets (Figure 6).

KEGG pathway analysis revealed that the representative anti-cancer prescriptions mainly achieved anti-cancer effects through pathways such as pathways in cancer, PI3K-Akt, IL-17, HIF-1, VEGF, TNF, and Wnt. Specifically, drugs promoting the body's energy tend to work through IL-17, and MAPK pathways. Drugs inhibiting tumor proliferation tend to work through pathways such as TNF. Drugs improving blood circulation tend to function through pathways such as VEGF. Drugs improving gas exchange tend to function through the HIF-1 pathway. Drugs improving water metabolism tend to work through the PI3K-Akt pathway. Drugs improving digestion and defecation function through P53, Wnt, and other pathways (Figure 7).

Clinical Practice Under the Guidance of Medication Rules

Lung cancer with brain metastases. A 58-year-old female patient was diagnosed with lung adenocarcinoma with brain metastasis in August 2020. She started treatment with herbal medicine on February 4, 2021, without the use of chemotherapy drugs. The herbal cocktail prescription was as follows:

ITP: Hedyotis diffusa 57 g
PBE: Atractylodis macrocephalae rhizome 57 g, Zingiberaceae 28 g, Cinnamomum cassia 28 g, Aconiti lateralis radix praeparata 28 g
IGE: Amomi fructus 28 g, Aucklandiae radix 28 g
IBC: Sparganii rhizome 28 g, Curcuma rhizome 28 g
IWM: Atractylodis rhizome 57 g
IDD: Rheum palmatum 7 g

In the first week of treatment, the patient's symptoms and physical strength improved significantly, and the tumor volume continued to shrink after 6 months of treatment (Figure 8).

Cervical cancer with HPV positivity. A 41-year-old female patient was diagnosed with cervical adenocarcinoma on May 10, 2023, and tested positive for HPV. The patient refused surgery and Western medicine treatment, so a herbal cocktail prescription was administered:

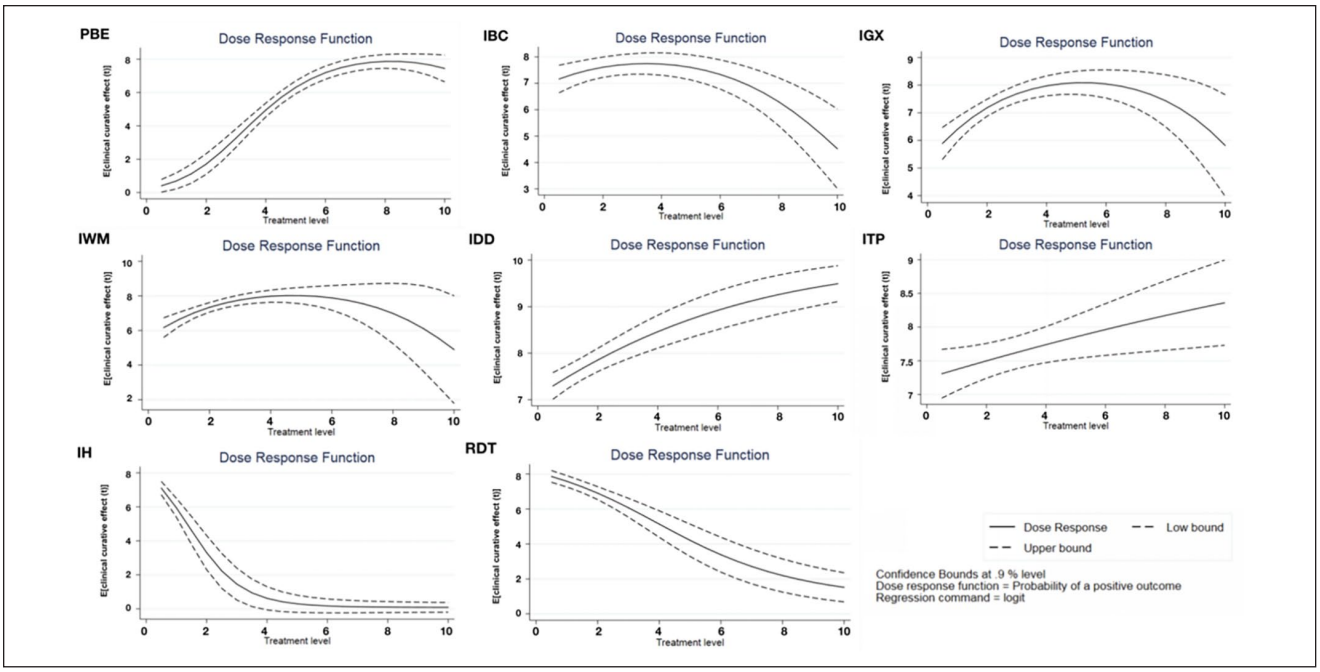

Figure 4. The dose-effect relationship of each kind of Chinese medicine based on GPSM. The ordinate represents the level of efficacy, and the abscissa represents the frequency of medication.

Table 4. Effect of Conventional Treatment History on Medication.

Drug classification	$\bar{x}$ (Untreated)	$\bar{x}$ (Treated)	*t*	*P*
Promoting the body's energy drugs*	3.343	4.348	2.9143	.0038
Improving blood circulation drugs	3.305	2.854	1.6419	.1017
Inhibiting tumor proliferation	3.277	3.303	0.0792	.9369
Improving water metabolism drugs	2.061	1.933	0.6179	.5371
Improving gas exchange drugs	2.061	2.18	0.47	.6387
Resistant pathogen drugs	1.089	0.798	1.7716	.0775
Improving digestion and defecation drugs	0.826	0.933	0.7442	.4573
Repairing damage tissue drugs*	0.714	1.326	3.7759	.0002
Inhibiting hyperfunction drugs*	0.08	0.225	2.7276	.0068

*$P < .05$.

ITP: Hedyotis diffusa 57 g
PBE: Astragali radix 77 g, Aconitum carmichaelii 35 g, Zingiberaceae 35 g, Cinnamomum cassia 28 g, Euodiae fructus 14 g
IGE: Lindera radix 28 g, Foeniculum vulgare 28 g
IBC: Curcuma rhizome 28 g, Leonuri fructus 28 g
IWM: Acorus tatarinowii rhizome 28 g, Poria cocos 57 g
IDD: Rheum palmatum 7 g,

After taking the herbal medicine for more than 3 months, the tumor markers returned to normal levels, and the carcinogenesis disappeared as confirmed by colposcopy basal cytology. Additionally, the HPV genotype subtypes turned negative. To date, the patient remains in good condition with no signs of tumor recurrence (Supplemental Figure 1).

Liver cancer with lung metastasis. A 45-year-old male patient was diagnosed with giant block liver cancer and lung metastasis on May 17, 2023. After consultation, it was determined that conventional clinical regimens such as interventional therapy and targeted therapy could not be used. Therefore, a herbal cocktail prescription was administered:

ITP: Hedyotis diffusa 57 g
PBE: Astragali radix 114 g, Zingiberaceae 28 g, Cinnamomum cassia 35 g, Gleditsiae spina 35 g

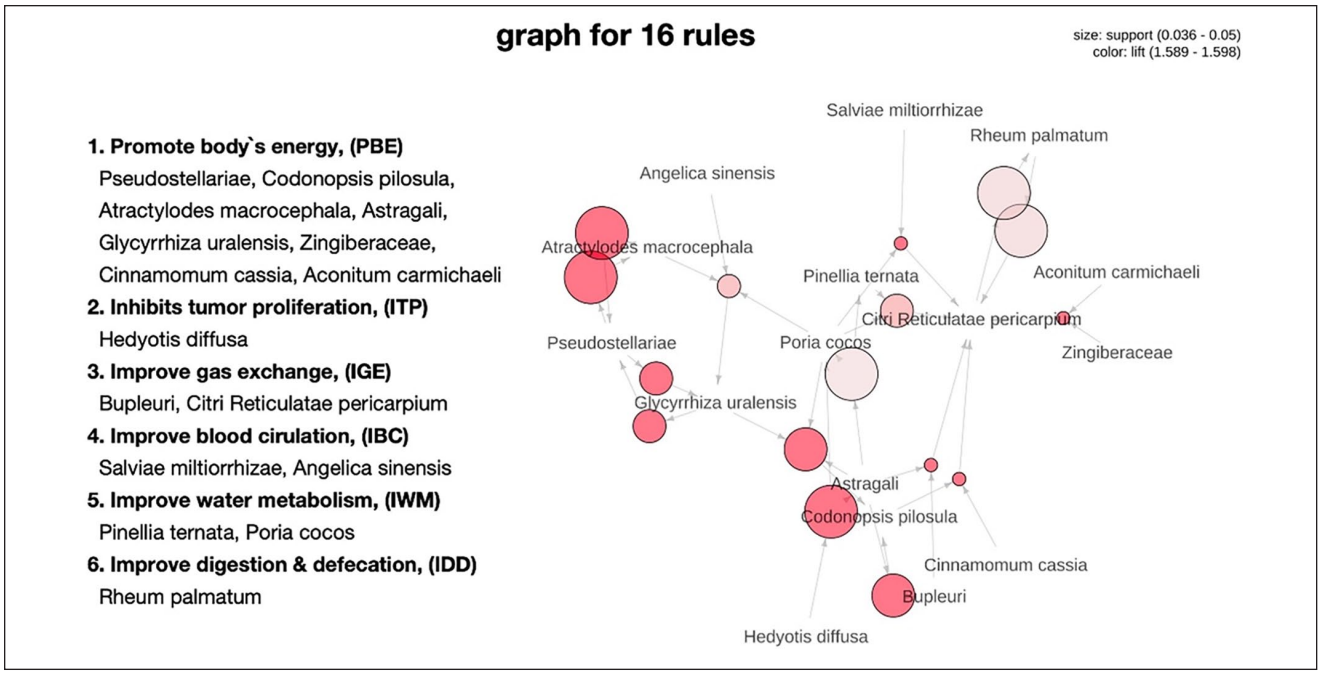

Figure 5. The association rule gains a core prescription for the effective treatment of tumors.

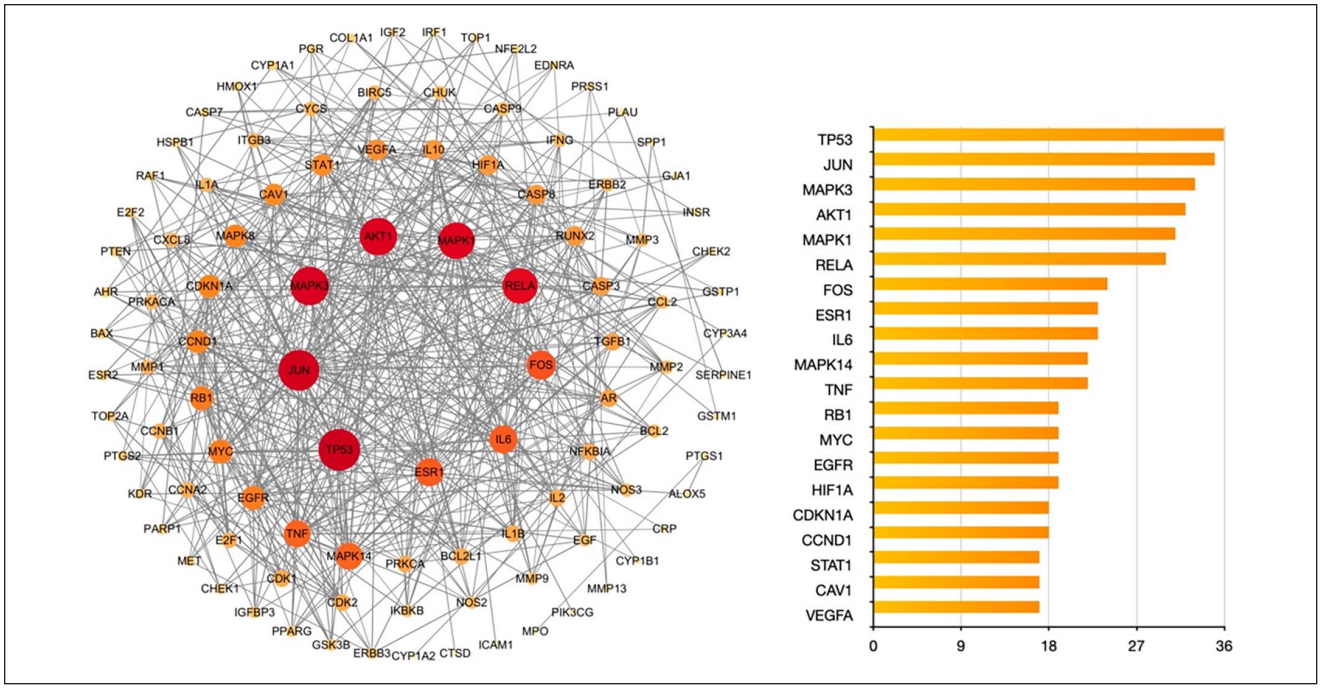

Figure 6. Core target analysis. the topology plot indicates the correlation between the targets, and the pie chart indicates the significance of the targets.

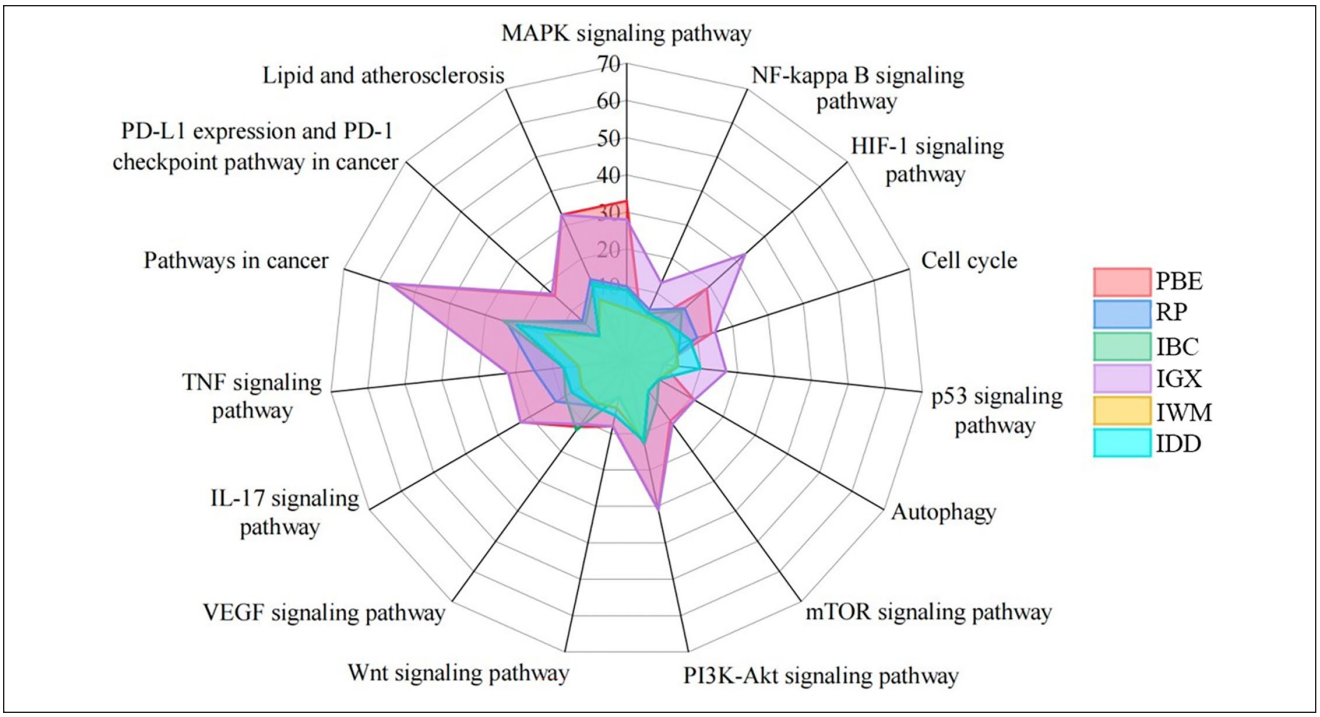

Figure 7. KEGG shows the pathways of different kinds of herbs in anti-cancer prescriptions.

IGE: Platycodon grandiflorum 35 g, Curcuma wenyujin 28 g, Raphanus sativus 35 g
IBC: Eupolyphaga sinensis 28 g, Curcuma aeruginosa 28 g
IWM: Pinelliae rhizome praeparatum 28 g, Alisma orientale 57 g
IDD: Rheum palmatum 7 g

After 6 weeks of treatment, the tumor volume had shrunk, pulmonary nodules disappeared, alpha-fetoprotein levels decreased significantly, and liver function returned to normal (Supplemental Figure 2).

Rectal cancer with multiple metastases. A 57-year-old female patient was diagnosed with rectal tumor at the end of December 2018. Following surgical resection, lung, brain, and bone metastases were successively found. Gamma knife, chemotherapy, radiotherapy, and targeted therapy were administered more than 10 times, and no targeted drugs were available. The patient presented with hydrocephalus, epilepsy, cancer pain, and insomnia. A herbal cocktail prescription was given:

ITP: Hedyotis diffusa 57 g
PBE: Astragali radix 135 g, Aconitum carmichaelii 57 g, Zingiberaceae 49 g, Cinnamomum cassia 57 g, Clematis chinensis 35 g
IGE: Amomum tsaoko 35 g, Aster tataricus 49 g
IBC: Spatholobus suberectus 35 g, Curcuma aeruginosa 35 g
IWM:Rhizoma pinellia 57 g, Tuckahoe 57 g, Alisma orientalis 57 g
IDD: Rheum palmatum 7 g

Two weeks after treatment, insomnia, and pain had improved. Two months after treatment, CA724 levels fell from 142.50 U/mL to 50.05 U/mL, and the epilepsy disappeared. The patient was followed up for 1 year showing significantly improved quality of life.

Immunoblastic T cell lymphoma (ITCL). A 74-year-old female patient was diagnosed with ITCL in July 2023, accompanied by severe hemolytic anemia and systemic lymph node enlargement. The survival assessment was only 3 months. She chose pure Chinese medicine for treatment, and the following herbal cocktail prescription was given:

ITP: Hedyotis diffusa 57 g
PBE: Agrimonia pilosa 57 g, Aconitum carmichaelii 28 g, Zingiberaceae 28 g, Cinnamomum cassia 28 g, Clematis chinensis 35 g
IGE: Platycodon grandiflorus35 g, Semen Raphani 42 g, Curcumae Radix 28 g
IBC: Padoniae Rubra 35 g
IWM: Atractylodes Lancea 35 g, Poria cocos 57 g
IDD: Rheum palmatum 3 g

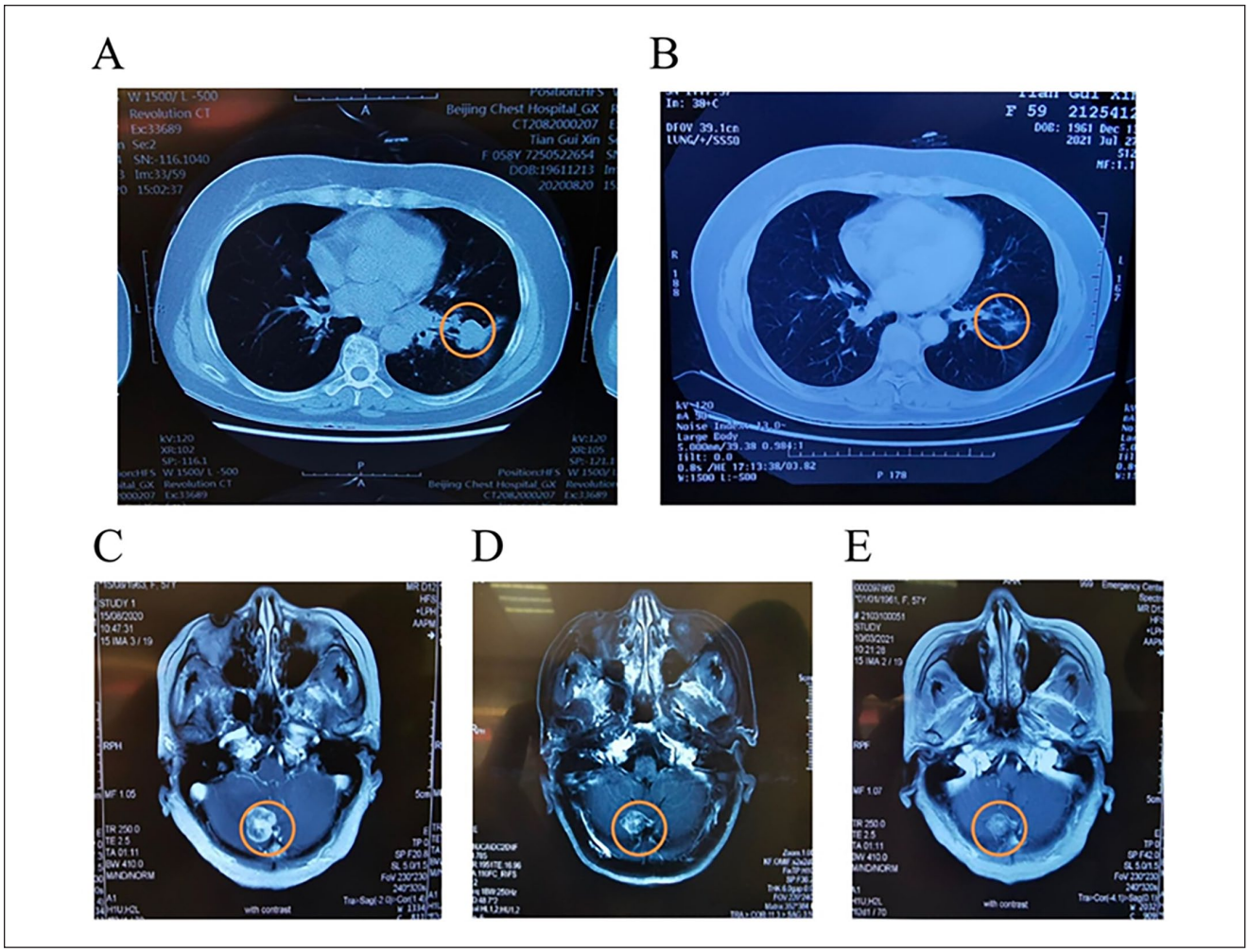

Figure 8. Comparison of examination indexes before and after treatment in a lung cancer patient. (A) Lung enhanced CT in August 2020. (B) Lung enhanced CT in July 2021. (C) Brain enhanced CT in August 2020. (D) Brain enhanced CT in March 2021. (E) Brain enhanced CT in July 2021.

After 4 months of treatment, all the enlarged lymph nodes disappeared. A 1-year follow-up showed good quality of life and no abnormalities in routine blood tests.

Discussion

In this study, a total of 787 herbal medicine literature sources and 25 herbal medical books were scrutinized, from which, 302 valid cases were identified, encompassing various common tumors, such as lung cancer, liver cancer, and gastric cancer. The findings indicate that herbal medicine has the potential to restrain and shrink tumors, as well as prolong the survival period of cancer patients.

The 15 most frequently used herbs are primarily effective in boosting the body's energy, inhibiting tumor proliferation, facilitating blood circulation, improving water metabolism, and fostering oxygen exchange. For instance, Poria cocos, an herb primarily used for improving water metabolism, can promote tumor cell apoptosis by downregulating the Notch1 pathway and affecting epithelial-mesenchymal transition.[11] Astragali, primarily a body's energy boosting herb, exerts anti-tumor effects by enhancing immune function and activating NK cells.[12] It can also inhibit the JNK/c-Jun/AP-1 pathway to reverse drug resistance in tumor cells.[13] Hedyotis diffusa, an herb primarily used for inhibiting tumor proliferation, can reduce the expression of HIF-1α, GLUT1 and HK2, promote apoptosis, and shrink tumors.[14] Angelica sinensis, an herb primarily used to facilitate blood circulation has been shown to significantly inhibit tumor cell proliferation by downregulating the expression of cell cycle regulators Cyclin B, D1, and E, while inducing tumor apoptosis by inhibiting Bcl-2 expression.[15] Citri reticulatae pericarpium, primarily an oxygen exchange improving herb, can inhibit

autophagy by upregulating the AKT pathway, thereby inducing tumor apoptosis.[16]

It is well established that the tumor microenvironment poses challenges for tumor therapy, such as immunosuppression, energy disturbance, hypoxia, hypercoagulability, and edema.[17-19] These challenges align with the application of herbs that inhibit tumor proliferation, boost the body's energy, facilitate blood circulation, foster oxygen exchange, improve water metabolism, and promote digestion and defecation. Interestingly, the results of comprehensive ordered logistic regression, random forest, and association rule analyses revealed that these six kinds of herbs are the key components of the core anti-cancer prescriptions. These herbs primarily target genes such as TP53, MYC, MAPK3, AKT1, IL6, TNF, EGFR, and HIF1-α, and exert their effects through pathways in cancer, PI3K-Akt, IL-17, HIF-1, VEGF, TNF, Wnt, and other channels.

Among the identified targets, TNF is the core factor of the TNF signaling pathway, which plays a crucial role in killing tumors.[20] MYC, on the other hand, is a key player in cell cycle, cancer, and other signaling pathways, and its abnormal expression can lead to tumor development.[21] Herbs that inhibit tumor proliferation have a direct inhibitory effect on tumor cells, including preventing DNA or RNA synthesis, preventing cell division, and inducing apoptosis, through these signaling pathways.[22] TP53 can participate in tumor progression by inducing TP53-induced glycolysis and apoptosis regulator to activate the MAPK signaling pathway.[23] Moreover, MAPK3 is the core gene of the MAPK pathway, and its abnormality can also increase the risk of tumor development. Herbs that boost the body's energy can alleviate cancer fatigue and enhance immune function by targeting the MAPK pathway, as well as adjust the immunosuppressive effect of the tumor microenvironment.[24,25] EGFR plays a central role in the mechanism of angiogenesis. Herbs that improve blood circulation target VEGF and other pathways to inhibit angiogenesis in the tumor microenvironment and alleviate hypoxia, thereby inhibiting tumor progression and metastasis.[26] These herbs also have a preventive effect on hypercoagulability, which is common in advanced tumors.[27] AKT1 is a core factor in the PI3K/AKT signaling pathway, and its overexpression is associated with the development of various tumors.[28] This pathway is a common target for TCM intervention in water metabolism related diseases.[29] Herbs that improve water metabolism target the PI3K-Akt pathway to alleviate the symptoms of effusion and edema in the advanced stage of tumors, and inhibit the proliferative effect of interstitial fluid in the tumor microenvironment on tumor cells.[30] HIF-1α is widely present in the hypoxic conditions of the tumor microenvironment, and induces a series of inflammatory reactions that promote tumor progression.[31] Herbs that improve gas exchange can target HIF-1 to regulate hypoxia and immune tolerance in the tumor microenvironment.[32] The activation of the Wnt signaling pathway is involved in the regulation of cell proliferation, tumor cell glycolysis, cancer initiation, development, deterioration, and metastasis.[33] Herbs that improve digestion and defecation can target Wnt pathways, alleviate the symptoms of constipation and irregular stool that are often associated with tumors, improve the intestinal flora, and achieve an anti-tumor effect.[34]

For patients who switched to herbal medicine treatment after the failure of conventional treatment, a significant increase was observed in the frequency of using drugs that promote the body's energy, repair damaged tissue, and inhibit hyperfunction (Supplemental Table 1). This may be attributed to the need for these patients to address the adverse reactions resulting from surgery, chemotherapy, and targeted therapy. Furthermore, differences in drug use may exist between different types of tumors (Supplemental Table 2). Taking liver cancer, which had the largest number of included cases, as an example, the frequency of using drugs that repair damaged tissue is lower in liver cancer patients, while the frequency of using drugs that improve blood circulation is higher. This observation may be related to the abnormal coagulation commonly seen in liver cancer patients.[35]

In the five representative case studies presented above, all patients had their prescriptions formulated under the guidance of medication rules, which are easy for clinicians to learn, reference, and standardize. The individual use of herbs depends on the differences in the severity of the various mechanisms in each patient. For instance, patients with abdominal or pleural effusion more frequently focus on herbs that improve water metabolism (IWM). Similarly, patients with hypoxemia use herbs that improve gas exchange (IGE) more often. Preliminary clinical practice has demonstrated certain effectiveness. However, due to the limited number of patients, further clinical research is necessary to validate these findings.

By analyzing a large number of previous successful cases, this study provides a more grounded reference for formulating rules and writing prescriptions in clinical practice. In the future, more qualified cases need to be included to further explore the rules and commonalities of the successful treatment of tumors using herbal medicine. Moreover, drug research will be upgraded to treatment strategy research, providing a reference for the breakthrough and innovation of herbal medicine in oncology clinics.

However, this study has some limitations. The number of cases of pure herbal treatment for cancer is still relatively small, and the quality of these cases is limited. Additionally, the current clinical practice is primary. Future clinical studies need to incorporate more high-quality data and design larger sample sizes to update and validate these conclusions.

Conclusion

Through data mining and statistical analysis of effective cases of herbal treatment for tumors, we have identified several key

prescription rules for the effective use of herbal medicine in tumor treatment. These rules include boosting the body's energy, inhibiting tumor proliferation, promoting digestion and defecation, facilitating blood circulation, fostering oxygen exchange, and improving water metabolism. These strategies act on important pathways involved in tumor therapy, such as PI3K-Akt, Wnt, HIF-1, VEGF, and TNF. Preliminary clinical practice has demonstrated the effectiveness of applying these rules in the treatment of cancer patients.

Abbreviations

ITP, inhibiting tumor proliferation; PBE, promoting the body's energy; IBC, improving blood circulation; IGX, improving gas exchange; IWM, improving water metabolism; IDD, improving digestion & defecation; IH, inhibiting hyperfunction; RDT, repairing damaged tissue; RP, resistant pathogen.

Author Contributions

TL directed the research and revised the manuscript. TH performed the research and wrote the paper with YZ. DD conducted statistical analyses. ZY, QZ, and QH refined the data and revised the manuscript.

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Supplemental Material

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