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Based on the "Turbidity-Toxin Induced Debility" Theory to Explore the Clinical Synergistic Effects of Fuzheng Kangai Formula in Post-Chemotherapy Treatment of Advanced Hepatocellular Carcinoma

Yating Zhang[1], Pengli Wang[2,*], Min Chen[1]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
Correspondence Author

Abstract: ***Hepatocellular carcinoma (HCC) is a common malignancy with a poor prognosis. The traditional Chinese medicine (TCM) formula Fuzheng Kangai Formula (FZKA) plays a distinctive role in HCC treatment. This article synthesizes relevant literature to comprehensively review the clinical application and research progress of FZKA in HCC therapy, including its effects on alleviating clinical symptoms, improving quality of life, modulating immune function, and influencing tumor biomarkers. Additionally, the study analyzes existing research limitations and future development directions, aiming to provide a reference for further clinical application of FZKA in HCC management.***

Keywords: Traditional Chinese Medicine, Fuzheng Kangai Formula, Hepatocellular Carcinoma, Chinese Herbal Medicine.

1. Introduction

Primary hepatocellular carcinoma (HCC) has become a major global health burden. According to the latest statistics from the International Agency for Research on Cancer, this malignancy accounts for nearly one million new cases annually (approximately 900,000), with about 830,000 deaths per year [1]. Primary liver cancer (hereafter referred to as HCC) is a malignancy originating from hepatocytes or intrahepatic bile duct epithelial cells, primarily including hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and mixed HCC-CCA types, among which HCC accounts for 75–85% or more of cases [2]. HCC is characterized by significant clinical insidiousness; its early pathological stages often present no specific symptoms, leading to diagnosis at advanced stages in most patients. The typical symptom cluster includes persistent dull pain in the right upper abdomen, progressive hepatomegaly, hepatic fibrosis, portal hypertension, jaundice, and ascites [3]. Moreover, HCC patients frequently suffer from critical complications such as acute upper gastrointestinal hemorrhage, hepatic capsule rupture, and metabolic encephalopathy, which can rapidly worsen prognosis, significantly shorten survival, and result in extremely high mortality. Globally, the high incidence and mortality of HCC impose a heavy burden on families and society and pose severe challenges to public health systems. Although Western medical treatments—including surgery, chemotherapy, radiotherapy, and targeted therapy—have made some progress, they have notable limitations, such as significant adverse effects and high recurrence/metastasis rates. TCM has a long history of treating HCC. As a commonly used TCM regimen, FZKA, grounded in holistic concepts and syndrome differentiation, demonstrates unique advantages in comprehensive HCC treatment through its functions of reinforcing healthy qi to consolidate the root and counteracting cancer toxins [4].

2. Western Medical Research on HCC

2.1 Understanding of the Pathogenesis of HCC

Due to the diversity of etiological factors in HCC, its pathogenesis varies. Studies have shown that the X protein of hepatitis B virus (HBV) can interact with multiple molecules to enhance HBV replication. The HBV genome may integrate into host hepatocyte DNA, causing genetic alterations that interfere with normal gene transcription regulation and protein synthesis, thereby significantly increasing the risk of malignant transformation of hepatocytes. Among environmental carcinogens, aflatoxin, particularly subtype B1 (AFB1), has been confirmed as an important hepatocarcinogenic factor [5]. AFB1, a secondary metabolite produced by Aspergillus fungi, exerts its carcinogenic effects through multiple molecular mechanisms, including metabolic activation, induction of oxidative damage, regulation of programmed cell death pathways (apoptosis and pyroptosis), immunosuppressive effects, and direct genotoxic actions, ultimately leading to hepatocarcinogenesis. Research indicates that HCC development results from the combined effect of host genetic susceptibility and environmental exposure, wherein dysregulation of key oncogenes and tumor suppressor genes plays a decisive role in tumorigenesis.

2.2 Understanding of the Pathological Classification of HCC

Histopathological classification includes:

1) Hepatocellular carcinoma (HCC): The most common type, accounting for approximately 90% of cases, arising from hepatocytes and usually associated with chronic liver diseases such as hepatitis B/C infection and cirrhosis. Tumor markers are primarily characterized by elevated alpha-fetoprotein (AFP). HCC readily invades portal vein branches, forming

portal vein tumor thrombi, thus facilitating intrahepatic metastasis.

2) Intrahepatic cholangiocarcinoma (ICC): Accounting for about 5% of primary liver cancers, this tumor originates from intrahepatic bile duct epithelial cells. Gross morphological types include nodular, periductal infiltrating, nodular-infiltrating, and intraductal growth types. Histologically, it predominantly exhibits an adenocarcinoma structure. Clinically, early jaundice and fever are common, while portal hypertension symptoms are rare. Only a small proportion of patients show mildly elevated AFP, with CA19-9 elevation being predominant. This subtype has a poorer prognosis.

3) Mixed type: Exhibiting both HCC and ICC components, each expressing their respective immunohistochemical markers [6].

2.3 Understanding of Treatment Modalities for HCC [6]

2.3.1 Surgical Treatment

1) Surgical resection: The optimal curative approach for primary HCC. Indications: confirmed diagnosis with lesions confined to one lobe or hemiliver; adequate liver function reserve with prothrombin time (PT) >50%, and absence of significant jaundice, ascites, or distant metastases; adequate cardiopulmonary and renal function.

2) Liver transplantation.

2.3.2 Transcatheter Arterial Chemoembolization (TACE)– i.e., interventional therapy in the narrow sense

For patients with intrahepatic tumor volume <70% of liver volume and without complete portal vein obstruction, intra-arterial administration of chemotherapeutic agents combined with embolic agents can shrink tumors, enabling secondary surgical resection in some patients and achieving cure in a minority. Performed via transfemoral arterial catheterization under superselective hepatic arteriography, TACE can be repeated multiple times. Principle: Pathological anatomy confirms that normal liver tissue receives 75% of its blood supply from the portal vein and only 25% from the hepatic artery; thus, hepatic artery embolization has minimal impact on normal liver tissue. Conversely, HCC nodules derive their blood supply predominantly from the hepatic artery, with only peripheral regions supplied by the portal vein; hence, hepatic artery embolization induces tumor necrosis. TACE is the first-line non-surgical treatment for HCC.

2.3.3 Locoregional Tumor Therapies

(1) Intratumoral injection for coagulation necrosis; (2) Local ablation therapy.

2.3.4 Radiotherapy

Limited-field irradiation is suitable for lesions <10 cm × 10 cm. For larger or multifocal tumors, moving-strip radiotherapy may be employed. Combining with other local therapies can improve tumor control rates.

2.3.5 Chemotherapy

HCC is generally not sensitive to chemotherapy, with overall poor efficacy. It is indicated for advanced-stage patients without significant liver function impairment. The FOLFOX4 regimen is recommended, which has shown objective responses and prolonged survival in advanced HCC.

2.3.6 Molecular Targeted Therapy

A study demonstrated that sorafenib improved survival in advanced HCC patients by 44% compared to controls, with median overall survival of 10.7 months vs. 7.9 months.

2.3.7 Supportive and Symptomatic Treatment

Includes rest, high-protein and high-carbohydrate diet, psychological counseling, analgesia, anti-infection, antipyretic, hemostatic therapies, etc. Individualized management can alleviate suffering and prolong life.

2.3.8 Complication Management

Advanced HCC may present with tumor rupture, gastrointestinal bleeding, hepatic encephalopathy, and other complications, requiring active emergency management according to standard critical care protocols.

3. Research on Traditional Chinese Medicine for HCC

3.1 Understanding of the Etiology and Pathogenesis of HCC in TCM

In classical TCM theory, there is no explicit disease name corresponding to “HCC.” However, based on its symptom patterns, it can be classified into categories such as “abdominal mass” (Zhengjia), “tympanites” (Guzhang), “jaundice” (Huangdan), and “hypochondriac pain” (Xietong) [7]. Specifically: when patients present with a fixed mass in the hypochondriac region that is hard and immovable, it is identified as Zhengjia; if the main manifestation is abdominal distension resembling a drum with a grayish-yellow complexion, it falls underGuzhang; when scleral and skin yellowing is observed, it corresponds to Huangdan; and persistent distending pain in the hypochondriac region is categorized as Xietong. In terms of etiology and pathogenesis, TCM emphasizes that HCC results from the long-term accumulation and interaction of multiple pathogenic factors, which can be summarized in four aspects: First, emotional dysregulation. Prolonged anxiety, anger, or brooding impairs liver function in maintaining free flow of qi, leading to qi stagnation. Over time, blood circulation becomes obstructed, causing stasis in the vessels and depriving the liver of nourishment. As stated in the Miraculous Pivot (Lingshu): “Worry and melancholy give rise to illness, and illness then accumulates into masses.” Second, improper diet. Excessive consumption of rich, fatty, or raw/cold foods damages the spleen and stomach, impairing their transport and transformation functions. This leads to water-dampness retention, which generates phlegm turbidity. Phlegm and blood stasis combine and accumulate beneath the

hypochondrium. As the Essentials from the Golden Cabinet (Jin Gui Yao Lue) states: "Dietary injury to the spleen and stomach leads to accumulation." Third, depletion of healthy qi. Congenital insufficiency or prolonged illness weakens the viscera, reduces defensive capacity, and allows pathogenic toxins to invade and lodge in the liver. The Required Readings for Medical Ancestors (Yi Zong Bi Du) points out: "Accumulations form when healthy qi is insufficient, allowing pathogenic qi to settle." Fourth, internal blood stasis. The above factors disrupt qi and blood circulation, causing extravasated blood to accumulate in the liver meridians, eventually forming masses. As emphasized in the Treatise on Blood Patterns (Xue Zheng Lun): "When blood stasis exists between meridians and viscera, it forms abdominal masses." The pathological evolution of HCC involves multiple intertwined factors, frequently characterized by the mutual aggravation of qi stagnation, blood stasis, phlegm-dampness congelation, and heat-toxin accumulation, collectively driving disease progression [8].

Turbidity-toxin induced debility is an important pathological concept in TCM, referring to the process wherein internal accumulation of turbidity-toxin leads to visceral functional decline and yin-yang and qi-blood imbalance [9]. Its pathological evolution proceeds through three stages: Initial stage: Endogenous turbidity-toxin generation, resulting from improper diet, external pathogenic factors, or emotional disturbances, causing spleen-stomach dysfunction and damp-turbidity retention. Middle stage: Turbidity-stasis intermingling, as damp-turbidity over time transforms into heat-toxin and combines with blood stasis, forming "turbidity-toxin with stasis," observable in the pathological process of malignancies. End-stage: Visceral failure, as turbidity-toxin pervades the Triple Burner (Sanjiao), leading to micro-accumulations and toxin-induced collateral damage, presenting a critical state of yin-yang separation. The core pathogenetic framework of HCC can be summarized as "healthy qi deficiency with turbidity-toxin and stasis accumulation, leading to liver collateral damage and mass formation." Here, "turbidity-toxin" refers to the interplay between exogenous damp-heat epidemic toxins (HBV/HCV) and endogenous phlegm-stasis turbid pathogens; "collateral damage" reflects the liver's unique property of storing yin and governing yang, with toxins primarily attacking the liver collaterals, following the pattern "disease first affects the meridians, then over time enters the collaterals"; "healthy qi deficiency" manifests as liver disease affecting the spleen and kidneys, consuming both qi and yin, forming a vicious cycle of "the more intense the toxin, the more deficient the qi." Overall, the pathogenesis can be characterized by toxin, deficiency, and stasis—manifesting as root deficiency with branch excess, mutually causative, with liver damage, toxin-stasis interlocking, and progressive depletion of healthy qi [10]. The transformation of pathological products follows the sequence: qi stasis → blood stasis → phlegm congelation → toxin accumulation (corresponding to the "chronic hepatitis → cirrhosis → HCC" evolution). The turbidity-toxin in HCC coalesces to form "cancer toxin" (characterized by concealment, metastasis, and consumptive properties), consistent with the TCM theory of "turbidity-toxin induced debility." For the treatment of turbidity-toxin debility patterns, National TCM Master Li Zhenhua proposed the therapeutic principle of "tonifying the spleen and kidney as the root, and eliminating dampness and descending turbidity as the branch" [11], which specifically includes:

Reinforcing healthyqiand consolidating the root: Restoring metabolic function by strengthening the spleen and tonifying the kidney; Detoxifying and expelling toxins: Utilizing herbs such as Scutellaria barbata (Banzhilian) and Hedyotis diffusa (Baihuasheshecao) to promote toxin excretion; Activating blood and resolving stasis: Incorporating herbs like Curcuma zedoaria (Ezhu) and Sparganium stoloniferum (Sanleng) to improve microcirculation and halt the "turbidity-stasis transforming into toxin" process. The concept of turbidity-toxin induced debility reflects the comprehensive pathological features of "environment-metabolism-immunity" dysregulation in modern diseases, offering a "toxin elimination and recovery" paradigm for the prevention and treatment of chronic conditions, with particular guiding value in refractory diseases such as chronic kidney disease and cancer.

3.2 Understanding of TCM Syndrome Differentiation Patterns in HCC

In TCM syndrome differentiation research on HCC, different academic schools have developed distinctive classification standards based on the four diagnostic methods (inspection, auscultation/olfaction, inquiry, and palpation). Through systematic analysis of clinical manifestations and pulse/tongue characteristics, the currently recognized basic syndrome types include: liver qi stagnation with spleen dysfunction, qi stagnation with blood stasis, phlegm-turbidity with blood stasis, liver-kidney yin deficiency, and spleen-kidney yang deficiency. Zhuang Tongzhuang et al. [12], through literature review, further classified HCC into eight syndrome types in clinical practice: liver depression with spleen deficiency, qi stagnation with blood stasis, liver heat with blood stasis, damp-heat with toxin accumulation, stasis-toxin intermingling, liver-kidney yin deficiency, spleen-kidney yang deficiency, and dual deficiency of qi and yin. Lü Shuyao et al. [13], through statistical analysis of relevant literature, further subdivided HCC syndromes into: liver depression with spleen deficiency, liver heat with blood stasis, liver-gallbladder damp-heat, spleen deficiency with dampness retention, and liver-kidney yin deficiency, providing more precise guidance for syndrome-based classification.

3.3 Understanding of TCM Herbal Treatment for HCC

The principles of herbal therapy for HCC include: invigorating the spleen and appetizing the stomach throughout treatment; prioritizing the regulation of qi movement; using heat-clearing and toxin-resolving herbs in appropriate dosages; and exercising caution in advanced stages and in patients with bleeding tendency when employing blood-breaking and stasis-expelling agents [14]. The Essentials from the Golden Cabinet proposes the view: "When treating liver disease, one should know that liver disease can transmit to the spleen, and therefore should strengthen the spleen first." Hence, for patients who commonly present with poor appetite, postprandial abdominal distension, loose stools, fatigue, pale tongue, and slow/soft pulse—symptoms indicative of spleen-stomach

weakness—reinforcing healthy qi and strengthening the spleen should be considered the core strategy throughout the entire treatment course.

The liver's physiological function is to govern the free flow of qi and regulate qi movement; the spleen's physiological function is to govern transportation and transformation and is known as the "foundation of acquired constitution." The spleen and stomach serve as the pivot for ascending and descending qi movement. Therefore, in treating HCC, regulating qi movement takes priority: when qi flows, blood circulates and stasis resolves; when qi flows, water moves and dampness dissipates. In the middle and advanced stages of HCC, heat transformation frequently occurs, with rapid disease progression. Most practitioners [15] tend to adopt heat-clearing and toxin-resolving methods, but these must be used in appropriate timing and dosage to avoid excessive cold-bitter herbs that may damage the spleen and stomach—especially insect-derived drugs, which may exacerbate liver function impairment or induce bleeding. HCC patients frequently present with various blood stasis symptoms in clinical practice. While appropriate use of blood-activating and stasis-resolving herbs is generally effective in early stages, caution is warranted in advanced HCC, particularly with blood-breaking and stasis-expelling agents, to prevent adverse outcomes.

4. The Principles of FZKA and Formulation and Mechanisms of Action Formula

4.1 TCM Formulation Principles

The formulation of FZKA adheres to TCM principles of holism and syndrome differentiation. Its core rationale lies in reinforcing healthy qi and eliminating pathogenic factors, by regulating yin-yang balance, enhancing the body's healthy qi, and simultaneously inhibiting tumor growth and spread.

FZKA typically consists of: Health-reinforcing herbs (e.g., Codonopsis pilosula [Dangshen], Astragalus membranaceus [Huangqi], Atractylodes macrocephala [Baizhu], Ligustrum lucidum [Nüzhenzi]), Anticancer herbs (e.g., Scutellaria barbata [Banzhilian], Hedyotis diffusa [Baihuasheshecao], Cremastra appendiculata [Shancigu]), Blood-activating herbs (e.g., Curcuma zedoaria [Ezhu], Salvia miltiorrhiza [Danshen]), with the foundational therapeutic principle of "reinforcing healthy qi and consolidating the root, detoxifying and dispersing masses." Astragalus and Atractylodes etc., supplement spleen and lung qi, enhance immunity, boost healthy qi, and resist pathogenic factors; Hedyotis and Scutellaria clear heat and remove residual cancer toxins; Curcuma and Salvia activate blood and unblock collaterals to disperse masses and improve microcirculation. The combination reinforces healthy qi without retaining pathogens, and dispels pathogens without harming healthy qi, collectively achieving the effect of reinforcing qi and combating cancer, regulating visceral functions and improving the internal environment for HCC treatment. Additionally, based on the patient's specific symptoms, signs, and syndrome differentiation results, herbs for regulating qi, resolving stasis, eliminating dampness, and transforming phlegm are flexibly incorporated to address both root and branch. Modifications may be made according to syndrome differentiation: for dual deficiency of qi and blood, add Panax ginseng (Renshen) 10g (or Panax quinquefolius [Xiyangshen]), Colla Corii Asini (Ejiao) 10g (melted), and Ziziphus jujuba (Dazao) 10g; for yin deficiency with internal heat, add Ophiopogon japonicus (Maidong) 15g and Dendrobium nobile (Shihu) 12g; for yang deficiency with cold congelation, add prepared Aconitum carmichaelii (Fuzi) 6g (decocted first), Cinnamomum cassia (Rougui) 6g, and Cervus elaphus antler glue (Lujiaojiao) 10g.

4.2 Western Pharmacological Mechanisms [16]

1) Immunomodulatory Effects: Qi-invigorating herbs such as Astragalus and Codonopsis in the formula exhibit significant immunomodulatory functions. Modern pharmacological studies indicate that these agents effectively stimulate immune cell proliferation and differentiation, enhance T lymphocyte and B lymphocyte antibody production, and significantly increase natural killer (NK) cell cytotoxicity. By simultaneously enhancing both cellular and humoral immune responses, they comprehensively improve immune defense and tumor immune surveillance.

2) Antiproliferative and Apoptosis-Inducing Activity: Bioactive constituents in anticancer herbs can interfere with tumor cell metabolism, inhibit DNA and protein synthesis, and induce apoptosis. For instance, flavonoids and alkaloids from Scutellaria barbata can induce HCC cell apoptosis through multiple signaling pathways.

3) Alleviation of Chemoradiotherapy Adverse Effects: During HCC chemoradiotherapy, FZKA can regulate the internal environment to mitigate damage to bone marrow, gastrointestinal tract, and other tissues caused by treatment.

5. Clinical Application Studies of FZKA in HCC Treatment

5.1 Serum Metabolomics Study of FZKA in Treating HCC with Liver Depression, Spleen Deficiency, Stasis, and Toxin Pattern

Cui Yi, Zhang Jiao, et al. [17] treated 12 HCC patients with conventional Western medicine combined with FZKA. Results showed that FZKA significantly influenced the serum metabolic profile of patients, identifying 14 differential metabolites. In-depth analysis of the main enrichment pathways, regulatory networks, and mechanisms revealed decreased L-tyrosine-L-glycine and increased valine-valine levels. Serum glycine levels were positively correlated with HCC progression. Glycine plays a key role in regulating methylation status and DNA/RNA synthesis in cancer cells, promoting tumor cell metastasis, transformation, and proliferation. Muthusamy et al. reported that glycine deficiency leads to accumulation of toxic deoxysphingolipids in tumors, thereby inhibiting cancer cell growth. This study provides a novel perspective on FZKA treatment for HCC from a serum metabolomics angle.

5.2 Comparative Laboratory Indicator Study of FZKA in HCC Treatment

Zhao Peixi, Xu Jianqin, et al. [18] conducted a clinical study

comparing a Western medicine control group with a group receiving Western medicine plus FZKA for HCC patients with liver depression, spleen deficiency, stasis, and toxin pattern. By analyzing pre- and post-treatment laboratory indicators, they confirmed the clinical synergistic effects of FZKA. Outcome measures included changes in liver function markers (ALT, TBIL, PT), white blood cell count (WBC), hemoglobin (HGB), alpha-fetoprotein (AFP), as well as TCM symptom scores and quality of life (EQ-5D) scores. Clinical results demonstrated that, in terms of liver function, ALT levels in the FZKA group showed a decreasing trend post-treatment, suggesting that FZKA has the potential to reduce transaminase activity and protect liver function, while effectively alleviating hypochondriac pain, anorexia, weight loss, fatigue, and abdominal distension. Moreover, the significant improvement in EQ-5D scores further indicated that combining FZKA with Western medical therapy can markedly ameliorate clinical symptoms and enhance quality of life in HCC patients.

5.3 Network Pharmacology-Based Investigation of FZKA Mechanisms in HCC Treatment

Zhao Peixi, Tang Shihao, et al. [19] investigated the active constituents, target proteins, and potential mechanisms of FZKA in HCC treatment through pharmacological pathway studies. Results revealed that FZKA inhibits tumor cell growth through its active ingredients acting on key protein targets, primarily including PTGS2, NCOA2, and ESR1, by reducing immune-inflammatory responses, inhibiting HCC cell proliferation and metastasis, and inducing apoptosis. Astragalus polysaccharides, as active components of Astragalus in FZKA, exert immunomodulatory effects; polysaccharides from Codonopsis also enhance immune function; and extracts (ethanol, aqueous, chloroform) of Scutellaria barbata all exhibit antitumor activity. This study provides new insights into FZKA treatment for HCC based on pharmacological and biological analyses.

Lou Jing, Zhao Lei, et al. [20] investigated the effects of Fuzheng Ruanjian Kangai Formula on the malignant biological behaviors of HCC HepG2 cells via signaling pathway regulation. Results showed that the formula effectively inhibited cancer cell proliferation in a dose-dependent manner. Specifically, with increasing drug concentration, HepG2 cell viability, proliferation activity, and clonogenic ability all declined. Furthermore, the formula induced changes in key protein expression, downregulating pro-proliferative proteins (PCNA, MMP-2, MMP-9) and upregulating pro-apoptotic proteins (Caspase-3, P53), thereby molecularly confirming the apoptosis-promoting effect of Fuzheng Ruanjian Kangai Formula. Additionally, the formula effectively prevented cancer cell metastasis, significantly inhibiting cell migration and invasion, and reducing metastasis-associated MMP-2 and MMP-9 levels. In summary, Fuzheng Ruanjian Kangai Formula inhibits HCC HepG2 cell proliferation, migration, and invasion, and promotes apoptosis through regulation of the Akt/MDM2/P53 signaling pathway.

5.4 Efficacy Evaluation of FZKA in HCC Patients Based on Pre- and Post-Treatment Assessment

Yan Ruijuan, Li Jingtao, et al. [21] used FZKA combined with TACE and three-dimensional conformal radiotherapy (3-DCRT) to treat primary HCC. Through assessment of solid tumor size, Karnofsky performance status, cellular immune function, adverse reactions, and survival rates, the study found that FZKA combined with TACE and 3-DCRT improved quality of life, reduced TACE- and 3-DCRT-induced cellular immunosuppression, prolonged survival, and demonstrated significant antitumor effects.

Zeng Hui, Wei Xiaoyan, et al. [22] established a HCC-bearing mouse model and administered FZKA to monitor tumor volume and weight changes. Pathological analysis of tumor tissues via HE staining, along with detection of angiogenesis, apoptosis, and related molecular expression, aimed to elucidate the specific mechanisms of FZKA in HCC progression. Additionally, HCC cells were treated with varying concentrations of FZKA to assess proliferation, migration, and invasion capabilities. In the HCC-bearing mouse model, FZKA significantly reduced tumor volume and weight, and exacerbated pathological damage. The formula also decreased expression of VEGF, CD34, and Bcl-2, while promoting Bax, cleaved caspase 3, and Cyt-C expression. In vitro experiments further confirmed that FZKA co-incubation inhibited HCC cell proliferation, migration, and invasion. Collectively, this study revealed that FZKA suppresses HCC progression by promoting apoptosis and inhibiting angiogenesis.

Fang Yu, Yang Yang, et al. [23] investigated the anti-HCC effects of FZKA via reversal of epithelial-mesenchymal transition (EMT) in HepG2 cells. They found that FZKA, through multi-component synergy, targets key EMT proteins, offering a low-toxicity therapeutic strategy for HCC metastasis. HCC cells acquire migratory and invasive capabilities through EMT. FZKA modulates key EMT proteins by upregulating E-cadherin (an epithelial marker maintaining cell-cell adhesion) and downregulating Vimentin (a mesenchymal marker promoting migration), forcing cancer cells to revert from a “mesenchymal state” to an “epithelial state,” thereby losing migratory and invasive capacities, reversing the EMT process. This significantly reduced HepG2 cell adhesion rate and wound healing rate, with enhanced efficacy when combined with cisplatin, reducing cancer cell invasion. Furthermore, the study suggested that combining FZKA with cisplatin may enhance efficacy through multi-target effects (e.g., inhibiting TGF-β pathway, regulating protein expression), reducing cisplatin dosage and side effects—not only decreasing cancer cell invasiveness but also potentiating cisplatin’s anticancer effects via protein expression regulation, demonstrating synergistic effects and offering new insights for integrated TCM-Western medicine treatment of HCC.

6. Conclusion

HCC is characterized by insidious onset, rapid progression, and extremely high mortality. China bears a heavy burden of HCC. Western medical treatments for advanced HCC have not achieved satisfactory outcomes. TCM, with its emphasis on holism, syndrome differentiation, and root-cause investigation, demonstrates unique advantages in improving quality of life and prolonging survival in advanced HCC

patients. In patients with advanced HCC who are not candidates for surgical resection, integrated TCM-Western medicine approaches and multimodal combination therapies can significantly reduce tumor aggressiveness, decrease recurrence and metastasis rates, and improve long-term survival and quality of life. FZKA exhibits remarkable therapeutic effects in clinical HCC management, including symptom improvement, quality-of-life enhancement, immune function regulation, and reduction of tumor biomarker levels. The application of FZKA in HCC prevention and treatment, combined with modern medical modalities (surgery, chemoradiotherapy, interventional therapy), complements and reinforces comprehensive treatment strategies, expands the scope of TCM applications, and leverages the strengths of various approaches from different angles to improve treatment specificity and effectiveness. With deepening research and accumulating clinical experience, the integration of FZKA with other treatment modalities is expected to provide more optimized and personalized therapeutic options for HCC patients. However, several issues in current research remain to be addressed. Future efforts should focus on standardizing study protocols, conducting large-scale, multi-center trials, and further elucidating mechanisms of action to fully harness the advantages of FZKA in HCC treatment, offering more effective therapeutic options and improving patient prognosis.

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