Chinese Journal of Natural Medicines

Modernization of traditional Chinese medicine in cancer therapy: "3 D" innovative Chinese medicine

Hui Liu, Yunxiao Ge, Zigang Dong

Citation: Hui Liu, Yunxiao Ge, Zigang Dong, Modernization of traditional Chinese medicine in cancer therapy: "3 D" innovative Chinese medicine, Chinese Journal of Natural Medicines, 2026, 24(2), 189–202. doi: 10.1016/S1875–5364(26)61090–4.

View online: https://doi.org/10.1016/S1875–5364(26)61090–4

Chinese Journal of Natural Medicines 24 (2026) 189-202

Contents lists available at ScienceDirect

Chinese Journal of Natural Medicines

journal homepage: www.cjnmcpu.com/

Review

Modernization of traditional Chinese medicine in cancer therapy: "3 D" innovative Chinese medicine

Hui Liu[a,b,c,*], Yunxiao Ge[a,c], Zigang Dong[a,c,*]

[a] *Department of Pathophysiology, School of Basic Medical Sciences, College of Medicine, Zhengzhou University, Zhengzhou 450001, China*
[b] *Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm 17177, Sweden*
[c] *China-US (Henan) Hormel Cancer Institute, Zhengzhou 450008, China*

ARTICLE INFO

Article history:
Received 18 February 2025
Revised 27 April 2025
Accepted 1 July 2025
Available online 20 February 2026

Keywords:
Traditional Chinese medicine
Innovative Chinese medicine
Definite active ingredient composition and content
Determined functional mechanism
Detection through evidence-based medicine
Cancer therapy
Drug discovery

ABSTRACT

Traditional Chinese medicine (TCM) has garnered increasing attention globally, with its modernization becoming a prominent research focus both within China and internationally. However, the lack of a precise definition for TCM modernization has hindered clear guidance for its development. Additionally, cancer remains a significant global public health challenge, largely untreatable with current methods. Therefore, a comprehensive understanding of TCM modernization is crucial for its evolution, revolution, drug discovery, and cancer therapy. This study provides an overview of the history, theory, characteristics, and evolution of TCM, highlighting its potential in cancer prevention and treatment. We propose a definition for TCM modernization, innovative Chinese medicine (ICM), and elucidate strategies to elevate TCM from a supporting role to a leading one. Electronic databases such as PubMed, Web of Science, ScienceDirect, and Clinical Trials were utilized to retrieve relevant literature spanning from 1979 to 2024, with most publications being from the last five years, using keywords like "Traditional Chinese medicine", "Cancer", "Mechanism", and "Clinical trial". In this study, we introduce the theory of TCM modernization following target identification and initial compound screening: ICM, defined by "3 D" elements: definite active ingredient composition and content, determined functional mechanism, and detection through evidence-based medicine. Overall, the "3 D" definition of ICM will establish a standard for ICM, accelerate TCM modernization, enhance drug discovery targeting cancer and various human diseases, and benefit patients worldwide.

1. Introduction

Traditional Chinese medicine (TCM) has a long history of treating diseases in China. Before 1835, when missionaries introduced Western science and medicine to China, TCM was the primary treatment strategy. Missionary hospitals expanded from 1861, and Western medicine became established in China in the early 20th century. Consequently, TCM gradually receded from its dominant position, replaced by Western medicine. However, the importance of TCM has been reevaluated due to the complexity of diseases and advancements in scientific research, particularly for conditions without cures, such as epidemic diseases and cancer.

The identification of therapeutic targets and initial compound screening in cancer has been advanced through structural biology, bioinformatics, and artificial intelligence (AI). The challenge lies in transforming TCM from a supportive role to a leading one. The modernization of TCM has spurred scientific research and technological innovation. Significant progress has been made in TCM pharmacology, pharmaceutical preparations, and quality control, providing more effective drugs and treatment methods for cancer therapy. Nevertheless, the lack of a precise definition for TCM modernization continues to hinder its development. Therefore, a comprehensive understanding of TCM modernization is pivotal for its evolution and revolution. In this review, we examine the history, theory, characteristics, and evolution of TCM and propose the theory of TCM modernization following target identification and initial compound screening: innovative Chinese medicine (ICM), defined by "3 D" elements: definite active ingredient composition and content, determined functional mechanism, and detection through evidence-based medicine.

Cancer remains a major global public health challenge that is largely untreatable at present. ICM may offer a novel strategy for cancer treatments by dampening cancer hallmarks, including key signal transduction, cell population reprogramming, immune response, metabolism, microbiota, and emotion regulation. Moreover, ICM exhibits protective and adjuvant therapeutic effects when combined with clinical chemotherapy, radiotherapy, targeted therapy, and immunotherapy, improving patient quality of life and survival time. The "3 D" definition will establish a standard for ICM, accelerating TCM modernization and drug discovery and benefiting patients worldwide.

* Corresponding author.
E-mail addresses: huiliu666@zzu.edu.cn (H. Liu); dongzg@zzu.edu.cn (Z. Dong)

https://doi.org/10.1016/S1875-5364(26)61090-4

2. Traditional Chinese medicine

2.1. History of traditional Chinese medicine

China possesses a rich medical heritage spanning approximately 5000 years, during which early civilizations identified the therapeutic potential of various plants and animals (Fig. S1A), laying the foundation for TCM. Key historical milestones in the development of TCM include advancements in pharmacological practices during the Xia and Shang dynasties, the formulation of the *Four Diagnostic Methods* by Que Bian in the Spring and Autumn period, and the compilation of seminal texts such as *Huangdi Neijing* and *Shennong's Herbal Classic of Materia Medica* in the Qin, Han, and Eastern Han dynasties. The late Eastern Han era saw Tuo Hua's pioneering use of surgical anesthesia, while the Ming dynasty witnessed the publication of Shizhen Li's *Compendium of Materia Medica.* In the Qing dynasty, Tianshi Ye made significant contributions to the understanding of febrile diseases. Despite experiencing a period of decline beginning in the mid-Qing dynasty, exacerbated during the Republic of China era with the widespread introduction of Western medicine, TCM has experienced a resurgence as its clinical efficacy becomes increasingly recognized. In parallel, the modernization of TCM has emerged as a major area of focus, driving continuous progress in both research and clinical application.

2.2. Theory, characteristics, and evolution of traditional Chinese medicine

The theoretical system of TCM mainly includes Yin and Yang, Five Elements (Metal, Wood, Water, Fire, and Earth), Qi and Blood, Zang-Fu, and Meridian (Fig. S1B). Characteristics of TCM include dialectical therapy, Ping He, individualization, prevention, and holistic healing (Fig. S1C). The original word or character of TCM in Chinese contains herbs and a Chinese musical instrument, which evolved into herbs and music, and finally the present character (Fig. S1D). The meaning of the character in Chinese is that music comes from nature and grows from plants. Based on this, TCM has Wuyin Therapy, also known as five-element music therapy, using the relationship between Gong (Do, 1), Shang (Re, 2), Jue (Mi, 3), Zhi (So, 5), Yu (La, 6), and the five elements of human body to select the music for treatment [1]. Heart belongs to Fire, liver belongs to Wood, spleen belongs to Earth, lung belongs to Gold, and kidney belongs to Water in the Five Elements (Fig. S1E). Therefore, listening to different types of music may help cure relevant diseases, and the potential mechanisms need deep investigation [2, 3]. From the perspective of TCM, the occurrence of diseases is related to the deficiency and excess of Yin and Yang in the Zang-Fu organs [4]. Herbal medicines are used to regulate Yin and Yang, prevent, and treat diseases. The theory and characteristics maintain the lineage development of TCM.

3. Modernization of traditional Chinese medicine

The theory and practice of TCM have significantly contributed to the development of Chinese medicine, including curing diseases (smallpox, plague, cholera), strengthening the body, and prolonging lifespan through traditional Chinese herbs, acupuncture, moxibustion, massage potting, Tai Chi, and Qigong. Meanwhile, TCM introduces new ideas and methods for global healthcare development. TCM has gradually gained recognition and study by the global medical community, making important contributions to human health. TCM posits that each drug ingredient possesses its own band and frequency. When the bands and frequencies of various drug ingredients are well adjusted, and their relationships are harmonized, it constitutes a good medicine according to music and chord theory. However, several issues persist with this TCM pattern. The composition and content of active ingredients are complex and lack quality control, the mechanisms of these ingredients remain unelucidated, and most therapies are not validated by evidence-based medicine. Critically, most TCM therapies are not tested through double-blind clinical trials due to limitations such as unclear active ingredients and compositions. Consequently, we propose the theory of TCM modernization following target identification and initial compound screening: ICM, defined by "3 D" elements.

3.1. Food and Drug Administration (FDA) approved anticancer drugs originating from herbal medicines

The development history of natural medicine can be divided into four stages: the primitive and embryonic stage (before the end of the 18th century); the formation of the discipline (the 19th century); rapid development of the discipline (the 21st century); multidisciplinary technology coupling and the call of "return to nature" (recent 20 years). We summarized FDA-approved anticancer drugs from 1946 to 2024 (Table S1). Approximately 65% of these drugs originate from natural compounds [5]. Natural products and their analogues have significantly contributed to disease treatments, particularly for cancer and infectious diseases. However, natural products also pose challenges to drug discovery, including technical barriers in screening, isolation, characterization, and optimization, leading the pharmaceutical industry to reduce its pursuit of natural products since the 1990s [6]. Excitingly, recent technological and scientific advancements, encompassing analytical tools, genomic mining, engineering strategies, and microbial culture, are addressing these challenges and opening new opportunities. As a result, interest in natural products as drug leads is reviving, especially in cancer therapy and antimicrobial resistance management [7]. Successful examples of FDA-approved anticancer drugs derived from natural plants include paclitaxel, camptothecin, podophyllotoxin, doxorubicin, daunorubicin, homoharringtonine, ginsenoside, vinblastine, colchicine, cepharanthine, indirubin, berbamine, monocrotaline, anethole, and gossypol. Among them, paclitaxel serves as a representative model of natural product-based anticancer agents.

3.2. Paradigm of natural anticancer drugs: discovery, optimized, and upgraded of paclitaxel

The United States accelerated the screening of anticancer drugs after World War II. The National Cancer Research Center (NCI) established the Cancer Chemotherapy National Service Center (CCNSC) in 1955, which is responsible for national anticancer drug screening. In 1960, they began screening anticancer drugs from natural extracts of plants and animals. Researchers collected and tested over 30 000 samples over the next 20 years, identifying paclitaxel as one of the best natural anticancer drugs in this extensive screening project [8]. Susan Horwitz revealed in 1979 that paclitaxel promotes tubulin polymerization and prevents microtubule depolymerization, causing cells to stall during division and leading to cell death [9]. Phase I clinical trials of paclitaxel began in 1984, advancing to phase II in 1985. The NCI reported phase II clinical trial results in 1988, showing a 30% response rate for recurrent ovarian cancer with paclitaxel treatment [10]. In December 1992, paclitaxel was approved by the FDA for treating advanced ovarian cancer under the trade name taxol. Furthermore, docetaxel was approved by the FDA in 1996 for treating advanced breast cancer and later for non-small cell lung cancer (NSCLC), prostate cancer, and gastric cancer [11].

Although paclitaxel showed dramatic anticancer effect, the incidence of hypersensitivity and severe allergic reactions in pa-

tients after paclitaxel treatment is 2% to 4% because of the poor water solubility, which results in the need for preconditioning with corticosteroids and antihistamines prior to medication, complicating the dosing schedule and increasing the financial burden on patients [12, 13]. Docetaxel, structurally similar to paclitaxel with the same parent nucleus but differing in two groups, exhibits better water solubility. Despite this, docetaxel still requires tween-80 and ethanol as solvents and is more likely to cause allergic reactions, necessitating anti-allergy drugs before use [14]. To mitigate paclitaxel's side effects, researchers have developed several novel formulations approved worldwide, including paclitaxel liposomes, albumin-bound paclitaxel, paclitaxel polymer micelles, and paclitaxel oral solution. In 2003, the world's first new paclitaxel formulation was approved in China, independently developed by a Chinese pharmaceutical company [15]. In 2005, the world's second new paclitaxel formulation, 130-nanometer albumin-bound paclitaxel (abraxane, nab-paclitaxel), emerged, approved by the FDA in the United States for second-line metastatic breast cancer and subsequently for first-line treatment of NSCLC, advanced triple-negative breast cancer, and other tumors [16, 17]. In 2007, paclitaxel polymer micelles were introduced, greatly reducing microbial contamination and immune resistance risks with higher tolerated doses [18]. The paclitaxel oral solution, liporaxel, appeared and was approved in several countries for treating advanced or metastatic gastric cancer [19-21].

4. Anticancer drugs originating from an innovative Chinese medicine paradigm

4.1. Definite active ingredient composition and content

Despite the verification of abundant therapeutic targets, effective inhibitors remain unavailable in clinics. Drug screening from the TCM database suggests that TCM may serve as promising inhibitors for cancer control. Numerous compounds originating from TCM prescriptions and Chinese natural compounds are in clinical trials or preclinical studies, representing potential medicines for human diseases. Five Chinese herbs are approved by the *United States Pharmacopoeia*, and more than 60 are approved by the *European Pharmacopoeia* (Tables S2 and S3). Chinese patent medicine (CPM) is widely used in China for cancer therapy, with over 70 CPMs applied to treat different cancer types (Table S4). However, most CPMs are mixtures used as adjuvant treatments to enhance efficiency, mitigate chemotherapy/radiotherapy side effects, and strengthen organic immunity. The main reasons are the unclear active ingredient composition and content, and the unelucidated functional mechanisms. Therefore, there is significant potential for CPM/TCM to evolve into ICM as a primary role in cancer therapy. In recent years, more and more TCM recipes and specific compounds originating from TCM have shown promising anticancer effects (Tables S5 and S6). Although active ingredient compositions exist, their exact content remains undefined. Further studies are needed to identify the content of active specific compounds and improve extraction efficiency. For low-content compounds, chemical synthesis offers a viable approach to generate sufficient quantities. In our previous study, we identified 5,7,4'-trimethoxyflavone as a major active ingredient in Chenpi with very low content, which we synthesized ourselves, achieving the same anti-cancer effects as the extracted compound [22].

4.2. Determined functional mechanism

Preclinical studies on potential ICM reveal that ICM dampens cancer progression through several hallmark mechanisms, including key signal transduction, cell population reprogramming, immune response, metabolism, microbiota, and emotion regulation. Moreover, ICM exhibits protective and adjuvant therapeutic effects when combined with clinical chemotherapy, radiotherapy, targeted therapy, and immunotherapy.

4.2.1. Potential ICM blocks dysregulated signal transduction

Dysregulated signal transduction is a hallmark of cancer and encompasses multiple interrelated processes, including sustained proliferative signaling, evasion of growth suppressors, tumor-promoting inflammation, induction of angiogenesis, genomic instability and mutation, as well as non-mutational epigenetic reprogramming. These alterations collectively enable cancer cells to achieve replicative immortality and resist programmed cell death [23]. ICM can act as protein kinase inhibitor or proteasome to block dysregulated signal transduction, primarily targeting the PI3K/AKT, WNT/β-catenin, JAK/STAT, TGF-β/SMAD, EGF/EGFR signaling pathway, HER2, NOTCH, cell death, and proteasome, leading to impaired cell proliferation, tumor growth, invasion, and metastasis (Tables S5 and S6, Fig. 1). For example, specific compounds (quercetin, capsaicin, celastrol, contharidin, and minnelide: water-soluble prodrug of triptolide) originated from TCM are currently in clinical trials [24-27]. Regrettably, most of these trials focus on human diseases other than cancer, including cardiovascular diseases, inflammatory conditions, pulmonary disorders, polycystic ovary syndrome, diabetes mellitus, obesity, antioxidant therapies, blood pressure regulation, recurrent spontaneous abortion, hypertension in preeclampsia, sperm motility, molluscum, and neuropathic pain. In recent years, several TCM-derived compounds have shown promise as ICM for cancer therapy, including gambogic acid, bufalin, brusatol, saikosaponin D, erianin, and 5,7,4'-trimethoxyflavone (TMF). Gambogic acid, a primary active ingredient in *Garcinia hanburyi*, exerts anti-cancer activity through the NF-κB signaling pathway, dependent on GPR108 [28]. Another study reported that gambogic acid induces pyroptosis by directly targeting CNPY3 (the canopy FGF signaling regulator) in prostate cancer, which was previously thought to be "undruggable". Gambogic acid recruits delactatease SIRT1, eliminating lysine lactylation and disrupting the cellular localization of CNPY3, thereby promoting lysosome rupture to trigger pyroptosis [29]. Additionally, celastrol and gambogic acid were identified as novel antagonists of the ERα (estrogen receptor alpha) Y537S mutation, exhibiting synergistic effects when combined with the FDA-approved CDK4/6 inhibitor abemaciclib in breast cancer [30]. Bufalin, a highly toxic ligand extracted from toad venom, demonstrates potent antitumor effects. It inhibits intrahepatic cholangiocarcinoma progression by targeting CAMKK2 *via* the WNT/β-catenin signaling pathway [31]. Bufalin targets the SRC3/MIF cascade to regulate M2 macrophage polarization in colorectal cancer [32]. Furthermore, bufalin can also bind to AHSA1-K137 and UBA3 [33, 34]. Brusatol, a known NRF2 inhibitor, directly binds to SKP1, disrupting its interaction with the F-box protein SKP2. This inhibition suppresses the SKP2-SCF E3 and β-TRCP-SCF E3 ligases, leading to the accumulation of substrates such as p27 and *E*-cadherin in NSCLC [35]. Saikosaponin D, a major bioactive component of *Bupleurum chinensie*, binds to the SH2 domain of STAT3, alleviating cancer cachexia [36]. Moreover, saikosaponin D interacts with FTO to increase global m^6A RNA methylation, destabilizing downstream gene transcripts and suppressing various pathways in leukemia [37]. Erianin is the main active ingredient in *Dendrobium chrysotoxum*, a well-known traditional Chinese herb used in gastric disease treatment, considered as the first of the "nine immortal grasses" [38]. Recent studies showed that erianin induces Ca^{2+}/CaM-dependent ferroptosis to inhibit lung cancer development [39]. Moreover, erianin binds to CRAF and MEK1/2, suppressing BRAF V600E or RAS mutant melanoma and colorectal cancer progression without affecting BRAF kinase activity [40]. TMF, extracted from Chen Pi, directly binds to LRPPRC,

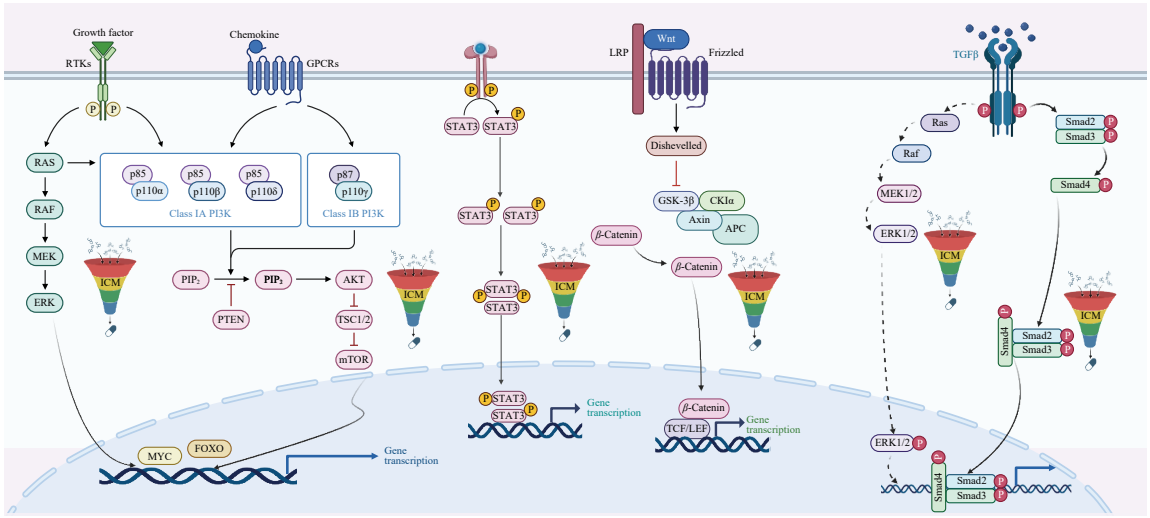

Fig. 1 Innovative Chinese medicine may act as protein kinase inhibitors or proteasomes to block dysregulated signal transduction pathways, including the MAPK, PI3K/AKT, JAK/STAT, WNT/β-catenin, TGF-β/SMAD, EGF/EGFR signaling pathways, HER2, NOTCH, cell death, and proteasome pathways, thereby impairing cell proliferation, tumor growth, invasion, and metastasis.

STAT3, and CDK1, dissociating the LRPPRC-JAK2-STAT3 and JAK2-STAT3-CDK1 complexes. This suppresses tumorigenesis in esophageal cancer with no apparent toxicity. Notably, TMF overcomes paclitaxel resistance and exhibits synergistic effects with PI3K/AKT inhibitors [22].

4.2.2. Potential ICM redresses cellular metabolism

An increasing number of studies reveal that ICM impedes cancer development by suppressing cellular metabolism. This suppression includes targeting glycolysis, regulating AMPK/mTOR signaling, modulating mitochondrial function, inducing autophagy, and inhibiting lipid metabolism (Table S5, Fig. 2). Cancer cells typically exhibit increased glycolysis, known as the Warburg effect, to meet their energy demands and support rapid proliferation. Research indicates that ICM can impair glycolysis to inhibit cancer progression [41]. For instance, dihydroartemisinin and artesunate block aerobic glycolysis in cancer cells through the ERK/c-MYC signaling pathway. These compounds reduce glucose uptake, ATP production, lactate secretion, and the expression of glucose transporter GLUT1, hexokinase, lactate dehydrogenase, and c-MYC, thereby inhibiting cancer cell growth [42]. Shikonin, a naphthoquinone compound extracted from the roots of *Lithospermum erythrorhizon*, reduces aerobic glycolysis in cancer-associated fibroblasts (CAFs). It decreases glucose uptake, ATP concentration, lactate production and secretion, and the expression of monocarboxylate transporter 4 (MCT4). Notably, shikonin exhibits synergistic effects with gemcitabine in mice, with no significant systemic toxicity observed [43]. Apigenin restricts glycolysis by targeting the K433 site of PKM2, thereby blocking CRC progression [44]. Cardamonin, a chalcone derived from *Alpinia katsumadai*, inhibits HIF-1α expression by repressing the mTOR/p70S6K pathway. This repression enhances mitochondrial oxidative phosphorylation (OXPHOS) and reactive oxygen species (ROS) accumulation in an NRF2-dependent manner, while reducing glucose uptake, lactic acid production, and efflux in breast cancer [45]. Arctigenin, a lignan component extracted from Arctium seed, dissipates mitochondrial membrane potential by suppressing mitochondrial complexes II and IV. It selectively kills OXPHOS-dependent cells through endoplasmic reticulum (ER) stress generation, mitochondrial membrane permeabilization, and caspase activation, ultimately leading to apoptosis and aponecrosis [46].

Resveratrol has been reported to counteract glucose uptake, reduce ROS production associated with excessive glycolysis, restore mitochondrial functional activity, and stimulate autophagy, thereby impairing cancer metastasis [47]. Curcumin was shown to attenuate fused in sarcoma aggregation-mediated liquid-liquid phase separation and pyruvate kinase sequestration while restoring cellular metabolism, leading to increased ATP levels [48]. Epigallocatechin gallate (EGCG), when combined with EGFR-TKIs, significantly reverses the Warburg effect by impairing glycolysis and enhancing mitochondrial respiration. This combination also increases ROS production and decreases lactate secretion. Additionally, it activates the AMPK signaling pathway while inhibiting both MAPK/ERK and AKT/mTOR signaling pathways, overcoming acquired drug resistance [49]. Dysregulated lipid metabolism is a hallmark of cancer, characterized by increased fatty acid synthesis and altered lipid metabolism that support rapid growth and proliferation [50, 51]. ICM can inhibit lipid metabolism, leading to impaired lipid synthesis and cancer. One study showed that cordycepin mediates the ERO1A/mTOR/SREBP1 axis, inhibiting lipid metabolism and metastasis in cholangiocarcinoma [52]. Quercetin and resveratrol have been reported to combat lipid droplet deposition in nonalcoholic fatty liver disease (NAFLD)-related liver cancer *via* AKT [53]. Berberine ameliorates abnormal lipid metabolism through the AMPK/SIRT1 signaling pathway, alleviating alcohol-induced liver injury in AFLD [54]. Picrasinoside F and luteolin in dandelion extract interfere with glycerophospholipids and unsaturated fatty acids metabolism by decreasing CHKA expression and impairing the PI3K/AKT/SREBP/FADS2 axis in TNBC [55].

4.2.3. Potential ICM reprograms cell population and immune response

ICM approaches to cancer treatment may involve strategies aimed at reprogramming cell populations within the tumor microenvironment (TME) to inhibit cancer development and progression. This is achieved by inducing tumor cell differentiation, modulating cancer stem cells, inhibiting angiogenesis, targeting cancer-associated fibroblasts (CAFs), as well as targeting immune cells (Tables S5 and S6, Fig. 3). Tumor cell differentiation refers to the process by which cancer cells acquire characteristics of more mature, specialized cell types, reducing their proliferative capacity and aggressiveness [56, 57]. ICM may induce tumor cell differentiation by modulating cell differentiation-related signal transductions (WNT/β-catenin pathway, NOTCH pathway, and hedgehog pathway), activating transcription factors, promoting epigenetic modifications (DNA methylation, RNA modification, and histone modification), inhibiting cancer stem cells, and enhancing cellular maturation processes [57-62]. ICM may exert anti-angiogenic effects by targeting endothelial cells and inhibiting the formation of new blood vessels within the tumor microenviron-

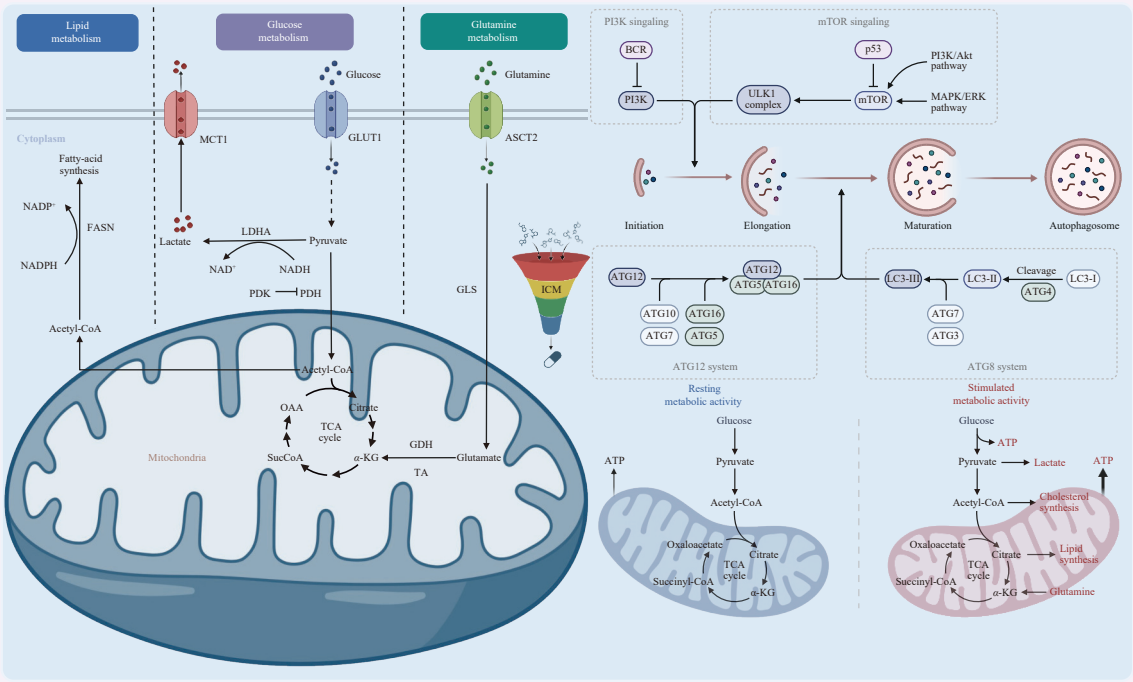

Fig. 2 Innovative Chinese medicine may impair cancer development through suppressing cellular metabolism, including targeting glycolysis and lipid metabolism, regulating AMPK/mTOR signaling, modulating mitochondrial function, and inducing autophagy.

ment. For example, the combination of baicalin and 5-FU significantly reduces inflammation and angiogenesis in breast cancer by suppressing the NF-κB/IL-1β and VEGF amplification loop [63]. CAFs are stromal cells within the TME that promote tumor growth, invasion, and metastasis. ICM formulations may target CAFs by inhibiting their activation, proliferation, and secretion of protumorigenic factors such as growth factors, cytokines, and extracellular matrix proteins. By disrupting the crosstalk between cancer cells and CAFs, ICM can impede tumor progression. Bufalin has been reported to reverse CAF-mediated CRC invasion and metastasis by inhibiting the STAT3 signaling pathway [63].

TCM has long been recognized for its ability to modulate the immune response, and its use in cancer treatment often involves strategies aimed at harnessing the body's immune system to target and eliminate cancer cells. ICM can enhance the activity of immune cells such as T cells, natural killer (NK) cells, and macrophages. By promoting the activation and proliferation of cytotoxic T cells and NK cells, ICM can facilitate the recognition and elimination of cancer cells. Additionally, ICM may inhibit immunosuppressive mechanisms, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), as well as induction of immunogenic cell death (ICD), which dampen antitumor immune responses (Fig. 3). Glycyrrhetinic acid was found to dramatically suppress breast cancer growth and metastasis by undermining macrophage M2 polarization *via* activating cytokine-stimulated JNK1/2 signaling pathway [64]. Another study identified that ginsenoside Rh2 augments anti-PD-L1 immunotherapy by reinvigorating $CD8^+$ T cells *via* increased intratumoral CXCL10 to inhibit cancer progression [65]. Furthermore, ginseng-derived nanoparticles were shown to reprogram macrophages by regulating ARG1 release, which alleviates T cell exhaustion in the TME through modulation of the mTOR-T-bet axis [66]. Salidroside regulates the HSP70/STUB1/FOXP3 signaling pathway in Tregs (a subset of T cells that suppress immune responses and maintain immune tolerance), suppressing Treg function and leading to reduced tumor growth [67]. In addition, calycosin, an active reagent of *Astragalus membranaceous*, can promote Treg cell differentiation and inhibit Th17 cell differentiation to exert its anti-inflammatory effects [68]. Euphohelioscopin A, extracted from *Euphorbia helioscopia* L., was identified to enhance NK cell-mediated killing of cancer cells by triggering pyroptosis [69]. Ginsenoside Rh2 was found to augment NK cell activity *via* modulating the NKG2D-MICA signaling pathway by binding to ERp5 in breast cancer [70]. MDSCs, a heterogeneous population of myeloid cells that suppress antitumor immune responses and promote tumor progression, can also be targeted by ICM. For example, dioscin, an active product of *Dioscorea nipponica*, promotes MDSC differentiation into M1 macrophages while inhibiting M2 macrophage differentiation, thereby suppressing CRC progression [71]. Periplocin reduces MDSCs recruitment *via* AKT/NF-κB signaling pathway to inhibit hepatocellular carcinoma (HCC) progression [72]. ICM can promote ICD, a form of cell death that stimulates an immune response against cancer cells. Study showed that γ-mangostin triggers ICD (HSP90B1, ANXA1, and IL1B) and activates cGAS signaling pathway *via* DNA damage response and epigenetic modification (HDAC4 degradation and acetylated histone H3 accumulation) in acute myeloid leukemia, resulting in activated and recruited $CD8^+$ T cells and suppressed cancer development [73].

4.2.4. Potential ICM regulates polymorphic microbiomes

The role of the microbiome in cancer initiation and progression is a hotspot in cancer research [74-76]. Increasing evidence suggests that ICM may impair cancer development by regulating polymorphic microbiomes through restoring microbial homeostasis, reducing inflammation, modulating immune responses, altering metabolism, inhibiting carcinogenic bacteria, and enhancing gut barrier function (Table S5, Fig. 4). ICM restores microbial homeostasis within the gut and other body sites by promoting the growth of probiotics and inhibiting pathogenic bacteria. For example, Pien Tze Huang treatment alters the gut microbiota profile by increasing the abundance of probiotics, such as *Pseudobutyrivibrio xylanivorans* and *Eubacterium limosum*, while depleting the pathogenic bacteria *Aeromonas veronii*, *Campylobacter jejuni*, *Collinsella aerofaciens*, and *Peptoniphilus harei* in CRC. This leads to improved gut barrier function and suppression of oncogenic and pro-inflammatory pathways, thereby inhibiting CRC tumorigenesis [77]. Berberine alleviates dextran sodium sulfate (DSS)-induced ulcerative colitis in mice by restoring disturbed gut microbiota, elevating unconjugated and secondary bile acids in the gastrointestinal tract, and activating the FXR and TGR5 signaling

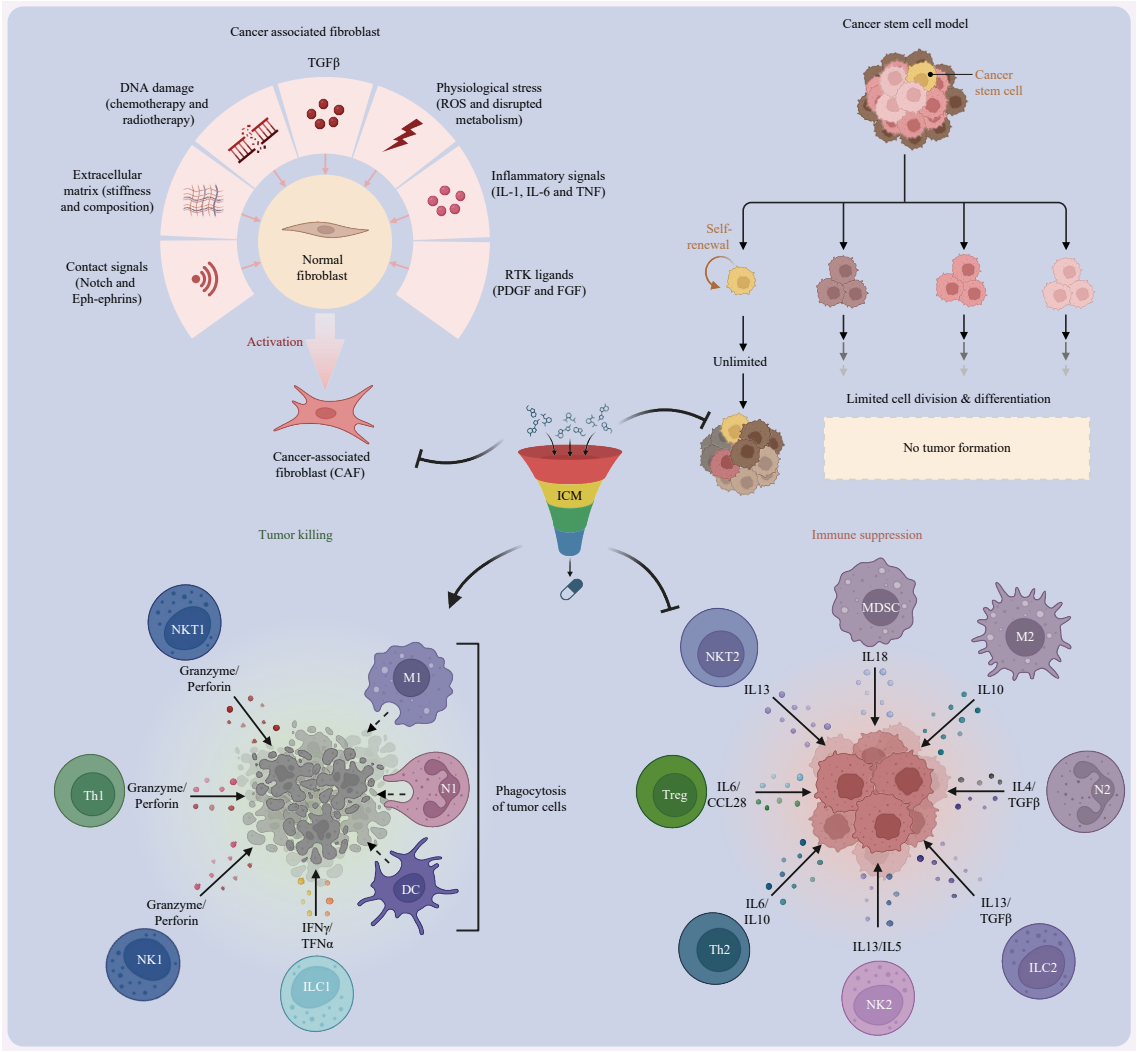

Fig. 3 Innovative Chinese medicine may involve strategies aimed at reprogramming cell populations within the tumor microenvironment (TME) to inhibit cancer development and progression. ICM employs strategies to reprogram cell populations within TME, thereby inhibiting cancer development and progression. These strategies include inducing tumor cell differentiation, modulating cancer stem cells, inhibiting angiogenesis, targeting cancer-associated fibroblasts (CAFs), and regulating immune cells. ICM enhances the activity of immune cells such as T cells, natural killer (NK) cells, and macrophages. By promoting the activation and proliferation of cytotoxic T cells and NK cells, ICM facilitates the recognition and elimination of cancer cells. Additionally, ICM may suppress immunosuppressive mechanisms, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), while also inducing immunogenic cell death (ICD), which dampens antitumor immune responses.

pathways [78]. Other studies identified that berberine treatment alleviates gut microbiota dysbiosis and increases the abundance of probiotics, including *Akkermansia* and *Parabacteroides* in high-fat diet-fed CRC mice, leading to inhibited lysophosphatidylcholine and CRC progression [79, 80]. Oral administration of baicalin was reported to enrich *Akkermansia* and *Clostridia_UCG-014*, resulting in increased short-chain fatty acids (SCFA), which improves the ratio of PD-1$^+$ (CD8$^+$ T cell/Treg), IFN-γ$^+$ CD8$^+$ T cells, and TNF-α$^+$ CD8$^+$ T cells within the TME to overcome anti-PD-1 resistance [81]. Echinacoside benefits short-chain fatty acids (SCFA)-producing microbiota without affecting total bacterial load under anaerobic conditions. It promotes the growth of butyrate-producing *Faecalibacterium prausnitzii* in a dose-dependent manner. Echinacoside inhibits liver metastasis by suppressing the PI3K/AKT signaling pathway and reversing the epithelial-mesenchymal transition (EMT) process in CRC [82]. A combination of quercetin and anti-PD-1 antibody reduces gut microbiota imbalance and increases the abundance of *Firmicutes*, *Actinobacteria*, and *Verrucomicrobiota* at the phylum level, *Dubosiella* and *Akkermansia* at the genus level, as well as macrophage immunity in HCC [83]. By targeting the gut microbiome, ICM creates an environment that supports host health and inhibits tumor growth and progression. However, further research is needed to fully elucidate the mechanisms by which ICM modulates the microbiome and its impact on cancer development.

4.2.5. Potential ICM neutralizes emotion

Emotion regulation influences cancer progression through its effects on immune function, neuroendocrine pathways, inflammation, oxidative stress, behavior, epigenetic modifications, and interactions with TME [84, 85]. Understanding the complex interplay between emotion regulation and cancer biology is essential for developing targeted interventions to improve emotional well-being and mitigate the impact of stress on cancer outcomes. ICM may suppress cancer development through emotion regulation by reducing stress, modulating the hypothalamic-pituitary-adrenal (HPA) axis, enhancing immune function, promoting positive emotions, reducing inflammation and oxidative stress, and improving quality of life (Table S5, Fig. 5). By addressing emotional well-being, ICM therapies may create a supportive environment for the body to resist cancer development and progression. For instance, curcumin has been reported to alleviate anxiety-like behaviors induced by DSS in mice by restoring disturbances in the gut microbiota (*Muribaculaceae*) and systemic disorders of lipid metabolism (phosphatidylcholine) *via* the gut-brain axis [86]. Additionally, naringenin, a major compound in Si-Ni-San, was shown to inhibit stress-induced breast cancer growth and metastasis by promoting estradiol metabolism through the FXR/EST

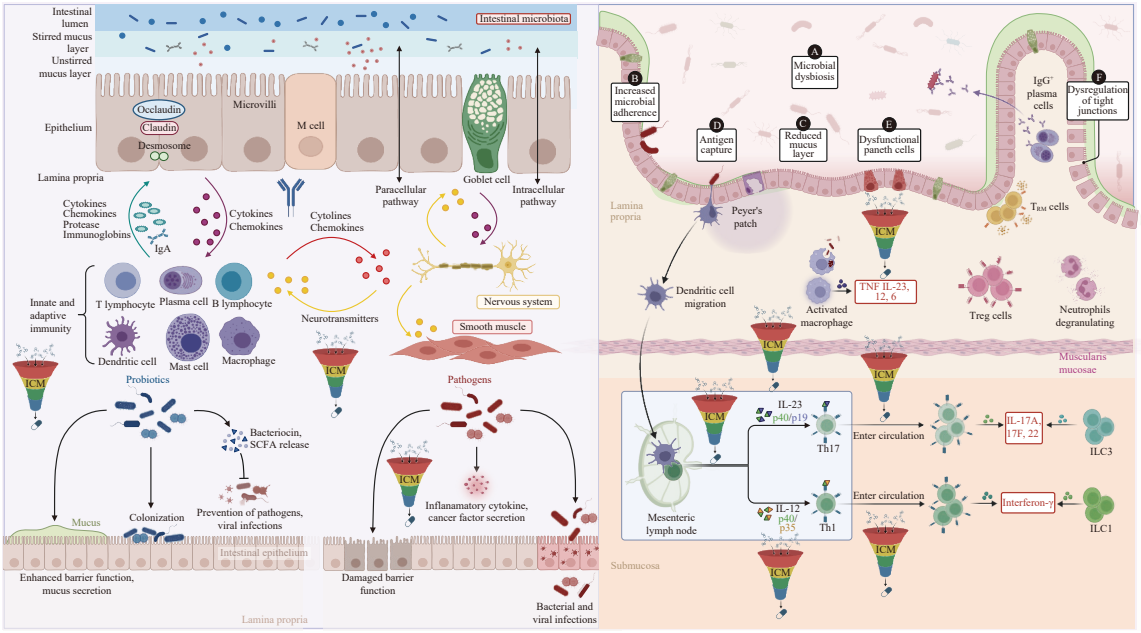

Fig. 4 Innovative Chinese medicine may suppress cancer development through regulating polymorphic microbiomes by restoring microbial homeostasis, reducing inflammation, modulating immune responses, altering metabolism, inhibiting carcinogenic bacteria, and enhancing gut barrier function.

signaling pathway [87]. In a clinical trial, Xiao-Chai-Hu Tang treatment significantly improved depressive scales, systemic inflammatory levels, and gut dysbiosis (reducing abundances of *Parabacteroides*, *Blautia*, and *Ruminococcaceae bacterium*). Moreover, Xiao-Chai-Hu Tang inhibited tumor growth and prolonged survival time in mice while exerting anti-depressive effects through the downregulation of the TLR4/MyD88/NF-*κ*B signaling pathway [88].

4.2.6. Potential ICM synergies with clinical cancer therapy

ICM can synergize with conventional cancer therapies by enhancing treatment efficacy, reducing resistance, inhibiting tumor progression, modulating immune responses, mitigating side effects, and providing supportive care and symptom management (Table S5, Fig. 6). By integrating ICM approaches into standard cancer treatment protocols, healthcare providers can offer patients a comprehensive and personalized approach to cancer care that addresses their physical, emotional, and spiritual needs. Studies have demonstrated that ICM sensitizes cancer cells to chemotherapy and radiation therapy, leading to increased cancer cell death. Additionally, ICM reduces chemotherapy-induced side effects, thereby improving treatment tolerance and compliance. Chemoresistance, where cancer cells become resistant to chemotherapy drugs, remains a significant challenge in cancer treatment [89, 90]. For instance, the combination of shikonin and cisplatin overcomes cisplatin resistance in ovarian cancer by inducing ferroptosis through the upregulation of HMOX1, which promotes Fe^{2+} accumulation [91]. Astragaloside IV weakens breast cancer stem cell (CSC) resistance to PTX by attenuating breast cancer stemness [92]. In addition, astragaloside IV enhances carboplatin sensitivity in prostate cancer by suppressing the AKT/NF-*κ*B signaling pathway [93]. The combination of erianin and doxorubicin hydrochloride exhibits a synergistic effect against breast cancer cells [94]. Matrine has been identified to inhibit self-renewal and resensitize 5-FU-resistant NSCLC stem cells through Let-7b-dependent CCND1 downregulation [95]. Luteolin attenuates CSCs in PTX-resistant oesophageal cancer cells by mediating SOX2 protein stability [96]. Moreover, luteolin combined with low-dose PTX synergistically inhibits EMT and induces cell apoptosis in esophageal carcinoma [97]. Berberine overcomes gemcitabine-associated chemoresistance through the in pancreatic ductal adenocarcinoma [98]. Furthermore, berberine enhances the sensitivity of radiotherapy to cancer cells [99]. The combination of berberine and low-glucose conditions inhibits gastric cancer progression *via* the PP2A/GSK3β/MCL-1 signaling pathway [100]. Quercetin reverses 5-FU resistance by modulating the NRF2/HO-1 pathway and enhances 5-FU sensitivity by regulating autophagic flux and inducing Drp-1-mediated mitochondrial fragmentation in CRC [101, 102]. Ginsenoside Rg3, when combined with artesunate, overcomes sorafenib resistance in HCC and alleviates cisplatin resistance by inhibiting SOX2 and the PI3K/AKT/mTOR signaling pathway in gastric cancer [103, 104]. Liquiritigenin enhances the inhibitory effects of RO 48-8071 (a cholesterol biosynthesis inhibitor) on hormone-dependent breast cancer [105]. Naringin combined with doxorubicin suppresses breast cancer growth through the JAK/STAT signaling pathway [106]. Moreover, naringin protects against doxorubicin-induced hepatotoxicity *via* reducing oxidative stress, inflammation, and apoptosis by SIRT1 upregulation [107]. Brusatol synergistically sensitizes acute myeloid leukemia to cytarabine by inhibiting NRF2-mediated glucose metabolism [108]. Dihydromyricetin reverses MRP2-induced multidrug resistance by preventing NF-*κ*B/NRF2 cascades in CRC [109]. Kaempferol synergistically enhances the antitumor activity of gefitinib by inhibiting the EGFR/SRC/STAT3 signaling pathway in glioma [110]. Ursolic acid enhances sorafenib effects in an SLC7A11-dependent ferroptosis manner [111] in TNBC *via* the ADRB2 signaling pathway in breast cancer [112, 113]. Dihydroartemisinin synergizes with capecitabine to inhibit CRC through the GSK-3β/TCF7/MMP9 signaling pathway [114]. Dihydroartemisinin can also overcome osimertinib resistance in EGFR-mutant NSCLC [115]. The combination of *β*-elemene and cetuximab is sensitive to KRAS-mutant CRC by inducing ferroptosis and inhibiting EMT [116]. In addition, *β*-elemene reverses gefitinib resistance through m^6A methyltransferase METTL3-mediated autophagy and sensitizes cells to gefitinib *via* FBP1 [117, 118]. Sodium cantharidinate and gemcitabine synergistically suppress pancreatic cancer by activating functional p53 [119]. Brucein D augments gemcitabine chemosensitivity by inhibiting the NRF2 signaling pathway in pancreatic cancer [120].

By promoting the activation and proliferation of immune cells such as T cells, NK cells, and dendritic cells, ICM can synergize with immunotherapy approaches such as checkpoint inhibitors and adoptive cell therapy. Additionally, ICM formulations may reduce immunotherapy-related adverse events and enhance treatment efficacy by modulating immune responses and reducing inflammation (Table S5, Fig. 6). For example, berberine re-

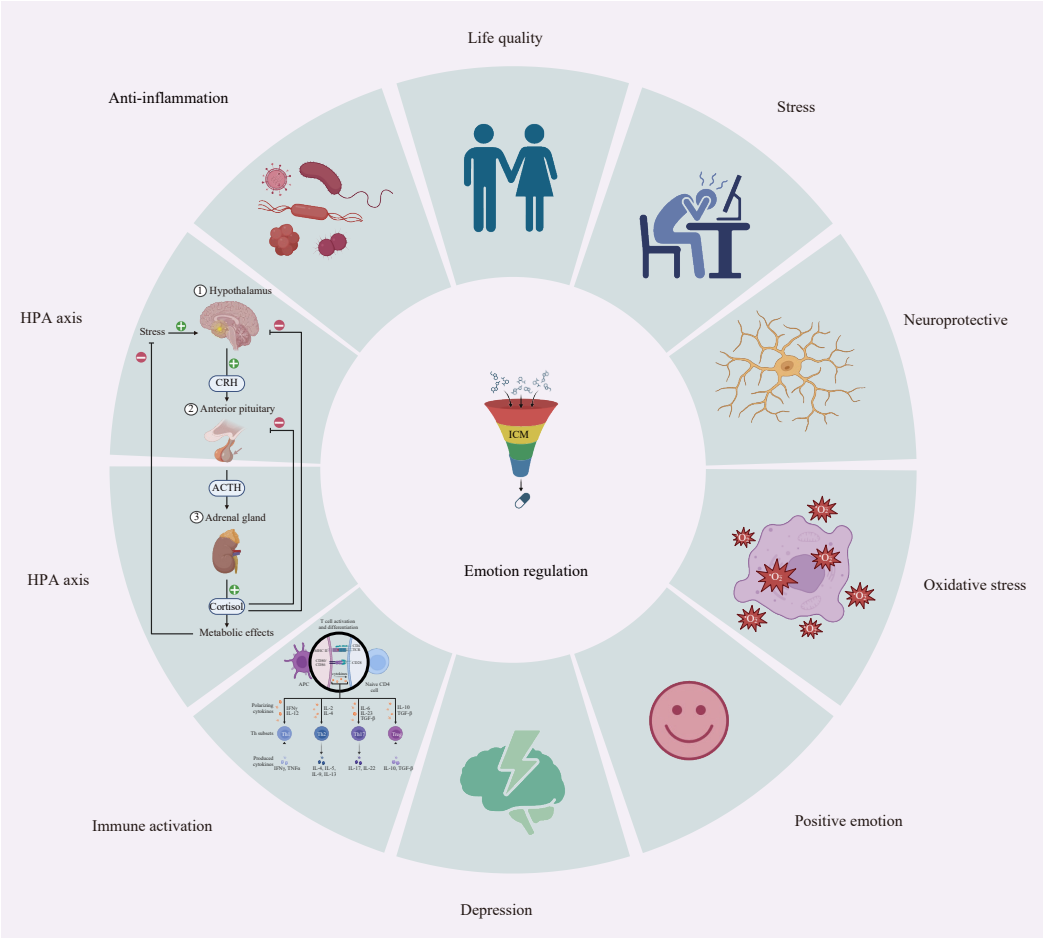

Fig. 5 Innovative Chinese medicine may impair cancer development through emotion regulation by reducing stress and depression, modulating the hypothalamic-pituitary-adrenal (HPA) axis, enhancing immune function, promoting positive emotions, reducing inflammation and oxidative stress, and improving quality of life.

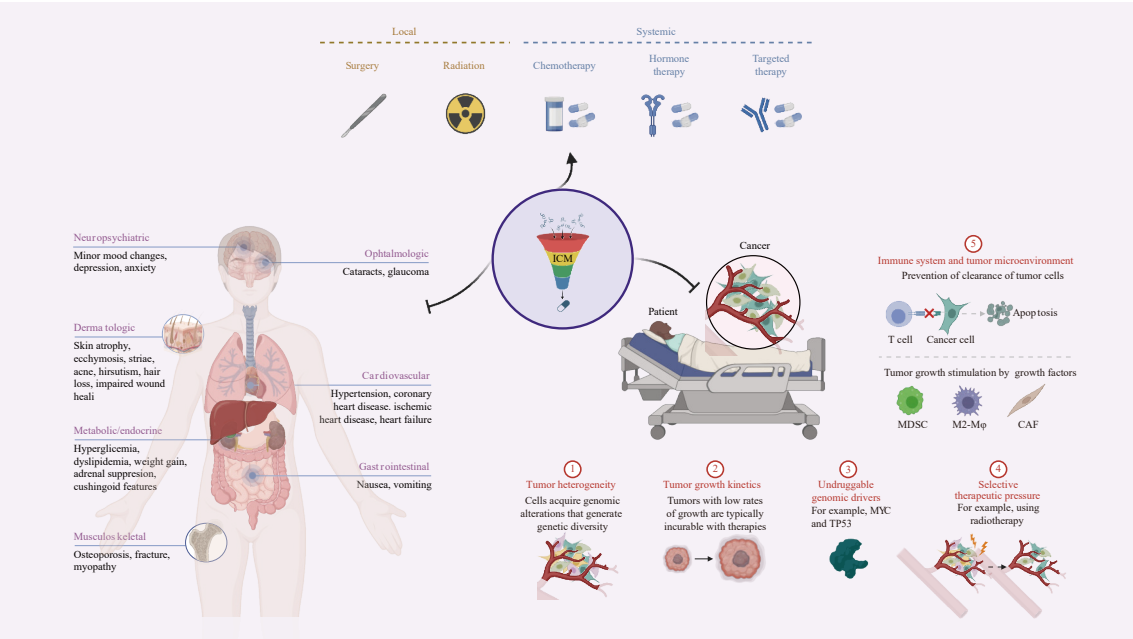

Fig. 6 Innovative Chinese medicine may synergize with clinical cancer therapy by enhancing treatment efficacy, reducing drug resistance, modulating the immune response, reducing treatment side effects, and providing supportive care and symptom management.

stores macrophage function in TME, enhances rituximab-mediated phagocytosis, and promotes anti-CD47 antibody function *via* suppressing CD47 expression in diffuse large B-cell lymphoma [121]. Bufalin regulates the polarization of M2 macrophages to enhance the anticancer effect of oxaliplatin [32]. The combination of evodiamine and anti-PD-1 mAb enhances tumor growth control and survival of mice by elevating $CD8^+$ T cells and downregulating the MUC1-C/PD-L1 axis in NSCLC [122]. Tanshinone IIA normalizes

HCC vessels and enhances PD-1 inhibitor efficacy by inhibiting ELTD1 [123]. The combination of tubeimoside-1 and anti-CTLA-4 effectively enhances antitumor T-cell immunity and reduces immunosuppressive infiltration of MDSCs and Tregs in cancer [124]. Similarly, piperlongumine, when used in conjunction with an anti-PD-1 antibody, effectively overcomes resistance to temozolomide-based chemoradiotherapy in refractory glioblastoma. This combination promotes an immune-mediated tumor response by amplifying oxidative stress, inflammatory signaling, and $CD8^+$ T cell activation [125].

Furthermore, conventional cancer therapy often leads to various side effects such as nausea, vomiting, fatigue, and immune suppression. ICM can alleviate treatment-related side effects and improve quality of life for cancer patients [126]. ICM offers a holistic approach to cancer care that extends beyond targeting the tumor itself. It emphasizes comprehensive patient support by addressing critical aspects of well-being, including nutrition, lifestyle modification, emotional and psychological health, and spiritual care. By integrating supportive therapies and symptom management into conventional cancer treatment, ICM has the potential to enhance patient comfort, reduce treatment-related side effects, and improve overall quality of life throughout the cancer care process.

4.3. Detected by evidence-based medicine

Evidence-based medicine (EBM) represents a medical practice model that consciously, explicitly, and judiciously integrates the best current research evidence, clinical expertise, and patients' values and preferences to guide clinical decision-making [127]. Its fundamental objective is to optimize clinical decisions and enhance healthcare quality. This approach rests on three essential pillars: the best available research evidence derived from rigorously designed clinical studies such as randomized controlled trials (RCTs), systematic reviews, and meta-analyses, where evidence is hierarchically graded with RCTs and meta-analyses typically ranked highest [128, 129]; clinical expertise, which involves clinicians applying their knowledge and experience to evaluate the applicability and clinical significance of evidence for individual patients; and patients' unique values and circumstances, emphasizing respect for their treatment goals, risk tolerance, and life contexts to ensure therapeutic alignment with their preferences.

EBM is an ongoing, dynamic process that requires clinicians to continuously identify, appraise, and incorporate the best available evidence into clinical decision-making. This cyclical methodology involves formulating specific clinical questions, efficiently retrieving the most relevant and high-quality evidence, critically evaluating its validity and applicability, integrating it with clinical expertise and patient values, and systematically assessing outcomes to inform future practice. While the use of evidence in medicine has deep historical roots, modern EBM emerged in the 20th century. The evolution of RCT methodology, highlighted by landmark studies such as the streptomycin trial for tuberculosis in the mid-20th century, laid the groundwork for generating rigorous clinical evidence. In 1972, Archie Cochrane emphasized the importance of systematically reviewing RCTs to optimize healthcare resource allocation, which significantly accelerated the evidence-based movement. During the 1980s, clinical epidemiologists at McMaster University pioneered the teaching of critical appraisal skills to practicing clinicians. The term Evidence-Based Medicine was formally introduced by Gordon Guyatt in a 1990 article published in *JAMA*, and further defined by the Oxford Centre for Evidence-Based Medicine in their seminal 1992 paper in *JAMA*, which outlined the conceptual framework of EBM. A major milestone occurred in 1993 with the establishment of the Cochrane Collaboration, an organization dedicated to producing systematic reviews of healthcare interventions, which became a cornerstone of global EBM practice. Since then, EBM has expanded significantly across disciplines, including nursing, public health, and pharmacy. This growth has been accompanied by ongoing methodological advancements, most notably the development of the GRADE system [130].

Application of EBM begins with defining focused clinical questions using the PICO framework. Subsequent steps prioritize identifying high-quality evidence, critically assessing its reliability (evaluating factors like concealed randomization and adequate sample size) and applicability (considering the match between the study population and the specific patient), and integrating this assessment with clinical expertise. Clinicians must then contextualize the evidence, accounting for comorbidities and social determinants, engage patients in shared decision-making by transparently discussing risks and benefits, and collaboratively select the optimal path aligned with patient values. Continuous tracking of outcomes, including disease control parameters and quality-of-life metrics, enables iterative refinement of care strategies based on feedback, fostering sustained quality improvement. TCM demonstrates significant conceptual alignment with EBM principles; its core tenet of "treatment based on syndrome differentiation" inherently addresses individual variation, resonating with EBM's patient-centered focus, while its holistic perspective offers valuable insights for managing complex chronic and multisystem conditions, potentially mitigating limitations of excessive subspecialization in modern medicine. TCM's extensive repository of documented clinical experience and classical texts like the *Shang Han Lun* (*Treatise on Cold Damage*) provides a unique historical evidence base. Furthermore, RCTs validating specific TCM interventions, such as Tongxinluo (CTS-AMI study) and Jinlida, published in premier journals including JAMA and the European Heart Journal, signify crucial milestones in achieving international scientific recognition for TCM efficacy [131, 132].

However, substantive challenges persist in harmonizing TCM with the EBM paradigm. Fundamental tensions arise between TCM's emphasis on "holistic regulation" and the predominantly "single-target" efficacy evaluation model of Western medicine; the complex synergistic actions characteristic of multi-component TCM formulas prove difficult to fully validate using traditional RCT designs. Lagging modernization and cross-cultural translation of foundational TCM theories like the Five Elements and Qi contribute to international academic misunderstandings. The absence of globally standardized, objective TCM efficacy indicators, such as validated syndrome scores, impedes the translation of traditional outcome measures like "improvement" into internationally accepted endpoints like survival rates or biomarkers. Additionally, quality control issues, including pesticide residues, heavy metal contamination in cultivated herbs, and inconsistent manufacturing standards, present significant hurdles to large-scale production and global regulatory compliance. Addressing these multifaceted challenges necessitates innovative strategies: developing integrated "disease-syndrome" evaluation models that incorporate quantifiable TCM parameters like fatigue indices and tongue characteristics alongside conventional biochemical markers within rigorous study designs; establishing stringent, science-based cultivation and processing protocols to ensure batch-to-batch consistency and safety; and conducting robust multicenter RCTs to validate the clinical efficacy of TCM compound formulas. Ultimately, the evidence-based evolution of TCM embodies a necessary dialogue between millennia of traditional wisdom and contemporary scientific methodology, demanding both rigorous validation through internationally accepted frameworks like RCTs and an expansion of the EBM paradigm to accommodate holistic evidence sources such as real-world data and patient-reported outcomes.

EBM serves as both the final step for drugs used in clinics and

the initial step for drug approval. The integration of EBM into drug discovery processes establishes rigorous standards for clinical trials, enhances drug efficacy and safety, increases regulatory scrutiny, facilitates data-driven decision-making, advances personalized medicine, supports cost-effectiveness analyses, promotes transparency and reproducibility, and strengthens postmarket surveillance, thereby significantly improving public health outcomes. Many TCMs have been validated by EBM, incorporating them into clinical practice due to their demonstrated efficacy and safety through rigorous scientific research (Table S4). However, most of them are CPM. Icaritin, originating from the traditional Chinese herb *Epimedium*, represents the inaugural small molecule immunomodulator (content: 98.0%–102.0%). Studies demonstrated that icaritin inhibits the TLR/MyD88/IKK/NF-κB inflammatory pathway by directly binding to MyD88/IKKα, leading to decreased production of inflammatory mediators like TNF-α and IL-6, and downregulation of the IL6/JAK2/STAT3 signaling pathway. Additionally, icaritin directly binds to IKKα, restraining TNF-α-induced activation of the IKK/NF-κB signaling pathway. Consequently, this inhibits PD-L1 expression and the function of MDSCs, while activating IFN-γ-positive $CD8^+$ T cells, ultimately exerting antitumor effects [133, 134]. Clinical trials were conducted and completed, and the National Medical Products Administration (NMPA) issued a notice approving the conditional marketing of Class I innovative drug icaritin (Icariin Soft Capsules) through the priority review and approval process in 2022 [135, 136]. This medication is indicated for patients with unresectable HCC who are ineligible for or have declined standard treatment and have not received prior systemic therapy. Moreover, it was reported that icaritin regulates O-GlcNAc modification of FOXC1 and thus the stability of FOXC1, resulting in the inhibition of endometrial cancer cell proliferation [137]. Icaritin combined with CpG augments the antitumor immune response to anti-PD-1/CTLA-4 immune checkpoint blockade treatment in melanoma [138]. More and more anticancer monomer drugs derived from TCM are under development, which will hopefully be used in clinics after the EBM.

5. Perspective

ICM can target multiple signal transduction pathways that are highly dysregulated in cancer. For example, ICM compounds like gambogic acid can target specific proteins to exert anticancer effects through pathways such as NF-κB. ICM also regulates cellular metabolism by inhibiting glycolysis and lipid metabolism in cancer cells, thus limiting their energy supply and growth. Dihydroartemisinin has been shown to reduce glucose uptake and lactate secretion in cancer cells *via* the ERK/c-MYC pathway. Moreover, ICM can reprogram the tumor microenvironment by inducing tumor cell differentiation, inhibiting angiogenesis, and modulating cancer-associated fibroblasts. Bufalin, for instance, can reverse the invasive and metastatic potential of colorectal cancer by targeting the STAT3 pathway. ICM also enhances immune responses by activating T cells, natural killer cells, and macrophages, and can synergize with immunotherapies to improve treatment efficacy. ICM's impact extends to modulating the microbiome, restoring microbial balance, and enhancing gut barrier function. Berberine has been found to alleviate gut microbiota dysbiosis and promote the growth of beneficial bacteria while inhibiting harmful ones. Lastly, ICM can regulate emotions, reduce stress, and improve the quality of life by influencing the HPA axis and immune function. In conclusion, ICM offers a multifaceted approach to cancer therapy, integrating TCM wisdom with modern scientific methods to target multiple biological processes and potentially improve patient outcomes.

Currently, some Chinese herbal medicines are undergoing clinical research. Icaritin for advanced liver cancer has completed a phase III trial (NCT03236636), enrolling 283 patients with unresectable hepatocellular carcinoma (Child-Pugh class A) [139]. The median overall survival (OS) in the monotherapy group reached 13.5 months, extending by 4.2 months compared to the control group ($P < 0.001$). Its mechanism of action has been reported as inhibiting the TLR/NF-κB signaling pathway by directly binding MyD88/IKKα, thereby downregulating PD-L1 expression [140]. Based on a randomized phase II trial (NCT 02647125) enrolling 126 elderly or chemotherapy-ineligible patients with locally advanced esophageal squamous cell carcinoma (ESCC), the addition of Huachansu to radiotherapy failed to improve locoregional control (median 12.9 *vs* 22.0 months; HR = 1.35, $P = 0.235$) or overall survival (median 15.0 *vs* 17.2 months; HR = 1.03, $P = 0.868$) compared with radiotherapy alone. Although the combination was well tolerated, with no significant difference in grade ≥ 3 acute toxicities (20.0% *vs* 11.5%; $P = 0.191$), Huachansu increased the risk of hyponatremia (9.2% *vs* 0%; $P = 0.015$) and esophageal hemorrhage (10.8% *vs* 1.6%; $P = 0.036$). These results indicate that, at the current dose schedule, Huachansu does not confer radiosensitizing or survival benefit in elderly or chemotherapy-ineligible ESCC patients [141]. This combination therapy may be a recommended adjuvant treatment option for NSCLC. According to a randomized, double-blind clinical trial (NCT03314805), astragalus polysaccharides can alleviate adjuvant chemotherapy-related fatigue in early-stage breast cancer patients. The study included 66 patients on the epirubicin combined with cyclophosphamide regimen. Results showed that in the pre-menopausal subgroup, the Astragalus polysaccharide group, compared to the placebo group, significantly reduced fatigue (based on BFI fatigue scores, $P < 0.05$) and improved quality of life (in terms of fatigue, insomnia, future outlook, and global health status on the EORTC QLQ-C30/BR23 scales, $P < 0.05$). Regarding safety, there was no significant difference between the Astragalus polysaccharide and placebo groups in the incidence of grade 3–4 neutropenia (87.9% *vs* 93.9%, $P = 0.195$) [142]. In a randomized controlled trial (NCT02226185), berberine demonstrated chemopreventive potential against colorectal adenoma recurrence. Berberine supplementation (0.3 g twice daily) for up to 2 years significantly reduced the risk of adenoma recurrence compared to placebo, with a relative risk ratio of 0.77 (95% CI 0.66–0.91; $P = 0.001$). Its mechanism may be related to modulating the gut microbiota and inhibiting tumorigenesis-related pathways [143].

The modernization of TCM, ICM, involves integrating ancient wisdom with contemporary scientific advancements to enhance its efficacy, safety, accessibility, and acceptance worldwide. Based on this concept, we proposed the "3 D" elements of ICM after the target identification and initial compound screening: definite active ingredient composition and content, determined functional mechanism, and detection through evidence-based medicine. The "3 D" definition of ICM suggests several key directions for the modernization and global integration of TCM: 1) Clarifying active ingredients and standardization: a key priority is the identification and quantification of bioactive compounds within TCM formulations. This includes improving extraction techniques or employing chemical synthesis to enhance purity and yield. Establishing standardized diagnostic protocols, treatment procedures, and herbal formulation guidelines is critical to ensure reproducibility, consistency, and safety. Quality control measures must include authentication of raw materials, chemical profiling, and strict manufacturing regulation. Such standardization enhances clinical reliability and supports integration into international healthcare systems. 2) Mechanistic elucidation through multidisciplinary approaches. 3) Emphasizing evidence-based practice to ensure that TCM interventions meet rigorous scientific standards. 4) Integration into conventional medical systems: embedding TCM within a pluralistic healthcare model al-

lows for synergistic collaboration between TCM and conventional Western medicine. Integrated approaches can be particularly effective in oncology, chronic disease management, pain control, and rehabilitation. Interdisciplinary cooperation facilitates patient-centered care, combining TCM's holistic perspective with evidence-driven modern medicine for optimized outcomes. 5) Innovation through advanced technologies: the integration of biotechnology, nanotechnology, pharmacogenomics, and precision medicine into TCM research is accelerating therapeutic innovation. Applications include targeted herbal formulations, nanoparticle-based drug delivery systems, and personalized TCM treatments based on genomic, proteomic, and metabolomic data. These advancements pave the way for next-generation TCM therapeutics that are safer, more effective, and tailored to individual patients. 6) Expanding access through digital health technologies: the adoption of digital health solutions and telemedicine can greatly enhance access to TCM services, particularly in remote or underserved regions. Mobile health applications, virtual consultations, and remote monitoring tools enable patients to access TCM resources, consultations, and educational materials conveniently. Integrating digital health into TCM practice enhances patient engagement, monitoring, and adherence to treatment regimens. 7) Strengthening education and training: advancing TCM modernization requires investment in education and professional development. This includes integrating TCM curricula into mainstream medical education, fostering interdisciplinary collaboration, and providing continuing education opportunities. Cultivating a new generation of TCM professionals with expertise in both traditional knowledge and modern scientific methods is critical for the future of TCM. 8) Promoting international collaboration, cultural exchange, and mutual recognition of TCM practices: international engagement plays a vital role in the global recognition and integration of TCM. Collaborative efforts with regulatory bodies, healthcare institutions, and academic organizations promote cross-cultural understanding and harmonization of standards. International conferences, exchange programs, and research collaborations contribute to the globalization of TCM and its integration into global healthcare systems.

The modernization of TCM involves a multidimensional approach that integrates scientific rigor, standardization, integration with conventional medicine, innovation, digital health, education, and globalization. By embracing these strategies, TCM can evolve into a comprehensive and sustainable healthcare system that addresses the complex health needs of diverse populations worldwide.

To clarify the active ingredients and their concentrations in TCM formulations, it is essential to establish standardized extraction protocols, complemented by advanced analytical techniques such as HPLC-MS and NMR for quantitative profiling. For bioactive compounds with inherently low natural yields, the development of efficient chemical synthesis pathways is recommended to ensure scalability and consistency. To date, the Pharmacopoeia Commission of China has established content standards for over 70 kinds of TCM, accessible *via* the TCMSP database. Future extraction optimization can be enhanced through AI-powered predictive modeling, such as TCM-BERT and DeepTCM. Molecular mechanisms can be elucidated through multi-omics (transcriptomics-metabolomics integration) and CRISPR-Cas9 target validation. To facilitate mechanism-driven drug discovery, an "ICM-Target-Disease" interaction database is proposed. Such a platform would systematically map bioactive compounds to molecular targets and associated disease pathways, promoting precision drug design and repurposing. In terms of evidence-based medical verification, the verification of ICM interventions should follow a comprehensive, multi-phase strategy. During the preclinical stage, the use of advanced models such as organoids and patient-derived xenograft (PDX) systems allows for the assessment of pharmacological efficacy and safety under physiologically relevant and patient-specific conditions. In the translational and clinical stages, while multicenter RCTs remain the gold standard for evaluating clinical efficacy, there is increasing emphasis on the integration of population-based big data and RWE. Finally, during the post-marketing surveillance phase, real-world studies play a critical role in monitoring long-term safety. To advance the modernization and global integration of TCM, it is imperative to fully leverage real-world research methodologies, including observational studies, registry analyses, and case series. These approaches enable the collection of RWD reflecting the actual clinical use of TCM, thereby enriching the evidence base for clinical evaluation, regulatory decision-making, and personalized care. Recognizing this, China's NMPA has established a priority review channel for new Chinese medicine products, significantly accelerating the translation of TCM research into clinical application. In the integration of TCM with conventional Western medicine, it is essential to establish standardized treatment pathways within combined clinical settings. One exemplary approach includes the use of Astragalus polysaccharides in conjunction with chemotherapy to mitigate myelosuppression, illustrating the synergistic potential of integrative therapies. Furthermore, interdisciplinary clinician training programs, such as the proposed "TCM–Immunotherapy Synergy " curriculum, are crucial for equipping healthcare providers with the knowledge needed to navigate integrative treatment strategies. Notable pilot programs, such as the Integrated Oncology Center at Shanghai Longhua Hospital, have successfully implemented TCM into standard-of-care protocols, evidenced by the inclusion of bufalin in treatment guidelines for NSCLC. Enhanced collaboration between TCM researchers and clinical practitioners is also vital. By translating EBM findings into real-time clinical practice, such partnerships can improve therapeutic efficacy, optimize clinical workflows, and elevate healthcare quality. From a technology innovation standpoint, the development of nanocarrier drug delivery systems and AI-assisted drug design platforms, for instance, using AlphaFold to predict the binding affinity of TCM compounds to molecular targets represents a forward-looking strategy. These innovations are currently supported by national funding initiatives such as the "14th Five-Year Plan" Key R&D Program (2021YFC2302500). In the digital health domain, efforts should focus on building intelligent prescription support systems capable of recommending syndrome-based proprietary TCM formulas, thus enhancing clinical decision-making and patient outcomes. Education and global outreach are equally crucial. Domestic initiatives could include making "Modern TCM Pharmacology" a core course in medical schools, while international collaboration can be strengthened through the WHO Collaborating Centres for TCM training. Participation in global standard-setting, such as contributing to the WHO ICD-11 Traditional Medicine Chapter, and promoting the recognition of TCM products within regulatory frameworks like the European Medicines Agency (EMA), as demonstrated by the approval of *Salvia miltiorrhiza* dropping pills, further supports the internationalization of TCM.

This hierarchical implementation strategy, from technological innovation to clinical application, and from domestic deployment to international integration, coupled with validation through existing case studies, provides a practical roadmap for aligning industry, academia, and research. It facilitates the transition of TCM modernization from theory to practice. Consequently, the "3 D" definition of ICM will establish a standardized benchmark for ICM development. This approach will accelerate the global advancement of TCM modernization and drug discovery, ultimately improving therapeutic outcomes and benefiting diverse patient populations worldwide.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82203343), the National Postdoctoral

Program for Innovative Talents of China (No. BX20220273), China Postdoctoral Science Foundation (No. 2022M712874), Henan Province Key Research and Development Promotion Special Project (Science and Technology) in 2023 (No. 232102311007), Henan Province Key Scientific Research Project of Colleges and Universities in 2023 (No. 23A310007), and the Outstanding Youth Project of Henan Provincial Natural Science Foundation (No. 252300421123).

Supporting information

Supporting information for this work can be obtained by contacting the corresponding authors *via* E-mail.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgements

We thank bioRENDER for supplying the materials of figure drawing.

References

1 An Y, Liu Z, Wang S, et al. Effect of Chaihu plus Longgu Muli Decoction plus five-element music therapy in the treatment of cancer-related depression. *Support Care Cancer*. 2022;30(10):7955-7962. https://doi.org/10.1007/s00520-022-07172-6.
2 Tao WW, Jiang H, Tao XM, et al. Effects of acupuncture, Tuina, Tai Chi, Qigong, and traditional Chinese medicine five-element music therapy on symptom management and quality of life for cancer patients: a meta-analysis. *J Pain Symptom Manage*. 2016;51(4):728-747. https://doi.org/10.1016/j.jpainsymman.2015.11.027.
3 Zhong K, An X, Kong Y. The effectiveness of five-element music therapy for post-stroke depression: a systematic review and meta-analysis. *Heliyon*. 2024;10(5):e26603. https://doi.org/10.1016/j.heliyon.2024.e26603.
4 Matos LC, Machado JP, Monteiro FJ, et al. Understanding traditional Chinese medicine therapeutics: an overview of the basics and clinical applications. *Healthcare (Basel)*. 2021;9(3):257. https://doi.org/10.3390/healthcare9030257.
5 Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *J Nat Prod*. 2020;83(3):770-803. https://doi.org/10.1021/acs.jnatprod.9b01285.
6 Harvey AL, Edrada-Ebel R, Quinn RJ. The re-emergence of natural products for drug discovery in the genomics era. *Nat Rev Drug Discov*. 2015;14(2):111-129. https://doi.org/10.1038/nrd4510.
7 Atanasov AG, Zotchev SB, Dirsch VM, et al. Natural products in drug discovery: advances and opportunities. *Nat Rev Drug Discov*. 2021;20(3):200-216. https://doi.org/10.1038/s41573-020-00114-z.
8 Cragg GM. Paclitaxel (taxol): a success story with valuable lessons for natural product drug discovery and development. *Med Res Rev*. 1998;18(5):315-331. https://doi.org/10.1002/(sici)1098-1128(199809)18:5<315::aid-med3>3.0.co;2-w.
9 Schiff PB, Fant J, Horwitz SB. Promotion of microtubule assembly *in vitro* by taxol. *Nature*. 1979;277(5698):665-667. https://doi.org/10.1038/277665a0.
10 McGuire WP, Rowinsky EK, Rosenshein NB, et al. Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. *Ann Intern Med*. 1989;111(4):273-279. https://doi.org/10.7326/0003-4819-111-4-273.
11 Docetaxel and gemcitabine released for cancer chemotherapy. *Am J Health Syst Pharm*. 1996;53(14):1643-1649. https://doi.org/10.1093/ajhp/53.14.1643.
12 Kohler DR, Goldspiel BR. Paclitaxel (taxol). *Pharmacotherapy*. 1994;14(1):3-34. https://doi.org/10.1002/j.1875-9114.1994.tb02785.x.
13 Alkan-Onyuksel H, Ramakrishnan S, Chai HB, et al. A mixed micellar formulation suitable for the parenteral administration of taxol. *Pharm Res*. 1994;11(2):206-212. https://doi.org/10.1023/a:1018943021705.
14 Ismail U, Killeen RB. Taxane Toxicity. Treasure Island: StatPearls Publishing LLC; 2025.
15 Xu X, Wang L, Xu HQ, et al. Clinical comparison between paclitaxel liposome (Lipusu®) and paclitaxel for treatment of patients with metastatic gastric cancer. *Asian Pac J Cancer Prev*. 2013;14(4):2591-2594. https://doi.org/10.7314/apjcp.2013.14.4.2591.
16 Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*. 2005;23(31):7794-7803. https://doi.org/10.1200/jco.2005.04.937.
17 Green MR, Manikhas GM, Orlov S, et al. Abraxane, a novel cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. *Ann Oncol*. 2006;17(8):1263-1268. https://doi.org/10.1093/annonc/mdl104.
18 Kim DW, Kim SY, Kim HK, et al. Multicenter phase II trial of genexol-PM, a novel cremophor-free, polymeric micelle formulation of paclitaxel, with cisplatin in patients with advanced non-small-cell lung cancer. *Ann Oncol*. 2007;18(12):2009-2014. https://doi.org/10.1093/annonc/mdm374.
19 Hong YS, Kim KP, Lim HS, et al. A phase I study of DHP107, a mucoadhesive lipid form of oral paclitaxel, in patients with advanced solid tumors: crossover comparisons with intravenous paclitaxel. *Invest New Drugs*. 2013;31(3):616-622. https://doi.org/10.1007/s10637-012-9841-7.
20 Ryu MH, Ryoo BY, Kim TW, et al. A Phase I/IIa study of DHP107, a novel oral paclitaxel formulation, in patients with advanced solid tumors or gastric cancer. *Oncologist*. 2017;22(2):129-e8. https://doi.org/10.1634/theoncologist.2016-0273.
21 Kang YK, Ryu MH, Park SH, et al. Efficacy and safety findings from DREAM: a phase III study of DHP107 (oral paclitaxel) versus i.v. paclitaxel in patients with advanced gastric cancer after failure of first-line chemotherapy. *Ann Oncol*. 2018;29(5):1220-1226. https://doi.org/10.1093/annonc/mdy055.
22 Liu H, Zhou Y, Fredimoses M, et al. Targeting leucine-rich PPR motif-containing protein/LRPPRC by 5,7,4'-trimethoxyflavone suppresses esophageal squamous cell carcinoma progression. *Int J Biol Macromol*. 2024;269(Pt 1):131966. https://doi.org/10.1016/j.ijbiomac.2024.131966.
23 Hanahan D. Hallmarks of cancer: new dimensions. *Cancer Discov*. 2022;12(1):31-46. https://doi.org/10.1158/2159-8290.Cd-21-1059.
24 Mirza MA, Mahmood S, Hilles AR, et al. Quercetin as a therapeutic product: evaluation of its pharmacological action and clinical applications-a review. *Pharmaceuticals (Basel)*. 2023;16(11):1631. https://doi.org/10.3390/ph16111631.
25 Boden A, Lusque A, Lodin S, et al. Study protocol of the TEC-ORL clinical trial: a randomized comparative phase II trial investigating the analgesic activity of capsaicin *vs* laroxyl in head and neck cancer survivors presenting with neuropathic pain sequelae. *BMC Cancer*. 2022;22(1):1260. https://doi.org/10.1186/s12885-022-10348-2.
26 Borazanci E, Saluja A, Gockerman J, et al. First-in-human phase I study of minnelide in patients with advanced gastrointestinal cancers: safety, pharmacokinetics, pharmacodynamics, and antitumor activity. *Oncologist*. 2024;29(2):132-141. https://doi.org/10.1093/oncolo/oyad278.
27 Skorupan N, Ahmad MI, Steinberg SM, et al. A phase II trial of the super-enhancer inhibitor Minnelide™ in advanced refractory adenosquamous carcinoma of the pancreas. *Future Oncol*. 2022;18(20):2475-2481. https://doi.org/10.2217/fon-2021-1609.
28 Lyu S, Zhang X, Tu Z, et al. GPR108 is required for gambogic acid inhibiting NF-κB signaling in cancer. *Pharmacol Res*. 2022;182:106279. https://doi.org/10.1016/j.phrs.2022.106279.
29 Zhang XW, Li L, Liao M, et al. Thermal proteome profiling strategy identifies CNPY3 as a cellular target of gambogic acid for inducing prostate cancer pyroptosis. *J Med Chem*. 2024;67(12):10005-10011. https://doi.org/10.1021/acs.jmedchem.4c00140.
30 Liu X, Hu Q, Wang W, et al. A protein-fragment complementation assay reveals that celastrol and gambogic acid suppress ERα mutants in breast cancer. *Biochem Pharmacol*. 2021;188:114583. https://doi.org/10.1016/j.bcp.2021.114583.
31 Zhang H, Dong X, Ding X, et al. Bufalin targeting CAMKK2 inhibits the occurrence and development of intrahepatic cholangiocarcinoma through Wnt/β-catenin signal pathway. *J Transl Med*. 2023;21(1):900. https://doi.org/10.1186/s12967-023-04613-6.
32 Chen J, Wang H, Jia L, et al. Bufalin targets the SRC-3/MIF pathway in chemoresistant cells to regulate M2 macrophage polarization in colorectal cancer. *Cancer Lett*. 2021;513:63-74. https://doi.org/10.1016/j.canlet.2021.05.008.
33 Gu C, Wang Y, Zhang L, et al. AHSA1 is a promising therapeutic target for cellular proliferation and proteasome inhibitor resistance in multiple myeloma. *J Exp Clin Cancer Res*. 2022;41(1):11. https://doi.org/10.1186/s13046-021-02220-1.
34 Zhang H, Yang J, Song Q, et al. UBA3 promotes the occurrence and metastasis of intrahepatic cholangiocarcinoma through MAPK signaling pathway. *Acta Biochim Biophys Sin (Shanghai)*. 2024;56(2):199-209. https://doi.org/10.3724/abbs.2024014.
35 Xing S, Nong F, Wang Y, et al. Brusatol has therapeutic efficacy in non-small cell lung cancer by targeting Skp1 to inhibit cancer growth and metastasis. *Pharmacol Res*. 2022;176:106059. https://doi.org/10.1016/j.phrs.2022.106059.
36 Chen LL, Xia LY, Zhang JP, et al. Saikosaponin D alleviates cancer cachexia by directly inhibiting STAT3. *Phytother Res*. 2023;37(3):809-819. https://doi.org/10.1002/ptr.7676.
37 Sun K, Du Y, Hou Y, et al. Saikosaponin D exhibits anti-leukemic activity by targeting FTO/$m^{(6)}$A signaling. *Theranostics*. 2021;11(12):5831-5846. https://doi.org/10.7150/thno.55574.
38 Wang Y, Chu F, Lin J, et al. Erianin, the main active ingredient of *Dendrobium chrysotoxum* Lindl, inhibits precancerous lesions of gastric cancer (PLGC) through suppression of the HRAS-PI3K-AKT signaling pathway as revealed by network pharmacology and *in vitro* experimental verification. *J Ethnopharmacol*. 2021;279:114399. https://doi.org/10.1016/j.jep.2021.114399.
39 Chen P, Wu Q, Feng J, et al. Erianin, a novel dibenzyl compound in *Dendrobium* extract, inhibits lung cancer cell growth and migration *via* calcium/calmodulin-dependent ferroptosis. *Signal Transduct Target Ther*. 2020;5(1):51. https://doi.org/10.1038/s41392-020-0149-3.
40 Wang P, Jia X, Lu B, et al. Erianin suppresses constitutive activation of MAPK signaling pathway by inhibition of CRAF and MEK1/2. *Signal Transduct Target Ther*. 2023;8(1):96. https://doi.org/10.1038/s41392-023-01329-3.
41 Liao M, Yao D, Wu L, et al. Targeting the Warburg effect: a revisited perspective from molecular mechanisms to traditional and innovative therapeutic strategies in cancer. *Acta Pharm Sin B*. 2024;14(3):953-1008. https://doi.org/10.1016/j.apsb.2023.12.003.
42 Zhang Y, Wang Y, Li Y, et al. Dihydroartemisinin and artesunate inhibit aerobic glycolysis *via* suppressing c-Myc signaling in non-small cell lung cancer. *Biochem Pharmacol*. 2022;198:114941. https://doi.org/10.1016/j.bcp.2022.114941.
43 Hu X, Peng X, Zhang Y, et al. Shikonin reverses cancer-associated fibroblast-

induced gemcitabine resistance in pancreatic cancer cells by suppressing monocarboxylate transporter 4-mediated reverse Warburg effect. *Phytomedicine*. 2024;123:155214. https://doi.org/10.1016/j.phymed.2023.155214.
44 Shi J, Ji X, Shan S, et al. The interaction between apigenin and PKM2 restrains progression of colorectal cancer. *J Nutr Biochem*. 2023;121:109430. https://doi.org/10.1016/j.jnutbio.2023.109430.
45 Jin J, Qiu S, Wang P, et al. Cardamonin inhibits breast cancer growth by repressing HIF-1α-dependent metabolic reprogramming. *J Exp Clin Cancer Res*. 2019;38(1):377. https://doi.org/10.1186/s13046-019-1351-4.
46 Brecht K, Riebel V, Couttet P, et al. Mechanistic insights into selective killing of OXPHOS-dependent cancer cells by arctigenin. *Toxicol In Vitro*. 2017;40:55-65. https://doi.org/10.1016/j.tiv.2016.12.001.
47 Vidoni C, Ferraresi A, Vallino L, et al. Glycolysis inhibition of autophagy drives malignancy in ovarian cancer: exacerbation by IL-6 and attenuation by resveratrol. *Int J Mol Sci*. 2023;24(2):1723. https://doi.org/10.3390/ijms24021723.
48 Shi WP, Lin WJ, Ge WY, et al. Curcumin inhibits liquid-liquid phase separation of fused in sarcoma and attenuates the sequestration of pyruvate kinase to restore cellular metabolism. *Food Funct*. 2023;14(10):4621-4631. https://doi.org/10.1039/d2fo03224d.
49 Zhou Y, Huang S, Guo Y, et al. Epigallocatechin gallate circumvents drug-induced resistance in non-small-cell lung cancer by modulating glucose metabolism and AMPK/AKT/MAPK axis. *Phytother Res*. 2023;37(12):5837-5853. https://doi.org/10.1002/ptr.7990.
50 Mossmann D, Müller C, Park S, et al. Arginine reprograms metabolism in liver cancer *via* RBM39. *Cell*. 2023;186(23):5068-5083.e23. https://doi.org/10.1016/j.cell.2023.09.011.
51 Wang Y, Wang M, Chen J, et al. The gut microbiota reprograms intestinal lipid metabolism through long noncoding RNA Snhg9. *Science*. 2023;381(6660):851-857. https://doi.org/10.1126/science.ade0522.
52 Zhou X, Li Y, Yang C, et al. Cordycepin reprogramming lipid metabolism to block metastasis and EMT *via* ERO1A/mTOR/SREBP1 axis in cholangiocarcinoma. *Life Sci*. 2023;327:121698. https://doi.org/10.1016/j.lfs.2023.121698.
53 Li S, Hao L, Deng J, et al. Coptidis Rhizoma and Evodiae Fructus against lipid droplet deposition in nonalcoholic fatty liver disease-related liver cancer by AKT. *Chem Biol Drug Des*. 2023;102(4):828-842. https://doi.org/10.1111/cbdd.14295.
54 Zhu L, Xu JJ, Li HD, et al. Berberine ameliorates abnormal lipid metabolism *via* the adenosine monophosphate-activated protein kinase/sirtuin 1 pathway in alcohol-related liver disease. *Lab Invest*. 2023;103(4):100041. https://doi.org/10.1016/j.labinv.2022.100041.
55 Wang S, Hao HF, Jiao YN, et al. Dandelion extract inhibits triple-negative breast cancer cell proliferation by interfering with glycerophospholipids and unsaturated fatty acids metabolism. *Front Pharmacol*. 2022;13:942996. https://doi.org/10.3389/fphar.2022.942996.
56 Zhou P, Shi H, Huang H, et al. Single-cell CRISPR screens *in vivo* map T cell fate regulomes in cancer. *Nature*. 2023;624(7990):154-163. https://doi.org/10.1038/s41586-023-06733-x.
57 Jaccard A, Wyss T, Maldonado-Pérez N, et al. Reductive carboxylation epigenetically instructs T cell differentiation. *Nature*. 2023;621(7980):849-856. https://doi.org/10.1038/s41586-023-06546-y.
58 Sun Q, Tao Q, Ming T, et al. Berberine is a suppressor of Hedgehog signaling cascade in colorectal cancer. *Phytomedicine*. 2023;114:154792. https://doi.org/10.1016/j.phymed.2023.154792.
59 Xu Q, Sheng L, Zhu X, et al. Jingfang Granules exert anti-psoriasis effect by targeting MAPK-mediated dendritic cell maturation and PPARγ-mediated keratinocytes cell cycle progression *in vitro* and *in vivo*. *Phytomedicine*. 2023;117:154925. https://doi.org/10.1016/j.phymed.2023.154925.
60 Wang W, Yuan X, Mu J, et al. Quercetin induces $MGMT^{(+)}$ glioblastoma cells apoptosis *via* dual inhibition of Wnt3a/β-Catenin and Akt/NF-κB signaling pathways. *Phytomedicine*. 2023;118:154933. https://doi.org/10.1016/j.phymed.2023.154933.
61 Jiang Y, Hu Y, Yang Y, et al. Tong-Xie-Yao-Fang promotes dendritic cells maturation and retards tumor growth in colorectal cancer mice with chronic restraint stress. *J Ethnopharmacol*. 2024;319(Pt 1):117069. https://doi.org/10.1016/j.jep.2023.117069.
62 Xu L, Duan H, Zou Y, et al. Xihuang Pill-destabilized CD133/EGFR/Akt/mTOR cascade reduces stemness enrichment of glioblastoma *via* the down-regulation of SOX2. *Phytomedicine*. 2023;114:154764. https://doi.org/10.1016/j.phymed.2023.154764.
63 Shehatta NH, Okda TM, Omran GA, et al. Baicalin; a promising chemopreventive agent, enhances the antitumor effect of 5-FU against breast cancer and inhibits tumor growth and angiogenesis in Ehrlich solid tumor. *Biomed Pharmacother*. 2022;146:112599. https://doi.org/10.1016/j.biopha.2021.112599.
64 Cheng Y, Zhong X, Nie X, et al. Glycyrrhetinic acid suppresses breast cancer metastasis by inhibiting M2-like macrophage polarization *via* activating JNK1/2 signaling. *Phytomedicine*. 2023;114:154757. https://doi.org/10.1016/j.phymed.2023.154757.
65 Huang MY, Chen YC, Lyu WY, et al. Ginsenoside Rh2 augmented anti-PD-L1 immunotherapy by reinvigorating $CD8^{(+)}$ T cells *via* increasing intratumoral CXCL10. *Pharmacol Res*. 2023;198:106988. https://doi.org/10.1016/j.phrs.2023.106988.
66 Lv Y, Li M, Weng L, et al. Ginseng-derived nanoparticles reprogram macrophages to regulate arginase-1 release for ameliorating T cell exhaustion in tumor microenvironment. *J Exp Clin Cancer Res*. 2023;42(1):322. https://doi.org/10.1186/s13046-023-02888-7.
67 Wen Z, Liu T, Zhang Y, et al. Salidroside regulates tumor microenvironment of non-small cell lung cancer *via* Hsp70/Stub1/Foxp3 pathway in Tregs. *BMC Cancer*. 2023;23(1):717. https://doi.org/10.1186/s12885-023-11036-5.
68 Ma X, Deng G, Tian N, et al. Calycosin enhances Treg differentiation for alleviating skin inflammation in atopic dermatitis. *J Ethnopharmacol*. 2024;326:117883. https://doi.org/10.1016/j.jep.2024.117883.
69 Gong C, Mu H, Luo J, et al. Euphohelioscopin A enhances NK cell antitumor immunity through GSDME-triggered pyroptosis. *J Leukoc Biol*. 2024;116(3):621-631. https://doi.org/10.1093/jleuko/qiae055.
70 Yang C, Qian C, Zheng W, et al. Ginsenoside Rh2 enhances immune surveillance of natural killer (NK) cells *via* inhibition of ERp5 in breast cancer. *Phytomedicine*. 2024;123:155180. https://doi.org/10.1016/j.phymed.2023.155180.
71 Xun J, Zhou S, Lv Z, et al. Dioscin modulates macrophages polarization and MDSCs differentiation to inhibit tumorigenesis of colitis-associated colorectal cancer. *Int Immunopharmacol*. 2023;117:109839. https://doi.org/10.1016/j.intimp.2023.109839.
72 Lin JP, Huang MH, Sun ZT, et al. Periplocin inhibits hepatocellular carcinoma progression and reduces the recruitment of MDSCs through AKT/NF-κB pathway. *Life Sci*. 2023;324:121715. https://doi.org/10.1016/j.lfs.2023.121715.
73 Long ZJ, Wang JD, Qiu SX, et al. Dietary γ-mangostin triggers immunogenic cell death and activates cGAS signaling in acute myeloid leukemia. *Pharmacol Res*. 2023;197:106973. https://doi.org/10.1016/j.phrs.2023.106973.
74 Park JS, Gazzaniga FS, Wu M, et al. Targeting PD-L2-RGMb overcomes microbiome-related immunotherapy resistance. *Nature*. 2023;617(7960):377-385. https://doi.org/10.1038/s41586-023-06026-3.
75 Song X, Zhang H, Zhang Y, et al. Gut microbial fatty acid isomerization modulates intraepithelial T cells. *Nature*. 2023;619(7971):837-843. https://doi.org/10.1038/s41586-023-06265-4.
76 El Tekle G, Garrett WS. Bacteria in cancer initiation, promotion and progression. *Nat Rev Cancer*. 2023;23(9):600-618. https://doi.org/10.1038/s41568-023-00594-2.
77 Gou H, Su H, Liu D, et al. Traditional medicine Pien Tze Huang suppresses colorectal tumorigenesis through restoring gut microbiota and metabolites. *Gastroenterology*. 2023;165(6):1404-1419. https://doi.org/10.1053/j.gastro.2023.08.052.
78 Sun X, Zhang Y, Cheng G, et al. Berberine improves DSS-induced colitis in mice by modulating the fecal-bacteria-related bile acid metabolism. *Biomed Pharmacother*. 2023;167:115430. https://doi.org/10.1016/j.biopha.2023.115430.
79 Chen H, Ye C, Wu C, et al. Berberine inhibits high fat diet-associated colorectal cancer through modulation of the gut microbiota-mediated lysophosphatidylcholine. *Int J Biol Sci*. 2023;19(7):2097-2113. https://doi.org/10.7150/ijbs.81824.
80 Yang T, Qin N, Liu F, et al. Berberine regulates intestinal microbiome and metabolism homeostasis to treat ulcerative colitis. *Life Sci*. 2024;338:122385. https://doi.org/10.1016/j.lfs.2023.122385.
81 Zhang Y, Liu XJ, Zhao W, et al. Baicalin circumvents anti-PD-1 resistance by regulating the gut microbiota metabolite short-chain fatty acids. *Pharmacol Res*. 2024;199:107033. https://doi.org/10.1016/j.phrs.2023.107033.
82 Wei J, Zheng Z, Hou X, et al. Echinacoside inhibits colorectal cancer metastasis *via* modulating the gut microbiota and suppressing the PI3K/AKT signaling pathway. *J Ethnopharmacol*. 2024;318(Pt A):116866. https://doi.org/10.1016/j.jep.2023.116866.
83 Wu R, Xiong J, Zhou T, et al. Quercetin/anti-PD-1 antibody combination therapy regulates the gut microbiota, impacts macrophage immunity and reshapes the hepatocellular carcinoma tumor microenvironment. *Front Biosci (Landmark Ed)*. 2023;28(12):327. https://doi.org/10.31083/j.fbl2812327.
84 Cao Q, Zhao M, Su Y, et al. Chronic stress dampens *Lactobacillus johnsonii*-mediated tumor suppression to enhance colorectal cancer progression. *Cancer Res*. 2024;84(5):771-784. https://doi.org/10.1158/0008-5472.Can-22-3705.
85 Globig AM, Zhao S, Roginsky J, et al. The β(1)-adrenergic receptor links sympathetic nerves to T cell exhaustion. *Nature*. 2023;622(7982):383-392. https://doi.org/10.1038/s41586-023-06568-6.
86 Zhang F, Zhou Y, Chen H, et al. Curcumin alleviates DSS-induced anxiety-like behaviors *via* the microbial-brain-gut axis. *Oxid Med Cell Longev*. 2022;2022:6244757. https://doi.org/10.1155/2022/6244757.
87 Zhang J, Wang N, Zheng Y, et al. Naringenin in Si-Ni-San formula inhibits chronic psychological stress-induced breast cancer growth and metastasis by modulating estrogen metabolism through FXR/EST pathway. *J Adv Res*. 2023;47:189-207. https://doi.org/10.1016/j.jare.2022.06.006.
88 Shao S, Jia R, Zhao L, et al. Xiao-Chai-Hu-Tang ameliorates tumor growth in cancer comorbid depressive symptoms *via* modulating gut microbiota-mediated TLR4/MyD88/NF-κB signaling pathway. *Phytomedicine*. 2021;88:153606. https://doi.org/10.1016/j.phymed.2021.153606.
89 Mousset A, Lecorgne E, Bourget I, et al. Neutrophil extracellular traps formed during chemotherapy confer treatment resistance *via* TGF-β activation. *Cancer Cell*. 2023;41(4):757-775.e710. https://doi.org/10.1016/j.ccell.2023.03.008.
90 Zheng H, Liu J, Cheng Q, et al. Targeted activation of ferroptosis in colorectal cancer *via* LGR4 targeting overcomes acquired drug resistance. *Nat Cancer*. 2024;5(4):572-589. https://doi.org/10.1038/s43018-023-00715-8.
91 Ni M, Zhou J, Zhu Z, et al. Shikonin and cisplatin synergistically overcome cisplatin resistance of ovarian cancer by inducing ferroptosis *via* upregulation of HMOX1 to promote $Fe^{(2+)}$ accumulation. *Phytomedicine*. 2023;112:154701. https://doi.org/10.1016/j.phymed.2023.154701.
92 Huang P, Li H, Ren L, et al. Astragaloside IV enhances the sensitivity of breast cancer stem cells to paclitaxel by inhibiting stemness. *Transl Cancer Res*. 2023;12(12):3703-3717. https://doi.org/10.21037/tcr-23-1885.
93 He Y, Zhang Q, Chen H, et al. Astragaloside IV enhanced carboplatin sensitivity in prostate cancer by suppressing AKT/NF-κB signaling pathway. *Biochem Cell Biol*. 2021;99(2):214-222. https://doi.org/10.1139/bcb-2020-0026.
94 Xie H, Feng S, Farag MA, et al. Synergistic cytotoxicity of erianin, a bisbenzyl in the dietetic Chinese herb *Dendrobium* against breast cancer cells. *Food Chem Toxicol*. 2021;149:111960. https://doi.org/10.1016/j.fct.2020.111960.
95 Li X, Wang M, Du N, et al. Matrine inhibitory effect on self-renewal and re-sensitization of 5-FU resistant NSCLC stem cells were through Let-7b

dependent downregulation of CCND1. *Cell Cycle*. 2020;19(23):3249-3259. https://doi.org/10.1080/15384101.2020.1838791.
96 Zhao J, Li L, Wang Z, et al. Luteolin attenuates cancer cell stemness in PTX-resistant oesophageal cancer cells through mediating SOX2 protein stability. *Pharmacol Res*. 2021;174:105939. https://doi.org/10.1016/j.phrs.2021.105939.
97 Qin T, Zhao J, Liu X, et al. Luteolin combined with low-dose paclitaxel synergistically inhibits epithelial-mesenchymal transition and induces cell apoptosis on esophageal carcinoma *in vitro* and *in vivo*. *Phytother Res*. 2021;35(11):6228-6240. https://doi.org/10.1002/ptr.7267.
98 Okuno K, Xu C, Pascual-Sabater S, et al. Berberine overcomes gemcitabine-associated chemoresistance through regulation of Rap1/PI3K-Akt signaling in pancreatic ductal adenocarcinoma. *Pharmaceuticals (Basel)*. 2022;15(10):1199. https://doi.org/10.3390/ph15101199.
99 Aleissa MS, Al-Zharani M, Alneghery LM, et al. Berberine enhances the sensitivity of radiotherapy in ovarian cancer cell line (SKOV-3). *Saudi Pharm J*. 2023;31(1):110-118. https://doi.org/10.1016/j.jsps.2022.11.009.
100 Peng Z, Wangmu T, Li L, et al. Combination of berberine and low glucose inhibits gastric cancer through the PP2A/GSK3β/MCL-1 signaling pathway. *Eur J Pharmacol*. 2022;922:174918. https://doi.org/10.1016/j.ejphar.2022.174918.
101 Tang Z, Wang L, Chen Y, et al. Quercetin reverses 5-fluorouracil resistance in colon cancer cells by modulating the NRF2/HO-1 pathway. *Eur J Histochem*. 2023;67(3):3719. https://doi.org/10.4081/ejh.2023.3719.
102 Li M, Fan J, Hu M, et al. Quercetin enhances 5-fluorouracil sensitivity by regulating the autophagic Flux and inducing Drp-1 mediated mitochondrial fragmentation in colorectal cancer cells. *Curr Mol Pharmacol*. 2024;17:e18761429283717. https://doi.org/10.2174/0118761429283717231222104730.
103 Chen YJ, Wu JY, Deng YY, et al. Ginsenoside Rg3 in combination with artesunate overcomes sorafenib resistance in hepatoma cell and mouse models. *J Ginseng Res*. 2022;46(3):418-425. https://doi.org/10.1016/j.jgr.2021.07.002.
104 Wang X, He R, Geng L, et al. Ginsenoside Rg3 alleviates cisplatin resistance of gastric cancer cells through inhibiting SOX2 and the PI3K/Akt/mTOR signaling axis by up-regulating miR-429. *Front Genet*. 2022;13:823182. https://doi.org/10.3389/fgene.2022.823182.
105 Liang Y, Besch-Williford C, Hyder SM. The estrogen receptor beta agonist liquiritigenin enhances the inhibitory effects of the cholesterol biosynthesis inhibitor RO 48-8071 on hormone-dependent breast-cancer growth. *Breast Cancer Res Treat*. 2022;192(1):53-63. https://doi.org/10.1007/s10549-021-06487-y.
106 Effat H, Abosharaf HA, Radwan AM. Combined effects of naringin and doxorubicin on the JAK/STAT signaling pathway reduce the development and spread of breast cancer cells. *Sci Rep*. 2024;14(1):2824. https://doi.org/10.1038/s41598-024-53320-9.
107 Xi Y, Chi Z, Tao X, et al. Naringin against doxorubicin-induced hepatotoxicity in mice through reducing oxidative stress, inflammation, and apoptosis *via* the up-regulation of SIRT1. *Environ Toxicol*. 2023;38(5):1153-1161. https://doi.org/10.1002/tox.23755.
108 Cheng C, Yuan F, Chen XP, et al. Inhibition of Nrf2-mediated glucose metabolism by brusatol synergistically sensitizes acute myeloid leukemia to Ara-C. *Biomed Pharmacother*. 2021;142:111652. https://doi.org/10.1016/j.biopha.2021.111652.
109 Wang Z, Sun X, Feng Y, et al. Dihydromyricetin reverses MRP2-induced multidrug resistance by preventing NF-κB-Nrf2 signaling in colorectal cancer cell. *Phytomedicine*. 2021;82:153414, https://doi.org/10.1016/j.phymed.2020.153414.
110 Zhou J, Liu Y, Chen J, et al. Kaempferol suppresses glioma progression and synergistically enhances the antitumor activity of gefitinib by inhibiting the EGFR/SRC/STAT3 signaling pathway. *Drug Dev Res*. 2023;84(3):592-610. https://doi.org/10.1002/ddr.22048.
111 Li H, Yu Y, Liu Y, et al. Ursolic acid enhances the antitumor effects of sorafenib associated with Mcl-1-related apoptosis and SLC7A11-dependent ferroptosis in human cancer. *Pharmacol Res*. 2022;182:106306. https://doi.org/10.1016/j.phrs.2022.106306.
112 Liang Y, Wu G, Luo T, et al. 10-Gingerol enhances the effect of taxol in triple-negative breast cancer *via* targeting ADRB2 signaling. *Drug Des Devel Ther*. 2023;17:129-142. https://doi.org/10.2147/dddt.S390602.
113 Baptista MMAC, Tomasin R, Luna-Dulcey L, et al. [10]-Gingerol improves doxorubicin anticancer activity and decreases its side effects in triple negative breast cancer models. *Cell Oncol (Dordr)*. 2020;43(5):915-929. https://doi.org/10.1007/s13402-020-00539-z.
114 Dai X, Chen W, Qiao Y, et al. Dihydroartemisinin inhibits the development of colorectal cancer by GSK-3β/TCF7/MMP9 pathway and synergies with capecitabine. *Cancer Lett*. 2024;582:216596. https://doi.org/10.1016/j.canlet.2023.216596.
115 Cai X, Miao J, Sun R, et al. Dihydroartemisinin overcomes the resistance to osimertinib in EGFR-mutant non-small-cell lung cancer. *Pharmacol Res*. 2021;170:105701. https://doi.org/10.1016/j.phrs.2021.105701.
116 Chen P, Li X, Zhang R, et al. Combinative treatment of β-elemene and cetuximab is sensitive to KRAS mutant colorectal cancer cells by inducing ferroptosis and inhibiting epithelial-mesenchymal transformation. *Theranostics*. 2020;10(11):5107-5119. https://doi.org/10.7150/thno.44705.
117 Liu S, Li Q, Li G, et al. The mechanism of $m^{(6)}A$ methyltransferase METTL3-mediated autophagy in reversing gefitinib resistance in NSCLC cells by β-elemene. *Cell Death Dis*. 2020;11(11):969. https://doi.org/10.1038/s41419-020-03148-8.
118 Li J, Dai P, Sun J, et al. FBP1 induced by β-elemene enhances the sensitivity of gefitinib in lung cancer. *Thorac Cancer*. 2023;14(4):371-380. https://doi.org/10.1111/1759-7714.14750.
119 Liu X, Zhang L, Thu PM, et al. Sodium cantharidinate, a novel anti-pancreatic cancer agent that activates functional p53. *Sci Chin Life Sci*. 2021;64(8):1295-1310. https://doi.org/10.1007/s11427-019-1753-3.
120 Zhang J, Xu HX, Cho WCS, et al. Brucein D augments the chemosensitivity of gemcitabine in pancreatic cancer *via* inhibiting the Nrf2 pathway. *J Exp Clin Cancer Res*. 2022;41(1):90. https://doi.org/10.1186/s13046-022-02270-z.
121 Ren S, Cai Y, Hu S, et al. Berberine exerts anti-tumor activity in diffuse large B-cell lymphoma by modulating c-myc/CD47 axis. *Biochem Pharmacol*. 2021;188:114576. https://doi.org/10.1016/j.bcp.2021.114576.
122 Jiang ZB, Huang JM, Xie YJ, et al. Evodiamine suppresses non-small cell lung cancer by elevating $CD8^{(+)}$ T cells and downregulating the MUC1-C/PD-L1 axis. *J Exp Clin Cancer Res*. 2020;39(1):249. https://doi.org/10.1186/s13046-020-01741-5.
123 Mao D, Wang H, Guo H, et al. Tanshinone IIA normalized hepatocellular carcinoma vessels and enhanced PD-1 inhibitor efficacy by inhibiting ELTD1. *Phytomedicine*. 2024;123:155191. https://doi.org/10.1016/j.phymed.2023.155191.
124 Liu X, Yin M, Dong J, et al. Tubeimoside-1 induces TFEB-dependent lysosomal degradation of PD-L1 and promotes antitumor immunity by targeting mTOR. *Acta Pharm Sin B*. 2021;11(10):3134-3149. https://doi.org/10.1016/j.apsb.2021.03.039.
125 Liu F, Zhou Q, Jiang HF, et al. Piperlongumine conquers temozolomide chemoradiotherapy resistance to achieve immune cure in refractory glioblastoma *via* boosting oxidative stress-inflamation-$CD8^{(+)}$-T cell immunity. *J Exp Clin Cancer Res*. 2023;42(1):118. https://doi.org/10.1186/s13046-023-02686-1.
126 Han Y, Kim HI, Park J. The role of natural products in the improvement of cancer-associated cachexia. *Int J Mol Sci*. 2023;24(10):8772. https://doi.org/10.3390/ijms24108772.
127 Ratnani I, Fatima S, Abid MM, et al. Evidence-based medicine: history, review, criticisms, and pitfalls. *Cureus*. 2023;15(2):e35266. https://doi.org/10.7759/cureus.35266.
128 Nagappa AN, Bhatt S. RCT, Systematic Reviews, and Evidence-Based Medicine: Randomized Clinical Trials (RCT). Perspectives in Pharmacy Practice: Trends in Pharmaceutical Care. Springer Singapore; 2022:321-332. https://doi.org/10.1007/978-981-16-9213-0_20.
129 Wallace SS, Barak G, Truong G, et al. Hierarchy of evidence within the medical literature. *Hosp Pediatr*. 2022;12(8):745-750. https://doi.org/10.1542/hpeds.2022-006690.
130 Djulbegovic B, Guyatt GH. Progress in evidence-based medicine: a quarter century on. *Lancet*. 2017;390(10092):415-423. https://doi.org/10.1016/S0140-6736(16)31592-6.
131 Yang Y, Li X, Chen G, et al. Traditional Chinese medicine compound (Tongxinluo) and clinical outcomes of patients with acute myocardial infarction: the CTS-AMI randomized clinical trial. *JAMA*. 2023;330(16):1534-1545. https://doi.org/10.1001/jama.2023.19524.
132 Ji H, Zhao X, Chen X, et al. Jinlida for diabetes prevention in impaired glucose tolerance and multiple metabolic abnormalities: the FOCUS randomized clinical trial. *JAMA Intern Med*. 2024;184(7):727-735. https://doi.org/10.1001/jamainternmed.2024.1190.
133 Li C, Yang S, Ma H, et al. Influence of icariin on inflammation, apoptosis, invasion, and tumor immunity in cervical cancer by reducing the TLR4/MyD88/NF-κB and Wnt/β-catenin pathways. *Cancer Cell Int*. 2021;21(1):206. https://doi.org/10.1186/s12935-021-01910-2.
134 Hao H, Zhang Q, Zhu H, et al. Icaritin promotes tumor T-cell infiltration and induces antitumor immunity in mice. *Eur J Immunol*. 2019;49(12):2235-2244. https://doi.org/10.1002/eji.201948225.
135 Fan Y, Li S, Ding X, et al. First-in-class immune-modulating small molecule icaritin in advanced hepatocellular carcinoma: preliminary results of safety, durable survival and immune biomarkers. *BMC Cancer*. 2019;19(1):279. https://doi.org/10.1186/s12885-019-5471-1.
136 Qin SK, Li Q, Jia MX, et al. Icaritin-induced immunomodulatory efficacy in advanced hepatitis B virus-related hepatocellular carcinoma: immunodynamic biomarkers and overall survival. *Cancer Sci*. 2020;111(11):4218-4231. https://doi.org/10.1111/cas.14641.
137 Wang Y, Wang G, Liu Y, et al. Icaritin inhibits endometrial carcinoma cells by suppressing *O*-GlcNAcylation of FOXC1. *Phytomedicine*. 2023;120:155062. https://doi.org/10.1016/j.phymed.2023.155062.
138 Dongye Z, Wu X, Wen Y, et al. Icaritin and intratumoral injection of CpG treatment synergistically promote T cell infiltration and antitumor immune response in mice. *Int Immunopharmacol*. 2022;111:109093. https://doi.org/10.1016/j.intimp.2022.109093.
139 Sun Y, Qin S, Li W, et al. A randomized, double-blinded, phase III study of icaritin versus Huachashu as the first-line therapy in biomarker-enriched HBV-related advanced hepatocellular carcinoma with poor conditions: interim analysis result. *J Clin Oncol*. 2021;39(15_suppl):4077-4077. https://doi.org/10.1200/JCO.2021.39.15_suppl.4077.
140 Mo D, Zhu H, Wang J, et al. Icaritin inhibits PD-L1 expression by targeting protein IκB kinase α. *Eur J Immunol*. 2021;51(4):978-988. https://doi.org/10.1002/eji.202048905.
141 Liu Q, Shen J, Chen Y, et al. Phase II trial of radiotherapy plus Huachansu in elderly or chemotherapy-ineligible patients with locally advanced esophageal squamous cell carcinoma. *Oncologist*. 2025;2025:oyaf325. https://doi.org/10.1093/oncolo/oyaf325.
142 Shen WC, Chen SC, Wang CH, et al. *Astragalus* polysaccharides improve adjuvant chemotherapy-induced fatigue for patients with early breast cancer. *Sci Rep*. 2024;14(1):25690. https://doi.org/10.1038/s41598-024-76627-z.
143 Chen YX, Gao QY, Zou TH, et al. Berberine versus placebo for the prevention of recurrence of colorectal adenoma: a multicentre, double-blinded, randomised controlled study. *Lancet Gastroenterol Hepatol*. 2020;5(3):267-275. https://doi.org/10.1016/s2468-1253(19)30409-1.