Journal of Integrative Medicine 22 (2024) 137–162

Contents lists available at ScienceDirect

Journal of Integrative Medicine

journal homepage: www.jcimjournal.com/jim
www.journals.elsevier.com/journal-of-integrative-medicine

Systematic Review

Herbal compounds as promising therapeutic agents in precision medicine strategies for cancer: A systematic review

Bizhar Ahmed Tayeb [a,*], Ikhwan Yuda Kusuma [b,d], Alaa A.M. Osman [a,c], Renáta Minorics [a]

[a] Institute of Pharmacodynamics and Biopharmacy, Faculty of Pharmacy, University of Szeged, 6720 Szeged, Hungary
[b] Institution of Clinical Pharmacy, Faculty of Pharmacy, University of Szeged, 6725 Szeged, Hungary
[c] Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, University of Gezira, 20 Wad Madani, Sudan
[d] Pharmacy Study Program, Faculty of Health, Universitas Harapan Bangsa, Purwokerto 53182, Indonesia

A R T I C L E I N F O

Article history:
Received 10 June 2023
Accepted 30 January 2024
Available online 28 February 2024

Keywords:
Cancer
Herbal medicine
Personalized medication
Active phytochemicals
Natural compound

A B S T R A C T

Background: The field of personalized medicine has gained increasing attention in cancer care, with the aim of tailoring treatment strategies to individual patients for improved outcomes. Herbal medicine, with its long-standing historical use and extensive bioactive compounds, offers a rich source of potential treatments for various diseases, including cancer.
Objective: To provide an overview of the current knowledge and evidence associated with incorporating herbal compounds into precision medicine strategies for cancer diseases. Additionally, to explore the general characteristics of the studies included in the analysis, focusing on their key features and trends.
Search strategy: A comprehensive literature search was conducted from multiple online databases, including PubMed, Scopus, Web of Science, and CINAHL-EBSCO. The search strategy was designed to identify studies related to personalized cancer medicine and herbal interventions.
Inclusion criteria: Publications pertaining to cancer research conducted through in vitro, in vivo, and clinical studies, employing natural products were included in this review.
Data extraction and analysis: Two review authors independently applied inclusion and inclusion criteria, data extraction, and assessments of methodological quality. The quality assessment and biases of the studies were evaluated based on modified Jadad scales. A detailed quantitative summary of the included studies is presented, providing a comprehensive description of their key features and findings.
Results: A total of 121 studies were included in this review for analysis. Some of them were considered as comprehensive experimental investigations both in vitro and in vivo. The majority (n = 85) of the studies included in this review were conducted in vitro, with 44 of them specifically investigating the effects of herbal medicine on animal models. Additionally, 7 articles with a combined sample size of 31,271 patients, examined the impact of herbal medicine in clinical settings.
Conclusion: Personalized medication can optimize the use of herbal medicine in cancer treatment by considering individual patient factors such as genetics, medical history, and other treatments. Additionally, active phytochemicals found in herbs have shown potential for inhibiting cancer cell growth and inducing apoptosis, making them a promising area of research in preclinical and clinical investigations.
Please cite this article as: Tayeb BA, Kusuma IY, Osman AAM, Minorics R. Herbal compounds as promising therapeutic agents in precision medicine strategies for cancer: A systematic review. *J Integr Med*. 2024; 22 (2): 137–162.

Contents

* Corresponding author.
E-mail address: drbat25@yahoo.com (B.A. Tayeb).

https://doi.org/10.1016/j.joim.2024.02.001
2095-4964/

1. Introduction

Cancer is a complex group of diseases characterized by heterogeneous features, including uncontrolled cellular proliferation, evasion of cell death mechanisms, and the acquisition of replicative immortality. It can be broadly classified into two main categories: hematologic malignancies, which involve cancers of the blood cells, and solid tumors, which arise from abnormal cell growth and form localized masses known as tumors. Solid tumors have the capacity to invade surrounding tissues locally and metastasize to distant sites via the bloodstream, bone marrow or lymphatic system [1,2].

Cancer remains a significant public health concern globally. It is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths. Nevertheless, there have been significant gains in patient survival rates over the last three decades due to early diagnosis and advancements in medical therapy [3,4].

Cancer management encompasses a comprehensive approach involving multiple modalities such as surgery, radiation therapy, chemotherapy, hormonal therapy, and targeted therapies. Chemotherapy includes the administration of various classes of drugs, including antimetabolites, alkylating agents, anthracyclines, antitumor antibiotics, mitotic inhibitors and topoisomerase inhibitors [5]. Hormonal therapy may involve the use of corticosteroids, while targeted therapies can include agents such as trastuzumab [6].

The primary goals of cancer management are to enhance cure rates, improve survival outcomes, and prevent local progression or distant metastasis [7]. Chemotherapy and chemoradiotherapy play a crucial role in the treatment of a significant proportion of cancer patients, and they have demonstrated benefits in terms of anticancer efficacy [3].

However, despite their therapeutic potential, these treatment modalities are not without limitations, which can compromise their efficacy and lead to treatment failure. One notable concern is the impact of these medications on normal cells and tissues, as they can elicit adverse effects that manifest as a wide range of side effects. For example, doxorubicin, a commonly used chemotherapy drug, can cause renal toxicity [8], myelosuppression [9] and heart problems [10]. Similarly, 5-fluorouracil, another frequently used chemotherapy, may induce cardiotoxicity [11], myelotoxicity [12], and in rare cases, vasospasm [13]. Cisplatin, an approved chemotherapy medication used for various types of cancers including breast, ovary, cervical, lung and head-neck cancers, can cause ototoxicity, renal toxicity and low blood counts [14,15].

In addition, several intrinsic disadvantages have been reported with chemotherapeutic medications, including nausea, vomiting, diarrhea, anorexia and oral mucositis, among others [16]. These side effects can significantly impact the quality of life for cancer patients undergoing chemotherapy or chemoradiotherapy. There is a need for continued research and development of innovative approaches to minimize the adverse effects of anticancer medications and improve the overall well-being of cancer patients.

The side effects of chemotherapy or chemoradiotherapy often significantly impact the quality of life of patients and may even pose challenges in continuing with the treatment [5]. Despite the establishment of various measures for managing or preventing these adverse effects, they remain inadequate [17–19].

Another significant limitation of anticancer therapies is the development of chemoresistance, whereby cancer cells become resistant to the effects of chemotherapy drugs, resulting in diminished treatment efficacy and ultimately, treatment failure [20–23]. Furthermore, the high cost associated with anticancer medications presents a substantial financial burden for many patients, particularly those residing in developing countries. According to a previous report, the average monthly cost of recently approved anticancer medications is estimated to be approximately 10,000 US dollars, with some treatments reaching as high as 30,000 US dollars per month [24]. Considering the existing limitations of conventional anticancer therapies, exploring alternative approaches such as incorporating herbal medicine alone or in combination with traditional anticancer treatments may offer a promising and cost-effective option.

Herbal medicine, also known as botanical medicine, phytomedicine or phytotherapy, refers to herbs, herbal substances, herbal preparations, and completed herbal products that contain active compounds derived from plants or other materials. Seeds, leaves, roots, berries, fruits, flowers, bark, and even entire plants are utilized in herbal treatments [25].

Anticancer medicines derived from plants have been developed over time and are now utilized in clinical practice to treat many forms of cancer. Archaeological studies have revealed that the use of herbal medicine dates back as far as 60,000 years in Iraq and 8,000 years in China [26–28]. Written records associated with medicinal plants date back at least 5,000 years to the Sumerians, who documented well established medicinal uses for plants such as thyme, caraway and laurel [29]. This clearly indicates that plant-based medications and therapies have been used by humans to treat various health problems [30].

Herbal medicines continue to be a valuable source of prospective pharmacological substances [31]. One widely used herbal modality is traditional Chinese medicine (TCM), which has been shown in several studies to have the potential to boost the efficiency and reduce the adverse consequences of chemotherapies, as well as induce apoptosis in cancerous cells [32–34]. TCM is a form of personalized or customized medicine, resembling traditional healing systems that were developed over centuries in many regions, used to treat a wide range of health problems, including cancer [35].

The aim of this work is to conduct a comprehensive systematic review of data related to the utilization of herbal medicine or plant-based ingredients in the treatment of cancers or cancer cells in human and animal studies. By synthesizing and analyzing the available evidence, this review contributes to our understanding of the role of herbal medicine in cancer therapy and identifies potential avenues for further research and clinical application. The findings of this review may have implications for clinicians, researchers and policymakers involved in cancer care, and may provide valuable insights into the use of herbal medicine as a complementary or alternative approach to conventional cancer treatments.

2. Methods

The Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews guidelines were followed in this review, ensuring a rigorous and transparent approach to the research process [36,37]. Relevant search phrases were determined based on the Population, Intervention, Context, Outcome (PICO) framework, which helped guide the search strategy and ensure consistency [38]. A series of processes were applied in searching each database, including utilizing pre-existing knowledge, brainstorming, and using thesaurus terms to identify appropriate keywords. This approach helped to ensure precision and consistency in terminology across all databases and allowed for flexibility in broadening or narrowing the search as needed. By adhering to established guidelines and employing a systematic approach, the integrity and rigor of this review were maintained, enhancing the reliability and validity of the findings.

2.1. Search strategy

On December 1st, 2022, a comprehensive literature search was conducted in several online bibliographic databases, including Scopus, PubMed, Web of Science, and CINAHL-EBSCO. The initial search strategies were developed by the authors and refined through team discussions. The following search terms were generated in accordance with the PICO framework [38] and were used in all databases: "personalized medicine" OR "precision medicine" OR "personalized medication" OR "precision medication" AND "cancer" OR "neoplasm" OR "oncology" OR "malignant" AND "herbal" OR "herb" OR "herbs" OR "botanic" OR "natural compound."

Given that many of the herbal medicines used in cancer treatment are derived from TCM, a search was also conducted in the Chinese National Knowledge Infrastructure Database, specifically in the subject areas of title, keyword and abstract. Subsequently, the final search was performed, and duplicate publications were removed. All relevant data and references were carefully documented and exported to reference management software Zotero (version 6.0.23; Virginia, USA) for organization.

The selected records were then imported into an online systematic review screening tool (Rayyan) [39], which automatically identified potential duplicates using a duplicate filter. The duplicated articles were reviewed, verified and removed manually by an author (IYK) to ensure the accuracy and reliability of the final set of references. This systematic search and screening process was conducted meticulously to ensure a comprehensive and rigorous review of the relevant literature.

2.2. Eligibility criteria

Animal, in vitro and clinical (randomized controlled trials, observational studies, case series, case reports) studies that tested the anticancer effects of herbal extracts for the treatment of human cancer and published in English were considered eligible for inclusion in this systematic review. We excluded studies that tested the effects of herbal extracts on cancer related symptoms or other conditions, such as quality of life, studies that tested the effects of herbal medicines in combination with chemotherapy or targeted therapy, and studies tested the effects of fruit-derived compounds or synthetic chemical compounds. In addition, we excluded in silico, or computational studies, review article, reports, dissertations, meeting abstracts, and non-English publications. Table 1 presents the inclusion and exclusion criteria that were applied to filter the references identified by the search strategy.

2.3. Selection of relevant studies

After the databases were searched, duplicate articles were removed, two authors (IYK and AAMO) screened the titles and abstracts to identify those suitable for full-text screening. Any disagreement in the decision to include or exclude an article was resolved by the third author (BAT). Following exclusion of the irrelevant records, eligibility criteria were applied to the full-text articles and those meeting all criteria were included in the final review.

The selection and decision-making process was based on discussions and consensus reached between the authors. These criteria were carefully applied to ensure that only relevant and high-quality articles meeting the established standards were included in the analysis; articles that did not meet the predetermined criteria were excluded.

Table 1
List of inclusion and exclusion criteria.

Item	Inclusion criteria	Exclusion criteria
Type of publication	Full-research articles, or conference papers	Review articles, reports, dissertations, or meeting abstracts
Language	English language	Not English
Type of research	Experimental and empirical studies in vivo or in vitro	Combinational therapy, commercial or online news, and feature articles

2.4. Data extraction

The data from the collected articles were independently extracted by three authors (BAT, AOAM and IYK). The synthesis process encompassed a comprehensive descriptive summary of the study characteristics, followed by a rigorous thematic analysis of the reported outcomes. This analysis was conducted using Microsoft Office Excel 365 (Microsoft Corporation, 2021, Redmond, USA), and a standardized template to ensure consistency and organization in the data analysis process. Each researcher entered the data into spreadsheets, capturing key characteristics such as the first author, publication year, location of the work, sample size, type of herbal product used, type of cancer, methodology, and outcome measures. After completing this process for all included articles, the reviewers cross-checked their recorded data and removed any duplicates. In case of inconsistent data interpretation, the reviewers further reviewed and discussed until reaching an agreement. This process was supervised by a different author (RM) to ensure accuracy and reliability of the extracted data. The use of spreadsheets and thorough data validation procedures helped to minimize errors and maintain data integrity during the data extraction process.

2.5. Quality assessment of the clinical studies

The quality of the included clinical studies in this review was assessed using the modified Jadad score [40,41]. The tool score consists of three items: randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 points). Each item is scored as either "yes" (1 point) or "no" (0 point). The final score can range from 0 to 5 points, with higher scores indicating better reporting. Studies possessing a Jadad score of 2 or lower were classified as low quality, whereas those attaining a Jadad score of 3 or higher were characterized as high quality (Supplementary Table 1). This process was carried out by two authors (BAT and IYK).

3. Results

3.1. Selection of sources of evidence

A total of 1068 records were identified and collected from the electronic databases that were queried. After duplicate articles were removed (n = 95), the titles and abstracts of the remaining 973 studies were screened. Based on this screening step, 838 irrelevant articles were excluded, and the remaining 135 publications were suitable for full-text screening. Among these, 14 publications were excluded for the following reasons: incorrect study designs (n = 3), incorrect drugs (n = 2), did not directly quantify effects on human health (n = 7), and not considered original quantitative research (n = 2). One study was excluded as the full text could not be found online. The remaining 121 studies were considered eligible and were included in the final review. A flow chart of the identification of eligible studies is shown in Fig. 1.

3.2. General characteristics of the included papers

Based on the results obtained from the included papers, the data were classified into three major groups: in vitro studies, animal studies and clinical studies. Since some of the studies included both in vitro and in vivo experiments, the exact number of articles may not be provided. However, the summarized results are presented in Tables 2–4, providing a comprehensive overview of the findings. The data from these studies were carefully analyzed and organized to facilitate a clear understanding of the key findings and trends in the field of interest.

3.2.1. Characteristics of the in vitro studies

The majority (n = 85) of the studies included in this review were conducted in vitro, utilizing various cell lines as models to evaluate the anticancer effects of herbal medicine extracts. The included papers encompassed a diverse range of cancer types, including colon, breast, cervical, and lung cancers (Table 2). The characteristics of all the studies that investigated the effects of herbal medicine extracts on cells are summarized and provide a comprehensive overview of the findings in this context.

3.2.2. Characteristics of the in vivo animal model

Out of the 121 studies included in this review, 44 of them investigated the effects of herbal medicine on animal models. The majority of these studies utilized BALB/c mice that were 6 to 8 weeks old. Additionally, one study employed *Drosophila* flies for experimental verification purposes [139]. Furthermore, two separate studies utilized transgenic zebrafish to investigate the antiproliferative and antimigration properties of herbal plants [69,103]. These studies provide valuable insights into the effects of herbal medicine on animal models, offering a deeper understanding of their potential therapeutic applications (Table 3).

3.2.3. Clinical studies and quality assessment

Seven articles with a combined sample size of 31,271 patients were deemed eligible for evaluation in this review. These 7 studies were randomized controlled trials, case reports, and retrospective studies, with moderate to good methodological quality. A concise description of each of these studies, along with their overall quality based on the modified Jadad scores, is provided, and a summary of their key characteristics can be found in Table 4.

Most of the clinical studies included in this systematic review were assessed as having a low risk in all domains, indicating a high quality of evidence. Specifically, 5 studies received a score of 4 or greater in the modified Jadad scale (Supplementary Table 2), further supporting the overall quality of the included studies. The heterogeneity and limited number of studies may introduce some risk of bias. The risk of bias in each of the 7 clinical studies is presented in Table 4 and Supplementary Table 3. These studies represent a valuable piece of evidence for the evaluation of herbal medicine in the context of clinical implementation, providing important insights into their efficacy and safety.

3.3. Pharmacological properties of herbal interventions

The papers included in this review explored diverse herbal interventions, with some focusing on single herbs and others investigating herbal formulations or combinations. Phytochemicals derived from plants possess diverse pharmacological properties and have shown promising anticancer effects in preclinical and clinical studies. The active phytochemicals from medicinal plants, along with their pharmacological properties, are presented in Table 5, providing a comprehensive overview of the potential mechanisms underlying the anticancer effects of these herbal interventions.

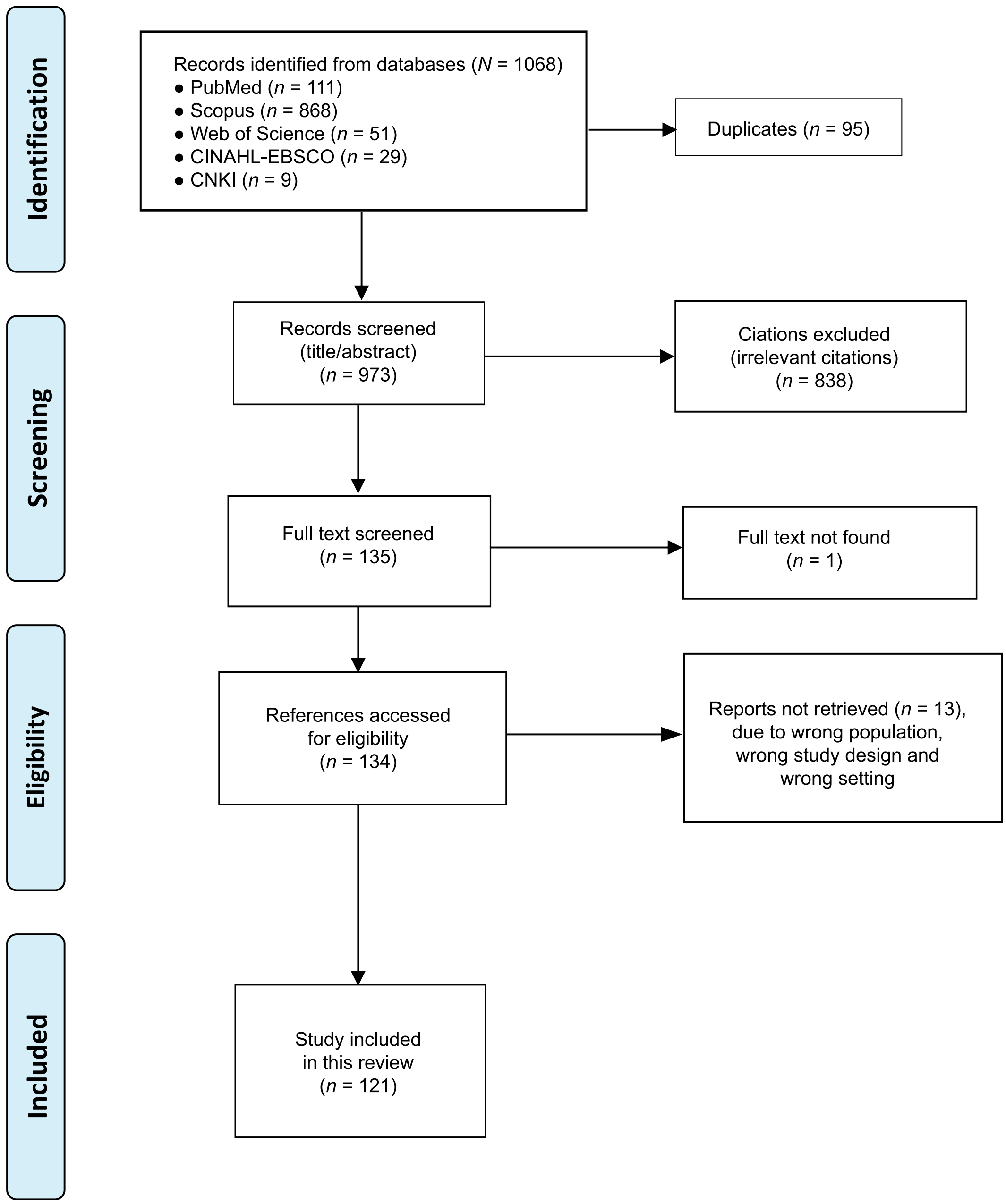

Fig. 1. The diagram illustrating selection and screening of the articles. CNKI: China National Knowledge Infrastructure.

4. Discussion

Recent research has greatly advanced our understanding of the molecular mechanisms and potential therapeutic approaches for cancer treatment. However, effective remedies are still needed to address the challenges posed by cancer. Herbal medicines and their phytochemicals have been extensively studied for their anticancer effects, and this area of research is actively pursued in the field of cancer treatment. This systematic review provides a comprehensive synthesis of the findings derived from 121 studies assessing the efficacy of herbal or plant extracts, as well as their active compounds, in the treatment of various cancer types. The included studies encompassed a wide range of research designs, including in vitro, in vivo and clinical investigations. The primary objective of this review was to investigate the impact of herbal medicine in cancer treatment, with the aim of informing future preclinical and clinical research endeavors and facilitating the integration of herbs with established anticancer effects into clinical practice.

Traditional herbal medicine, rooted in historical practices spanning centuries, is enduringly popular and continues to be extensively used in various cultures worldwide. However, the effectiveness of herbal medicine in cancer treatment remains a controversial topic in the medical field. Some studies have shown that certain herbs and plants contain chemicals that can help prevent and treat cancer. For instance, the compound curcumin, found in turmeric, has been shown to possess anti-inflammatory and anticancer properties. Increasing evidence suggests that curcumin has a wide range of biological effects, impacting various cellular and molecular pathways, including apoptosis, mitogen-activating protein kinase (MAPK), p53 and microRNA [161].

Table 2
Anticancer effects of medicinal plant extracts in in vitro studies (85 studies).

Study	Botanical name	Part used	Cell line	Methodology	Outcome
Al-Zahrani 2021 [42]	*Chaetomorpha ligustica* algae	Whole plant	Human cancer cell HT 29 and HCT 116	Cell viability MTT assay, gene expression level such as checkpoint genes *ATM*, *ATR*, *CHEK1* and *CHEK2* by using RT-PCR	Cytotoxic activity was observed in the employed plant extract on the cell lines, leading to an increase in the expression levels of the genes.
Al-Zahrani 2022 [43]	*Commiphora gileadensis* and silver nanoparticles	Extracts and nanoparticles	SW620, HCT 116 and HT 29	Cell viability MTT assay, gene expression level via cell cycle genes measurements (*CHEK1*, *CHEK2*, *ATR* and *ATM*) by RT-PCR	Both extracts exhibited toxicity in a dose-dependent manner on the cells. The expression levels of the genes mostly increased after treatment.
Alim 2022 [44]	*Clinacanthus nutans*	Leaves	Human gingival fibroblasts-1	GCMS analysis for identification of compounds, and MTT assay for cytotoxicity	Forty-four compounds were identified through GCMS analysis. The extracts did not demonstrate cell proliferation.
Alper 2022 [45]	*Colchicum boissieri* and *Colchicum balansae*	Aerobic parts	Caco-2 human cancer cell	MTT antiproliferative assay, antioxidant, and radical-scavenging assays (FRAP, CUPRAC, DPPH, ABTS and the β-carotene/linoleic acid)	The extracts from both herbs demonstrated antioxidative and antiproliferative effects on this cell line in a dose-dependent manner.
Anusmitha 2022 [46]	Different species of *Ocimum* plants	Leaves	Human breast cancer cells MCF-7	LCMS for phytochemical analysis; antiproliferation, anti-inflammatory, and antioxidation assays	The extracts exhibited anticancer characteristics in a dose-dependent manner.
Arya 2015 [47]	*Eclipta alba*	Whole plant	Human MCF-7 and MDA-MB-231, mouse breast cancer 4T1, and human breast epithelial cells MCF 10A	LCMS, HPLC, cytotoxicity, flow-cytometry, apoptosis-array analysis, and Western blotting	This plant exhibited inhibitory effects on breast tumors.
Ayeka 2016 [48]	*Glycyrrhiza uralensis* (Chinese liquorice)	Not reported	Mouse intestinal epithelial cell line-6 and colon carcinoma cell line-26	Cell proliferation and cytotoxicity assays, and RT-PCR for gene expression	Antitumor and immunomodulatory activities were demonstrated in the study.
Babu 2016 [49]	*Syzygium alternifolium*	Fruit	Human gastric adenocarcinoma AGS cells	Cytotoxicity assay and cell cycle analysis by flow cytometry	The herb demonstrated a notable inhibition of cellular growth, as evidenced by an IC_{50} ranging from 30.3 to 35.5 µg/mL. This effect was accompanied by cell cycle arrest, culminating in the induction of apoptosis.
Ballesteros-Ramírez 2020 [50]	*Petiveria alliacea* and *Caesalpinia spinosa*	Leaves and the pods	Human leukemic cell line K562, U937 and Jurkat cells	Antioxidant (ORAC, FRAP, ABTS radical-scavenging assay) and cytotoxicity by MTT and XTT assays	The extracts induced cell death and *P. alliacea* demonstrated higher efficacy compared to *C. spinosa.*
Bi 2022 [51]	*Ligusticum chuanxiong*	Not reported	HCC HepG2 cell line	Cell viability analysis by CCK-8, flow cytometer analysis of cell cycle and apoptosis, and analysis of mitochondrial function	The compounds exhibited a significant increase in HepG2 cell inhibition in a dose-dependent manner ($P < 0.01$) and induced cell apoptosis.
Buriani 2017 [52]	*Pistacia* species (*P. lentiscus*, *P.* lentiscus var. chia, *P. vera*, and *P. integerrima*)	Aerial parts (leaves, berries, branches, galls and nuts)	Human adenocarcinoma: breast (MCF-7), ovarian (2008), and colon (LoVo)	Cytotoxic activity assay and component analysis	Cytotoxic activity was observed in a dose-dependent manner in the utilized plant components.
Cao C 2022 [53]	Not reported	Not reported	Panc-1 and Capan-2 cells	Purification of paeoniflorin was checked by UPLC-MS; cell culture and viability assay, ELISA, and Western blotting	The compound demonstrated antiproliferative activity against the cell lines within 24 h in a dose-dependent manner.
Cao X 2022 [54]	KangXianYiAi mixture of Radix Bupleuri, *Astragalus membranaceus*, Rhizoma Dioscoreae, and Sinapis Semen	Granules	Hepatoma cell lines (HepAD38, HepG2, Huh7 and SK-Hep1)	Cell viability by using CCK-8 assay, migration assay, cell cycle, and apoptosis with flow cytometer, and qPCR	The formula has been reported to exhibit antiproliferative and migration-inhibitory capabilities in a dose-dependent manner, promoting apoptosis of HepAD38 cells.
Chang 2016 [55]	*Withania somnifera*	Roots	Glioblastoma multiforme (GBM2, GBM39 and U87-MG)	HPLC for plant analysis, cellular proliferation, cytotoxicity (ABA), Western blotting, and apoptosis assays	Antiproliferative effects were observed in a dose-dependent manner.
Chang 2021 [56]	Lychee	Seed	Human prostate cancer cells (PC-3, DU145 and PC-3^{-luc})	Chromatography for seed analysis, cell proliferation (MTT), colony formation, cell migration, cell invasion, Western blot, TUNEL, and immunofluorescence assays	The study revealed inhibition of cell proliferation and viability, induction of apoptosis, and hindrance of cell migration and invasion.

(*continued on next page*)

Table 2 (*continued*)

Study	Botanical name	Part used	Cell line	Methodology	Outcome
Chen 2017 [57]	*Garcinia hanburyi*	Not reported	Human myeloma cell line, MM.1S	Cell proliferation (CCK-8) assay, cell cycle and Western blotting	This compound had antiproliferative effects and induced apoptosis.
Chen 2022 [58]	Chinese herbal injections (AD, KA, SXT, XNJ, XBJ, TRQ, DZXX, SF, QKL, XYP and Danshentong IIA)	Not reported	WEHI 164 clone 13 cell line (WEHI-13VAR) and CT26 colon cancer cell line	Cytotoxicity by MTT assay and flow cytometry	The formula displayed anti-tumor effects.
Choi 2016 [59]	*Astragalus membranaceus*, *Angelica gigas*, *Trichosanthes kirilowii* Maximowicz.	Not reported	HUVECs	Proliferation, scratching, tube formation, invasion and zymography assays	The formula has demonstrated inhibition of cancer cell migration, as well as prevention of invasion and angiogenesis.
Dong 2022 [60]	*Solanum nigrum* L.	All parts	Human bladder cancer cell lines T24 and 5637	Cell viability (CCK-8), apoptosis, and cell cycle analysis by flow cytometry, and Western blotting	This medication exhibited activity in inhibiting cell viability and proliferation, while inducing apoptosis.
Duan 2020 [61]	Cortex Fraxini	Not reported	Clear cell renal cell carcinoma (786-O and SN12-PM6)	Cytotoxic, colony-forming and wound healing assays, cell migration, and flow cytometry	This herb showed the capacity to decrease cell viability in a dose-dependent manner, induce cell cycle arrest, and inhibit cell migration and invasion.
Garufi 2021 [62]	Not reported	Not reported	Human breast cancer SKBR3 and glioblastoma U373	Cell viability assay, chromatin immunoprecipitation assay, Western blotting, and qPCR	The compound has triggered cell death and apoptosis in cancer cell lines.
Guo 2022 [63]	Sinikangai fang	Not reported	HCC cells (HCCLM3 and MHCC97H)	Cell viability, colony formation assay, invasion-migration assay, flow cytometry, and immunofluorescence	Inhibitory effects on viable cells and anti-apoptotic properties were observed.
Guo 2020 [64]	*Epimedium koreanum* Nak	Not reported	Human liver cancer cell line HuH-7 and HepG2	CCK-8 assay, cell migration (wound-healing) assay, Western blotting, flow cytometry, Transwell assay, and colony formation assay	Baohuoside-1 inhibited the migration of HepG2 and Huh7, induced apoptosis, and demonstrated antiproliferative effects.
Han 2022 [65]	Alismatis Rhizoma	Not reported	Colorectal cancer cell lines (HCT 116 and HT 29)	MTT assay, cell cycle and apoptotic analysis, colony formation, migration (wound healing), LDH, and Western blotting	Alisol A exhibited antiproliferative, antimigration, apoptotic, and cell cycle arrest activities.
Hao 2019 [66]	*Clinacanthus nutans*	Leaves	HeLa cells	Antiproliferation assay, annexin V analysis of apoptosis, morphological analysis, GCMS analysis, and cell cycle analysis	The extracts demonstrated time- and dose-dependent antiproliferative activity in HeLa cells. The plant extract induced apoptosis of the cells at a concentration of 70 µg/mL after 72 h of incubation.
Hassan 2023 [67]	*Annona muricata* L.	Leaves	Cervical cancer HeLa cells	MTT assay and qPCR	The extracts showed cell inhibition with low cytotoxicity in high selectivity.
Huang 2022 [68]	Qi-Yu-San-Long decoction	Not reported	Human lung adenocarcinoma cell line A549	UPLC-MS, antioxidant assays (DPPH and FRAP); CCK-8, wound-healing, migration, and invasion assays	The decoction exhibited strong inhibitory effects on cell proliferation, migration and invasion activities.
Huang 2021 [69]	*Salvia miltiorrhiza*	Not reported	Acute promyelocytic leukemia (HL-60 and NB4) cell lines	Flow cytometry and cell sorting	The herbal extraction markedly induced apoptosis in leukemic cells and promoted myeloid differentiation in both cell lines.
Ji 2022 [70]	*Elephantopus scaber* L.	Not reported	Colorectal cancer cells (HCT116 and sw620)	Cell proliferation (MTT), RNA sequencing and qPCR, flow cytometry, Western blotting, and luciferase reporter assay	The herbal extraction significantly inhibited cell growth and induced apoptosis.
Jiang 2019 [71]	Safflower	Not reported	Human NSCLC cell lines, A549 and H1299	CCK-8 assay, EdU assay, colony formation assay, flow cytometry, wound-healing (cell migration) assay, Transwell chamber (cell invasion) assay, and Western blotting	Cell reduction and apoptosis significantly occurred after 72 h of treatment with this herbal medicine. Furthermore, the herbal extract exhibited the capacity to decrease cell migration and invasion in a dose-dependent manner.
Jiang 2021 [72]	*Sanguisorba officinalis* L.	Dried roots	HCC cells (HepG2, MHCC97H, SMCC7721 and BEL-7404)	Cell viability assay, EdU assay, wound-healing and Transwell invasion assay, flow cytometry and Western blotting	The plant was found to inhibit cell proliferation, induce apoptosis, and reduce cell migration and invasion in HCC cells.
Kaipa 2020 [73]	*Silybum marianum*	Not reported	Human lung adenocarcinoma cell lines H1650, H1975, A549, H838 and H2030	Cell Titer-Blue cell viability, cell migration, immunofluorescence, microscopic imaging, and immunoblotting assays	The cells exhibited significant inhibition of cell proliferation and migration after 72 h in a time- and dose-dependent manner.

(*continued on next page*)

Table 2 (*continued*)

Study	Botanical name	Part used	Cell line	Methodology	Outcome
Kazi 2022 [74]	Green tea (polyphenon 60)	Not reported	Human A375 melanoma cell line	Cell viability MTT, antityrosinase activity, and Western blotting assays	This compound inhibited mushroom tyrosinase and significantly decreased cell viability in a dose-dependent manner.
Khan 2022 [75]	*Moringa oleifera*	Leaves	Human osteoblast SaOS-2 cell line	Trypan blue staining and MTT assay, antioxidant activity, flow cytometry, and qPCR	The viable cell number decreased in a dose- and time-dependent manner, with cell proliferation inhibited at 100–200 μg/mL, leading to apoptosis and cell arrest.
Kim 2019 [76]	Naesohwangryeon-tang formula	Not reported	Human NSCLC, A549 and NCI-H460	MTT assay, cell cycle analysis, Western blotting, DAPI staining, autophagy detection, and antioxidant assays	The cell viability decreased in a dose-dependent manner, and the formula induced apoptosis.
Kim 2019 [77]	*Rhus verniciflua* Stokes extract	Not reported	MCF-7 cells	Antiproliferative activity by MTT assay, cell cycle analysis by flow cytometry, anti-apoptotic activity by annexin V labeling; p53 and p21 expressions by Western blotting	The extract inhibited cell proliferation in a dose-dependent manner and triggered apoptosis.
Kocanci 2017 [78]	*Glaucium acutidentatum* and *Glaucium corniculatum* extracts	Above-ground tissues	HT-29 and HeLa cancer cells	Antiproliferative activity by MTT assay	The inhibition of cell proliferation was shown, and this led to a decrease in cell viability.
Kubatka 2020 [79]	*Cinnamomum zeylanicum* L.	Bark	MCF-7 and MDA-MB-231 cells	MTS colorimetric assay; EdU, cell cycle, flow cytometry, caspase-3/7, Bcl-2, PARP, and mitochondrial membrane potential analyses	This herb demonstrated notable anticancer activity.
Lachkar 2022 [80]	*Chamaerops humilis* L. var. argentea Andre	Leaves	*Lepidium sativum* seeds	Antimitotic activity by phytotest *Lepidium sativum* test, and enzymatic activity	All extracts inhibited cell growth in a dose-dependent manner and demonstrated antimitotic activity.
Lee 2021 [81]	Moutan Radicis Cortex, Persicae Semen, and Rhei Radix et Rhizoma	Dried plant materials	HeLa human cervical cancer cells	MTT cell viability assay	Cell viability decreased in a dose-dependent manner (P < 0.001 at 500 and 1000 μg/mL).
Lee 2021 [82]	Moutan Radicis Cortex, Persicae Semen, and Rhei Radix et Rhizoma	Dried plant materials	MCF-7, MDA-MB-453 and MDAMB-231 cells	MTT cell viability assay	Cell viability decreased in a dose-dependent manner (P < 0.001 for all concentrations except at 5 μg/mL in MCF-7, P < 0.01).
Lee 2022 [83]	*Cordyceps militaris*, *Artemisia capillaris* Thunberg and *Lonicera japonica* Thunberg	Dried plant materials	AGS cells	Cell viability assay using WST-1	Cell viability decreased in a dose-dependent manner (P < 0.01 at 10 μg/mL, P < 0.001 at 50–1000 μg/mL).
Lee 2022 [84]	*Cordyceps militaris*, *Artemisia capillaris* Thunberg and *Lonicera japonica* Thunberg	Dried plant materials	HepG2 cells	Cell viability assay using WST-1	Cell viability dropped in a dose-dependent manner (P < 0.001 at all doses)
Li 2018 [85]	Ginsenoside Rh2 from ginseng	Not reported	Murine macrophage-like cell line RAW264.7; human NSCLC cell lines A549 and H1299; and human THP-1 cells	CCK-8 cell proliferation assay, wound-healing and cell migration assays, qPCR and Western blotting, and VEGF ELISA kit	Inhibited the growth of A549 and H1299 cells in a dose-dependent manner. The expression levels of MMP-2 and −9, and VEGF-C were assessed, and the release of VEGF in the supernatant was measured.
Li 2020 [86]	Compound Xishu Granule	Polyherbal decoction	Murine macrophage-like cell line RAW264.7, human NSCLC cell lines A549 and H1299, and human THP-1 cells	Cell viability assay using CCK-8, colony formation assay, and cell apoptosis and cell cycle assays using flow cytometry	Inhibited cell proliferation in a time- and dose-dependent manner, reduced the number of cells in the G_0/G_1 phase, and elevated the number of cells in the G_2/M phase in a dose-dependent manner (P < 0.01).
Li 2022 [87]	Dendrobium	Not reported	HCC cell lines Hep3B, SMMC-7721 and HCC-LM3	Cell viability assay using CCK-8 assay kit, EdU staining assay, wound-healing assay, Transwell invasion assay, matrigel invasion assay, and Western blotting	Inhibits the proliferation of HCC cells and suppresses the migration and invasion of these cells.
Liu 2020 [88]	*Ophiorrhiza pumila*	Dried whole plant	HepG2, SMMC-7721 and BRL3A cells	Anti-proliferation by CCK-8 kit and colony formation assay, apoptosis and cell cycle analysis by flow cytometry and Hoechst 33,258 staining, Transwell migration/invasion assays, Western blotting of cell cycle-related proteins, and DCFH-DA staining for ROS generation	This plant markedly inhibited cell viability and colony formation in a time- and dose-dependent manner and induced apoptosis and significantly inhibited cell migration.

(*continued on next page*)

Table 2 (*continued*)

Study	Botanical name	Part used	Cell line	Methodology	Outcome
Liu 2020 [89]	Babao Dan	Not reported	AGS and MGC80-3 cells	Cell viability by MTT assay, live cell ratio analysis, cell invasion and migration by Transwell assay, Western blotting for EMT biomarkers	The compound demonstrated antiproliferative, anti-invasion, and antimigration effects, along with the induction of apoptosis.
Liu 2021 [90]	*Berberis amurensis* Rupr.	Not reported	Lung cancer cell line A549 and PC9 cells	Cell viability and proliferation by MTT assay, EdU assay and colony formation assay, migration and invasion by wound scratch assay and Transwell assay, cell death by trypan blue staining assay and cell death detection ELISA, and Western blotting	The compound inhibited cell viability, induced cell death, and hindered cell migration and invasion in a dose-dependent manner.
Liu 2022 [91]	*Ophiopogon japonicus* (Thunb.) Ker Gawl. ethanol extracts	Formula	NCI-H1299 and A549	Cell viability by MTT assay, cell apoptosis assay, flow cytometry assay, cell migration by Transwell chamber, LCMS-based cell metabolomics	Cell viability and cell migration were inhibited by this formula in a time- and concentration-dependent manner, and apoptosis was induced.
Luan 2018 [92]	*Codonopis bulleynana* Forest ex Diels	Not reported	Colon cancer cells HCT116 and SW480	Antiproliferation by CCK 8 assay, cell cycle assay by flow cytometry, cell apoptosis assay, immunofluorescence staining, and Western blotting	Cell proliferation was inhibited in a dose-dependent manner; induced cell cycle arrest at S phase, and significantly decreased expression of autophagic markers LC3B I/II and Beclin 1.
Luce 2021 [93]	*Polygonum cuspidatum*	Not reported	Human osteosarcoma cell lines MG-63 and Saos-2	Cell viability by MTT assay, alkaline phosphatase activity by colorimetric kit, cell cycle analysis by flow cytometry, immunostaining, wound-healing assay, and RT-PCR	This product exhibited inhibition of cell proliferation and induced cell cycle arrest.
Lv 2021 [94]	Rhizoma Curcumae	Roots	U251 and A172 glioma cell lines, and chemoresistant cell lines against temozolomide	Cell viability by MTT assay, Transwell migration and invasion assays, colony formation assay, cell apoptosis assay, self-renewal ability by neurosphere formation analysis, flow cytometric analysis, and Western blotting	This extract significantly decreased cell viability in a dose-dependent manner, inhibited cell migratory and invasive abilities, induced apoptosis in a dose-dependent manner, and inhibited self-renewal ability, as evidenced by a reduction in the number of spheres.
Lv 2019 [95]	Radix Bupleuri	Not reported	HepG2 cells	Cell proliferation by CCK-8 assay kit, and cell migration by wound-healing assay	Inhibited cell viability in a dose-dependent manner ($P < 0.01$) and reduced wound-healing percentage ($P < 0.05$).
Ma 2015 [96]	*Salia miltiorrhiza*	Not reported	Human NSCLC cell lines H1299, A549, SPCA-1, HCC827 and SPCA-1	Cell proliferation by CCK-8 assay kit, cell apoptosis, cell cycle analysis, flow cytometry analysis, qPCR, Western blotting, and dual luciferase reporter assay	Inhibited cell proliferation, induced apoptosis, and impeded cell-cycle progression.
Machana 2012 [97]	*Polyalthia evecta* (Pierre) Finet	Leaves	HepG2 cell line	Cytotoxicity by neutral red uptake assay, apoptosis induction by evaluation of nuclei morphological changes using DAPI staining, and DNA fragmentation detection assay	High cytotoxicity ($P < 0.005$) and greater selectivity for cancer cells, with a moderate percentage of apoptotic cells, albeit higher than melphalan ($P < 0.05$).
Magcwebeba 2016 [98]	Green tea and rooibos	Not reported	Basal carcinoma cell line (CRL 7762) skin cells	Cell proliferation assay by EdU chemiluminescent immunoassay kit, apoptotic cell death by Hoechst nuclear DNA stain, flow cytometry, mitochondrial integrity by BD mitoscreen (JC-1) kit, and DNA damage induction during apoptosis	Green tea and rooibos extracts inhibited proliferation at lower concentrations and induced caspase-3 activity in a dose-dependent manner.
Meng 2021 [99]	*Uncaria rhynchophylla*	Bark	Jurkat clone E6-1 cells of human T-cell leukemia	Cell viability by CCK-8 assay, flow cytometry for cell cycle progression and apoptosis, qPCR, and Western blotting	Cell proliferation was inhibited in a concentration- and time-dependent manner ($P < 0.01$), followed by cell cycle arrest and induced apoptotic death.
Nordin 2021 [100]	*Clinacanthus nutans*	Leaves	MDA-MB-231 breast cancer cells	Cytotoxicity assay, migration assay, and cytokine analysis	This herb exhibited antiproliferative and antimigratory effects.

(*continued on next page*)

Table 2 (*continued*)

Study	Botanical name	Part used	Cell line	Methodology	Outcome
Ou 2022 [101]	*Ficus carica*	Fruit	Human PaCa cell lines, Panc-1 and QGP-1	Cell viability, cell death by Hoechst satin, Western blotting, would healing assay, metastasis and invasion assay, colony formation assay, and intracellular ROS determination	The viability of the cells was reduced. The herb inhibited the migration, metastasis, invasion and colony formation of PaCa cells, ultimately leading to apoptosis.
Pak 2021 [102]	*Inonotus obliquus*, *Pinellia ternata*, rhizome *of Sparganium stoloniferum* Buchanan Hamilton, *Alpinia galanga*, *Cinnamomum cassia*, *Astragalus membranaceus*, *Psoralea corylifolia* L., *Tetradium ruticarpum* and *Melia azedarach* L.	Formula	Human pancreatic carcinoma cell line PANC 1	Cell cycle, flow cytometry, and qPCR	The formula showed activity in arresting the cell cycle and inducing apoptosis.
Pan 2022 [103]	*Gnetum montanum* Markgr. (Gnetaceae)	Stems and rhizomes	Human colon cancer SW480 cells	Cell viability, colony-forming, migration and flow cytometry, and Western blotting assays	The herb significantly inhibited tumor cells, exhibited antimigration, and induced apoptosis.
Park 2020 [104]	Peanut sprout extracts cultivated with fermented sawdust medium	Not reported	Human bladder cancer T24 cell line and primary human bladder fibroblast cell line	MTT assay, cell counting, cell cycle analysis, immunoblots and propidium iodide apoptosis assay, wound-healing migration assay, and Boyden chamber invasion assay	The extract had antiproliferative, antimigration and anti-invasion properties.
Park 2019 [105]	*Trichosanthes kirilowii*	Seeds	HT-29 and CT-26 colorectal cancer cells	Cell viability assay, measurement of mitochondrial membrane potentials, Western blotting, wound-healing migration assay, matrigel Transwell invasion assay, and DAPI staining for apoptosis	The extract decreased cell migration and invasion and exhibited antiproliferative effects.
Park 2017 [106]	*Scutellaria baicalensis* Georgi	Roots	B16F10 melanoma cells, Lewis lung carcinoma cells, and HUVECs	Cell proliferation and cell viability assay, wound-healing assay, in vitro tube formation assay, Western blotting, and immunocytochemical analysis	Cell proliferation and migration were inhibited, and tumor angiogenesis was also suppressed.
Pipatrattanaseree 2019 [107]	*Baliospermum montanum*	Roots	Rat basophilic leukemia cell line (RBL-2H3), RAW 264.7 and HepG2 cells	Cytotoxic activity, anti-allergic activity, anti-inflammatory activity, and HPLC for the crude analysis	The crude extracts demonstrated anti-allergic and anti-inflammatory activities, with potent cytotoxic effects on the cells.
Prabhu 2017 [108]	*Embelia ribes*	Fruits of the plant	K562 and U937 cells	MTT assays, cell cycle analysis and apoptotic assay by flow cytometry, gene silencing study using siRNA technology, cell lysis and immunoblotting, and cytochrome *c* release assay	The herb induced a dose-dependent suppression of proliferation in leukemic cells, followed by apoptosis.
Qu 2017 [109]	Cucurbitacin B from traditional Chinese medicinal herbs	Whole plant	Human paclitaxel-resistant ovarian cancer A2780/Taxol cells	Cell viability was evaluated by a cell counting assay; cell cycle arrest and apoptosis were assessed by microscopy and flow cytometry, and Western blotting	This plant significantly demonstrated cell inhibition and induced apoptosis.
Rahman 2020 [110]	*Eurycoma longifolia* Jack	Root	Prostate adenocarcinoma PC-3 cells	TUNEL assay	The apoptotic level of PC-3 increased proportionally with the dose of *E. longifolia* root extract.
Rendón 2022 [111]	Genistein (chemical compound)	Not reported	Human colon adenocarcinoma cell line SW480, its metastatic derivative SW620, and the nonmalignant cell line HaCaT	Cell viability assay, antiproliferation assay by SRB, ROS measurement assay, and apoptosis assay by flow cytometry	Genistein exhibited selectivity for the SW480 and SW620 cell lines, inhibited cell viability, exerted an antiproliferative effect in a dose-dependent manner, and increased the production of ROS.
Roy 2020 [112]	*Peganum harmala*	Seeds and roots	A549 cells, lymph node-derived cancer (H1299) cells and human embryonic kidney cells (HEK293)	Cell viability by MTT assay	The MTT assay demonstrated that harmaline selectively reduced the growth of H1299 and A549 cells, with minimal impact on the growth of HEK293 cells, and induced apoptosis.
Sayyadi 2021 [113]	*Inula oculus-christi*	Flower	Acute promyelocytic leukemia cell lines (NB4) and MDBK cells (bovine kidney cell line)	Cell viability by MTT assay, apoptosis, and expression levels of Bax and Bcl-2 by RT-PCR	Gaillardin at 7, 8 and 9 μmol/L significantly reduced the percentage of live cells and increased the percentage of apoptotic cells.

(*continued on next page*)

Table 2 (*continued*)

Study	Botanical name	Part used	Cell line	Methodology	Outcome
Shao 2013 [114]	Chinese thunder god vine	Whole plant	VCaP cells, and PC-3 and DU145 cell lines	Antiproliferative assay, Western blotting, and qPCR	Celastrol markedly inhibited the growth of T/E fusion-expressing prostate cancer cells.
Shi 2018 [115]	*Rhodiola rosea*	Not reported	Colorectal cancer cell HT-29, and L-OHP resistance HT-29/L-OHP cell line	Cell activity with SRB assay, expressions of targeted proteins, cell cycle, cell apoptosis, cell scratch assay, Transwell chamber assay, and RT-PCR technique	Salidroside decreased the activity and invasive capacity of HT-29/L-OHP cells and increased apoptosis of cancer cells through the regulation of specific genes.
Sun 2022 [116]	ZZXJD	Decoction	Human liver cancer SMMC-7721	Cell viability using CCK-8 assay, fluorescence microscope and transmission electron microscope for cell morphology, Western blotting, RT-PCR, and gene chip	ZZXJD induced autophagy and apoptosis in liver cancer cells by inhibiting the protein kinase B/mechanistic target of rapamycin and Janus kinase 2/signal transducer and activator of transcription 3 signaling pathways, thus influencing the growth and survival of liver cancer cells.
Tang 2022 [117]	Solanaceae plants	Fruit	HCC, HepG2 and Huh-7 cells	Cell viability, EdU, Western blotting assay, qPCR, RNA fluorescence, in situ hybridization assay, dual-luciferase reporter assay, RNA immunoprecipitation assay, transient transfection assays, and IHC analysis	The plant inhibited the growth of HCC and enhanced the anticancer effect of SF through the HOXA distal transcript antisense RNA-taurine upregulated gene 1/miR-4726-5p/MUC1 signaling pathway.
Ullah 2022 [118]	*Achillea fragrantissima*	Arial parts	Breast cancer (MDA-MB-231, MCF-7 and SKBR3), pancreatic cancer (BxPC-3 and MiaPaCa-2), prostate cancer (LNCaP, C4-2B and PC-3), and lung cancer (A549)	MTT assay, homogeneous caspase-3/7 assay for apoptosis, soft agar colonization assay, invasion assay, NF-κB inhibition assay, and ELISA assay for VEGF secretion	The mechanism underlying the extract's effects against cancer cells potentially involves the modulation of NF-κB signaling and the downregulation of its target cytokines, including VEGF.
Wang 2021 [119]	Feiyanning	Formula	Lung NSCLC cell lines A549, 95D and H1975	Cell viability by CCK-8, cell migration and invasion by wound-healing and Transwell assays, transcriptome and chromatin accessibility analysis by RNA-seq and ATAC-seq	The Feiyanning formula demonstrated inhibitory effects on cellular activities such as proliferation, migration and invasion of A549, H1975 and 95D cells. Additionally, it was implicated in the modulation of transcriptional activity related to migration-associated genes.
Wihadmadyatami 2020 [120]	*Ocimum sanctum* Linn.	Leaves	Human adenocarcinoma A549 cells	Angiogenesis assay, ELISA for $\alpha v\beta 3$, MMP-2 and MMP-9	The extract from this herb exhibited anti-angiogenic properties on A549 cells by suppressing the expression of integrin heterodimer alpha v and beta 3 subunits, MMP-2 and MMP-9.
Xiao 2021 [121]	Resveratrol	Not reported	CAL-27 oral squamous cell carcinoma cells	Cell viability and proliferation assays, invasion assay, Western blotting, and qPCR	The compound demonstrated antiproliferative, antimigratory and antiapoptotic effects on this cell line.
Zhang 2021 [122]	*Solanum lyratum* Thunb	Not reported	Human ovarian cancer cell lines, A2780 and SKOV3 cells	LDH and MTT assays, cell cycle, wound healing, Transwell assay, annexin violet-fluorescein isothiocyanate apoptosis assay, flow cytometry, Western blotting analysis, and DCFH-DA	The effects of the herb on cancer cell proliferation, apoptosis, migration, invasion and EMT were significantly reversed by an ROS inhibitor, N-acetyl-L-cysteine.
Zhang 2016 [123]	*Ophiopogon japonicus*	Not reported	SGC-7901 human gastric cancer	CCK-8, flow cytometry, Hoechst staining, Western blotting, mitochondrial membrane potential detection, and ROS generation assay	Ophiopogonin B (5, 10 and 20 μmol/L) demonstrated potent antiproliferative effects on SGC-7901 cells in a dose-dependent manner. Additionally, apoptotic rates were increased, and there were alterations in cell morphology.
Zhang 2016 [124]	*Scutellaria baicalensis* and *Scutellaria lateriflora*	Roots	HEC59, HEC59-2, LoVo, HeLa, MRC5 and HEK293T cells	Cell viability assay, Western blotting, hematoxylin-eosin staining, IHC, immunoprecipitation, and TUNEL	Baicalein exhibited a preference for binding to mismatched DNA and induced a DNA damage response in a manner dependent on mismatch repair.

(*continued on next page*)

Table 2 (*continued*)

Study	Botanical name	Part used	Cell line	Methodology	Outcome
Zheng 2016 [125]	*Angelica dahurica*	Roots	HT 29 colon cancer cell line	MTT assay, LDH activity assay, TUNEL-based detection of DNA fragmentation, flow cytometric analysis of apoptosis, caspase-3/7 assay, Western blotting, and ROS generation assay	The phytochemical derived from this herb has markedly inhibited the growth of HT-29 colon cancer cells, demonstrating an IC_{50} value of 78 μmol/L, and induced apoptosis.
Zhou 2022 [126]	*Paeonia lactiflora* Pall	Roots	Neuroblastoma SH-SY5Y cells	Cell proliferation assay using CCK-8, miRNA transfection, colony formation assay, cell apoptosis assay, cell scratch and Transwell assays, qPCR, luciferase assay and immunoblotting analysis	The proliferation and survival of neuroblastoma cells were impeded, and both the migration and invasion of the cells were inhibited.

ABA: Alamar blue assay; ABTS: 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); AD: Aidi injection; AGS: human gastric adenocarcinoma; ATAC: assay for transposase-accessible chromatin; ATM: ataxia telangiectasia mutated; ATR: ataxia telangiectasia and Rad3 related; CCK-8: cell counting kit-8; CHEK: checkpoint kinase gene; CUPRAC: cupric ion reducing antioxidant capacity; DAPI: 4′,6-diamidino-2-phenylindole; DCFH-DA: dichloro-dihydro-fluorescein diacetate; DPPH: 2,2-diphenyl-1-picrylhydrazyl; DZXX: Dengzhanxixin injection; EdU: 5-ethynyl-2́-deoxyuridine; ELISA: enzyme-linked immunosorbent assay; EMT: epithelial-to-mesenchymal transition; FRAP: ferric reducing antioxidant power; GCMS: gas chromatography mass spectroscopy; HCC: human hepatocellular carcinoma; HPLC: high-performance liquid chromatography; HUVEC: human umbilical vein endothelial cell; IHC: immunohistochemistry; IC_{50}: half-maximal inhibitory concentration; KA: Kangai injection; LCMS: liquid chromatography-mass spectrometry; LDH: lactate dehydrogenase; L-OHP: oxaliplatin; MMP: matrix metalloproteinase; MTT: 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide; NF-κB: nuclear factor κB; NSCLC: non-small cell lung cancer; ORAC: oxygen radical absorbance capacity; PaCa: pancreatic cancer; PARP: poly(ADP-ribose)polymerase; qPCR: quantitative polymerase chain reaction; QKL: Qingkailing injection; ROS: reactive oxygen species; RT-PCR: reverse transcriptase-polymerase chain reaction; SF: Shenfu injection; SRB: sulforhodamine B; SXT: Shuxuetong injection; T/E fusion: fusion of the transmembrane protease, serine 2, gene (TMPRSS2) with the erythroblast transformation-specific (ETS)-related gene (ERG); TRQ: Tanreqing injection; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling; UPLC-MS: ultra-performance liquid chromatography-mass spectrometry; VEGF: vascular endothelial growth factor; WST: water-soluble tetrazolium salt; XBJ: Xuebijing injection; XNJ: Xingnaojing injection; XTT: (2,3-bis (2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino) carbonyl]-2H-tetrazolium hydroxide); XYP: Xiyanping injection; ZZXJD: Zhenzhu Xiaoji Decoction.

Herbal medicines have been scientifically shown to possess diverse pharmacological properties, including antiproliferation, anti-apoptotic, tranquilizing, memory enhancing, analgesic, aldosterone antagonizing, immune modulating, antioxidant, anti-inflammatory, cholinesterase inhibiting, smooth muscle relaxing, central nervous system depressing, and dopamine modulating (Table 4). For instance, flavonoids or alkaloids exhibit anticancer activity through a variety of molecular signal transduction pathways or cell cycle disturbance.

The process of cell cycle arrest is a significant mechanism that can prevent cells from progressing through the usual cell cycle via a chemical agent [162]. Data show that the effectiveness of these chemical agents is improved by the presence of phytochemicals, which regulate the transition of the cell cycle and trigger apoptosis. The Akt signaling pathway can be regulated by nitric oxide, which directly suppresses cancer cell growth by causing G_0/G_1 phase arrest. Some of the compounds were also found to enhance nitric oxide production by inducing phosphorylation of endothelial nitric oxide synthase via the estrogen receptor-mediated phosphoinositide 3-kinase/protein kinase B pathway. Additionally, phenols and terpenoids can target the human epidermal growth factor receptor 2 and extracellular signal-regulated kinase 2 pathways to overcome drug resistance and reduce programmed death ligand 1 expression in lung cancer cells [163].

There are herbal remedies that induce anticancer actions via a variety of mechanisms, including generating cleavages that produce reactive oxygen species (thus creating oxidative stress), triggering apoptosis, inhibiting cell proliferation through cell cycle arrest, blocking tumor angiogenesis and tissue migration, and inhibiting tumor metastasis [164]. Additionally, certain herbs such as green tea and ginger have been shown to reduce inflammation and improve immune function, both of which can aid the body in fighting cancer.

Furthermore, depending on the dosage, several phytochemicals exhibit various anticancer activities. For example, *Catharanthus* alkaloids suppress microtubule dynamics and maintain them at low doses (< 1 μmoL), while at higher concentrations (> 1–2 μmoL), they denature the microtubules and disrupt the mitotic spindle, inducing apoptosis by inhibiting mitosis [150]. In addition to isolated and known active compounds, it is critical to highlight that other active constituents may exist in herbal extracts that can stimulate anticancer action in a synergistic manner through multiple molecular mechanisms [31]. Furthermore, an in vitro study on human prostate cancer cells found that a flavonoid from lychee seeds induced apoptosis via overexpression of apoptotic proteins such as Bax and Bcl-2, thereby regulating the Wnt3a and MAPK pathways [56].

Although preclinical studies have consistently demonstrated the anticancer effects of several herbal extracts and phytochemicals, the effectiveness of many herbal medicines used in cancer treatment is not clearly supported by clinical evidence [165]. Nevertheless, some clinical studies have suggested that the use of herbal medicines in cancer treatment may reduce the risk of death in patients with lung, breast and esophageal squamous cell carcinoma, improve their quality of life by alleviating cancer symptoms and minimizing side effects of conventional drugs such as nausea and vomiting, and prevent certain types of cancer [35,166].

However, other clinical studies have indicated that certain herbal remedies may interfere with cancer treatments or have negative effects on the body. For example, herbs such as St. John's wort have been shown to interfere with chemotherapy [167], and high doses of certain herbs can be toxic to the liver or kidneys. Despite these mixed findings, herbal medicines are still used by many cancer patients as complementary or alternative treatments. This is because herbal remedies are often perceived as more natural and safer than traditional cancer treatments such as

Table 3
Anticancer effects of medicinal plant extracts in animal models (44 studies).

Study	Botanical name	Part used	Animal model used	Methodology	Duration	Outcome
Arya 2015 [47]	*Eclipta alba*	Whole plant	4–6-week-old female BALB/c mice	Mouse breast cancer (4T1) cells were injected subcutaneously to mice.	2 weeks	In comparison to the control group, those subjected to the experimental conditions exhibited a reduction in tumor volume, size and weight.
Chen 2015 [127]	Qingrejiedu, Huoxuehuayu, and Fuzhengguben	Not reported	Both sexes of SPF BALB/c mice weighing 18–20 g	About 3×10^6 H_{22} hepatoma cells in 0.03 mL were injected directly to the mice's liver. After 3 d, a dose of 10 mL/kg of the medicine was given.	15 d	The administration of the medication maintained the weight of the mice, suppressed tumor growth and size, indicating that this herbal formula possesses antiangiogenic activity.
Chang 2016 [55]	AshwaMAX and withaferin A	Not reported	6–10 weeks female nu/nu mice	Human-derived glioblastoma cells (GBM2 and GBM39) were intracranially injected into the right parietal region of the murine brain using a stereotactic instrument, and the resulting tumors were visualized through magnetic resonance imaging. Subsequently, the tumor characteristics were tracked using fluorescent and bioluminescent microscopy. The herbal extract was administered orally every 2 days at a dosage of 40 mg/(kg·d).	2 months	Antiapoptotic and antiproliferative effects of the formula were observed. The bioluminescent signal increased from 0 to 20 d post-implantation ($P < 0.02$) and stabilized after 2 months.
Chang 2021 [56]	Lychee	Seeds	4–5 weeks old Kunming mice and 5–6 weeks old nude male mice	Two million PC-3^{-luc} cells were subcutaneously injected into the right flank of each mouse. The pharmaceutical intervention (20 mg/kg) was administered orally on a daily basis, and at three-day intervals, measurements of tumor size and the anthropometric parameters of the mice were meticulously recorded.	Not reported	The administration of the total flavonoid extract has demonstrably reduced tumor size without any discernible complications.
Chen 2017 [57]	Gamboge	Not reported	6-week-old male BALB/c nude mice	Mice were subcutaneously injected with 1×10^7 cells, and subsequently received a dosage of 2.0 mg/kg every 2 d ($n = 5$). Tumor size measurements were conducted bi-daily. Immunohistochemistry and apoptosis analysis were performed through TUNEL.	14 d	Following the induction of herbal extraction and subsequent regulation of apoptotic proteins, there has been a notable reduction in tumor size, as evidenced by immunohistochemical analysis.
Chen 2022 [58]	Chinese herbal injections (AD, KA, SXT, XNJ, XBJ, TRQ, DZXX, SF, QKL, XYP and Danshentong IIA)	Not reported	Female wild-type C57BL/6J and BALB/c mice, aged 8 to 12 weeks	Mice were administered scutellarin at 25 or 50 mg/kg, and FACS analysis was conducted 24 h post-injection. In a separate group, CT26 tumor cells (2×10^5 cells) were injected, and once the tumor size reached 5–6 mm, a daily administration of scutellarin at a dose of 50 mg/kg in a volume of 0.2 mL was initiated.	40 d	Treatment with scutellarin significantly augmented the effectiveness of tumor immunotherapy in CT26 colon cancer model. Furthermore, there was a remarkable reduction in tumor size, leading to an enhanced overall survival rate of approximately 80% ($P < 0.001$) compared to the wild type group.
Chen 2018 [128]	LSW	Not reported	Male Kunming mice weighing 18–22 g	The liver cancer mice underwent treatment with LSW twice a week via intragastric administration or oral ingestion, with a dosage of 9.639 mg/kg in the sesame oil group.	30 weeks	Alterations in serum albumin levels in mice were observed, indicating changes in lipid accumulation and liver metabolism among the treatment groups. Histopathological findings further demonstrated the anticancer activity of LSW.
Choi 2016 [59]	*Astragalus membranaceus*, *Angelica gigas*, and *Trichosanthes kirilowii* Maximowicz	Not reported	Male BALB/c nude mice, aged 5 weeks	A dosage of 20 µg of SH003 was administered through injections into the back skins or ears of the mice.	50 d	The SH003 formula demonstrated the ability to inhibit tumor growth in mice without exhibiting any discernible toxicity. Additionally, it displayed inhibitory effects on angiogenesis.
Dai 2010 [129]	Mirabilite and Chinese rhubarb	Decoction	Male C57 mice, aged 4 to 6 weeks	Each mouse received herbal decoction (0.2 mL) daily from day 1 to day 7. Subsequently, pancreatic cancer cell lines (Panc02) at a concentration of 2×10^6 cells in 0.2 mL of free-serum medium were injected subcutaneously into the right axilla of the mice.	30 d	The herbal decoction significantly delayed tumor growth and played a role in the regulation of mRNA expression of specific genes, as detected by qPCR and IHC.
Guo 2022 [130]	SNKAF	Decoction	Male BALB/c nude mice aged 4 weeks	MHCC-97H cells, at a density of 2×10^6/µL, were combined with Matrigel and subsequently injected subcutaneously into the right front leg of nude mice. The positive group of mice received daily doses of SNKAF at low (15.3 g/kg), medium (30.6 g/kg), and high dosage (61.2 g/kg).	15 d	The administration of SNKAF decoction resulted in a reduction in tumor size, evident from day 8 onwards.

(*continued on next page*)

Table 3 (*continued*)

Study	Botanical name	Part used	Animal model used	Methodology	Duration	Outcome
Guo 2020 [64]	*Epimedium koreanum* Nak	Not reported	Male nude mice (BALB/c), aged 6 to 8 weeks and weighing 18–22 g	The mice were subcutaneously injected with 5×10^6 Huh7 cells, followed by intragastric administration of baohuoside-1 at a dosage of 25 mg/kg for a duration of 30 d. Subsequent to the treatment period, histopathological analyses were conducted.	30 d	This botanical specimen demonstrated a conspicuous inhibitory effect on tumor dimensions, thereby accentuating its potential as a promising candidate for therapeutic interventions within the milieu of tumorigenesis.
Hao 2019 [66]	*Clinacanthus nutans*	Leaves	Male and female mice of the C57BL/6 strain, aged 6 to 8 weeks	The mice were subcutaneously injected into the right axilla with 2×10^5 B16F10 cells. Subsequently, the mice were treated with icaritin starting from day 3, followed by a T-cell proliferation assay.	30 d	The herbal intervention resulted in the inhibition of tumor growth and a concomitant increase in the survival rate by 50%, particularly at a dosage of 70 mg/kg.
Huang 2021 [69]	*Salvia miltiorrhiza*	Not reported	Zebrafish (transgenic lines)	Human NB4 or HL-60 cells (200–300 cells) were introduced into 30 zebrafish embryos. Subsequently, a comprehensive analysis was conducted utilizing RT-PCR, RNA-seq, Western blotting, and in situ hybridization techniques.	72 h post-fertilization	The active compound exhibited inhibitory effects on the proliferation of leukemic cells in the zebrafish model.
Ji 2022 [70]	*Elephantopus scaber* L.	Not reported	Immunodeficient mice	HCT116 cells were injected into the left and right armpits of the mice. After a one-week interval, the mice were subjected to intraperitoneal administration of a dosage of 30 mg/kg every 2 days.	15 d	The tumor growth, encompassing both size and weight, exhibited a notable and statistically significant reduction following the treatment.
Kubatka 2020 [79]	*Cinnamomum zeylanicum* L.	Bark	Female rats of the Sprague-Dawley strain and female mice of the BALB/c strain, aged 5 weeks	Chemically induced rat mammary carcinomas and a syngeneic 4T1 mouse model were employed in the study.	15 d	There was a decrease in both tumor incidence and volume, accompanied by reduced mitotic activity and a decreased ratio of high- to low-grade carcinomas.
Li 2021 [131]	*Curcuma longa*	Dried rhizome	Mice of the non-obese diabetic/severe combined immunodeficiency strain, aged 6 to 8 weeks	A colorectal cancer PDX mouse model, incorporating Western blotting and RT-PCR analyses, along with histological assessments and TUNEL assay.	2 months	There was a significant decrease in tumor size observed in 2 out of the 3 PDX samples. Furthermore, a notable reduction in liver metastasis was observed in all PDX samples, and lung metastasis exhibited a significant decrease in 3 out of the 4 PDX samples.
Li 2020 [86]	Compound Xishu Granule	Polyherbal decoction	Male BALB/c nude mice, aged 4 weeks	A liver tumor xenograft model was established by injecting HepG2 cells into nude mice. The evaluation involved the measurement of growth-related metrics, histological assessment, and Western blotting.	30 d	The compound exhibited inhibition of graft tumor growth and was implicated in the regulation of both pro- and anti-apoptotic proteins.
Lin 2020 [132]	Bulbus *Fritillaria cirrhosa* D. Don	Not reported	Male BALB/c nude mice, aged 6 weeks	Intravenous administration of 10 mg/kg of the compound once every 2 d, totaling 5 administrations. This was conducted in mice challenged with human lung adenocarcinoma A549 tumors, followed by survival analysis.	Not reported	The compound demonstrated an overall improvement in the anti-tumor effect and exhibited the capability to suppress both NSCLC tumors and associated inflammation. This effect was achieved through modulation of an inflammation-cancer feedback loop, involving NF-κB activity.
Luan 2018 [92]	*Codonopis bulleynana* Forest ex Diels	Root	Female BALB/c athymic nude mice, aged 5 to 6 weeks	The mice were subcutaneously injected in the right flank with 2.0×10^6 SW480 cells, and subsequent IHC analysis was performed.	6 weeks	A significant decrease in tumor volume was observed, concomitant with the inhibition of autophagy, which was achieved through the activation of the NF-κB signaling pathway.
Luo 2022 [133]	Chang Qing formula	Decoction	Male C57BL/6 mice, 6 weeks old and weighing 200–220 g	The study utilized a mouse model of azomethane/dextran sodium sulfate-induced colitis-associated colorectal cancer. Various analytical techniques were employed, including RNA sequencing analysis, hematoxylin-eosin staining, apoptosis assessment through TUNEL assay, ELISA, Western blotting, and immunofluorescence assay.	60 d	The study revealed a significant reduction in both the number and volume of tumors, accompanied by an increase in apoptosis at a low dose. Furthermore, the treatment suppressed the phosphorylation of STAT3, reduced the expression of MMP-9, and promoted apoptosis.
Lv 2021 [94]	Rhizoma Curcumae	Root	BALB/c nude mice 16–20 g	U251/TMZ cells were subcutaneously injected into nude mice, followed by intraperitoneal injections of 20 mg/kg curcumol every 3 days. The study assessed self-renewal ability through neurosphere formation analysis, flow cytometric analysis, IHC, and Western blotting.	12 d	The intervention exhibited the ability to suppress the proliferative capacity, self-renewal capacity, metastasis and TMZ-resistance of glioma cells. Furthermore, it significantly decreased the sphere-forming ability of the cells.

(*continued on next page*)

Table 3 (*continued*)

Study	Botanical name	Part used	Animal model used	Methodology	Duration	Outcome
Ou 2022 [101]	*Ficus carica*	Fruit	Male BALB/c nude mice, aged 4–6 weeks, and weighing 14–16 g	QGP-1 cells, prepared at a concentration of 1×10^7 cells/mL in serum-free medium, were subcutaneously inoculated into the right axillary region to establish a xenograft model for PaCa.	8 d	The herbal intervention resulted in a notable reduction in both the size and mass of the tumor following the course of treatment, highlighting its potential therapeutic efficacy in the context of tumor management.
Pan 2022 [103]	*Gnetum montanum* Markgr. (Gnetaceae)	Stems and rhizomes	The AB strain of adult zebrafish and the BALB/c strain of nude mice, males aged 4 to 6 weeks with an average weight of (18.0 ± 2.0) g	Fluorescent cell labeling was performed for zebrafish embryos, followed by drug treatments. Tumor xenografts were established in nude mice through subcutaneous injection of 1×10^6 SW480-luc cells. Subsequently, oral administration of the drug was carried out at doses of 56 and 28 mg/(kg·d) once per day.	24 d	In a time-dependent manner, the treatment group exhibited a notable reduction in both tumor area and migration distance compared with the model group.
Park 2020 [104]	PSEFS	Not reported	Male BALB/c nude mice, aged 6 weeks	Bladder cancer T24 cells, 1×10^7 cells per mouse, were subcutaneously injected. Subsequent analyses included immunohistochemistry and biochemical assessments.	20 d	The product demonstrated a dose-dependent decrease in tumor growth, leading to a reduction in mice tumor volume in PSEFS-treated mice. Moreover, both Ki-67 and hematoxylin-eosin stains of tumor tissues indicated fewer tumor cells in PSEFS-treated animals.
Park 2019 [105]	TKSE	Seeds	Male BALB/c nude mice, aged 6 weeks	Subcutaneous inoculation of 1×10^6 CT26 cells in 100 μL of phosphate-buffered saline was performed into the right flanks. Subsequently, the mice received low- (100 mg/kg) and high-dose (300 mg/kg) TKSE 5 times per week.	3 weeks	The intervention led to a significant decrease in both tumor volume and tumor weights. Notably, there was no observed hepatic toxicity, as evidenced by the absence of statistically significant changes in the levels of glutamic oxaloacetic transaminase and glutamic pyruvic transaminase in the serum of experimental mice.
Park 2017 [106]	*Scutellaria baicalensis* Georgi	Roots	Male C57BL/6 mice, 7 weeks old	B16F10 melanoma cells were injected into mice. Subsequently, mice were intraperitoneally administered 1.5 mg/kg baicalein daily, and tumor size and volume were measured. Finally, the mice were sacrificed for histopathological analysis.	2 weeks	The baicalein resulted in a reduction in both tumor size and volume. Histopathological examination revealed a significant decrease in blood vessel density, and there was a notable delay in tumor metastasis.
Ren 2022 [134]	*Taraxacum officinale* (L.) Weber ex F.H. Wigg	Not reported	Female Kunming mice, aged from 6 to 8 weeks	Western blotting, TUNEL assay, IHC, and immunofluorescence.	14 d	The herbal intervention demonstrated inhibitory effects on tumor growth in H22-bearing mice. Additionally, it modulated the immune response by upregulating the expression of Ki67 and regulating immunity, as evidenced by an increased ratio of $CD4^+$ T cells in the spleen and elevated T cell infiltration in tumor tissue.
Shao 2013 [114]	Chinese thunder god vine	Not reported	Nude mice, aged 12 weeks	Prostate cancer cells (VCaP-Luc) subcutaneous mouse model was established. Mice were administered 0.5 mg/kg celastrol 4 times per week and subsequent analyses included immunohistochemistry and apoptosis.	3 weeks	Celastrol resulting in significant growth inhibition without noticeable toxicity or significant weight loss.
Sui 2020 [135]	Yi-Yi-Fu-Zi-Bai-Jiang-San	Not reported	C57BL/6J $Apc^{Min/+}$ mice were utilized to induce CRC	Histology and IHC, gut microbiota analyses, fecal microbiota transplantation, cytokine antibody arrays, qPCR, and bioinformatics analyses of RNA-Seq, analysis of cytokine expression in serum, bacterial attachment assay, and Western blotting.	20 weeks	The intricate interplay between gut microbiota and regulatory T cells emerges as a pivotal factor influencing the multifaceted processes underlying the development and progression of CRC.
Tang 2022 [117]	Solanaceae plant	Fruit	Female nude mice, aged from 6 to 8 weeks	HepG2-luc cells (5×10^6/mice) were subcutaneously injected into the submaxillary skin of nude mice. Subsequent analysis of the tumor included immunohistochemistry, bioluminescent imaging, and qPCR.	25 d	The compound inhibits the cell growth of HCC by inactivating long non-coding RNAs HOXA distal transcript antisense RNA and taurine upregulated gene. This inactivation leads to an increase in the expression of miR-4726-5p, ultimately resulting in the suppression of promoter activity and protein expression of gene Mucin 1.

(*continued on next page*)

Table 3 (*continued*)

Study	Botanical name	Part used	Animal model used	Methodology	Duration	Outcome
Sun 2018 [136]	Zuo Jin Wan	Formula	Male athymic nude mice, aged from 4 to 6 weeks	Hematoxylin-eosin staining, and IHC staining.	4 weeks	Zuo Jin Wan demonstrated the inhibition of tumor growth and induction of apoptosis in the xenograft animal models.
Takaku 2020 [137]	JTT/Kampo	Polyherbal formula	Female BALB/c mice, aged over 6 weeks, and BALB/c CD1d$^{-/-}$ mice	Tumor assay and antibody treatment, isolation of tumor-infiltrating lymphocytes, flow cytometric analysis, functional Ly6G^{+} Ly6Clo PMN-MDSCs suppressive function assay.	28 d	JTT enhanced antitumor immunity through the activation and augmentation of CD8^{+} T cells. This highlighted the potential of JTT as an immunotherapeutic agent for bolstering the host's immune defenses against tumor progression.
Wang 2017 [138]	XIAOPI formula	Polyherbal formula	MMTV-PyMT$^{+/-}$ transgenic mouse model	Flow cytometry analysis, immunofluorescence assay, herb-ingredient-target interaction analysis, and qPCR analysis.	55 d and 120 d	Administration of CXCL-1 significantly counteracted the metastatic inhibition effects of XIAOPI on breast cancer, including migration, invasion, stem cell subpopulations, and mammosphere formation abilities.
Wang 2022 [139]	XFZYD	Polyherbal formula and decoction	Flies (*Drosophila* stock w1118 (#3605))	The XFZYD aqueous extract was utilized in conjunction with the RasV12/lgl$^{-/-}$-induced *Drosophila* tumor model for experimental validation. The study encompassed fertility assays, qPCR and IHC for comprehensive analysis.	Not specified	XFZYD may potentially stimulate tumor cell apoptosis through the activation of caspase signaling, thereby exerting control over primary growth. Simultaneously, XFZYD may impede tumor cell invasion by suppressing JNK/AP-1 signaling activity.
Yang 2022 [140]	YFSJ	Polyherbal formula and decoction	SPF Female C57BL/6N mice, 6 to 8 weeks old	Enrichment analysis of gene ontology, live imaging of mouse tumor, fluorescence, Western blot, and transmission electron microscopy.	20 d–3 weeks	YFSJ markedly decreased tumor size and prolonged survival time in contrast with those in the orthotopic model group ($P < 0.05$), and it also significantly regulated the protein expression levels of apoptosis- and autophagy-related proteins.
Zeng 2021 [141]	*Buxus microphylla* (CVB-D)	Not reported	Male nude mice, 6 weeks old	Western blotting, qPCR, confocal microscopy imaging, transmission electron microscopy, and IHC analysis.	20 d	CVB-D inhibited tumor growth and had the capacity to induce mitophagy.
Zhang 2020 [142]	*Nigella sativa*	Seed	Nude mice, 5 weeks old, and weighing 20 g	Histology and IHC.	36 d	The active compound from this intervention demonstrated an antimetastatic effect in bladder cancer cells, with a significant inhibition of lung metastasis foci.
Zhang 2020 [143]	*Plumbago scandens* L.	Root	BALB/c57 nude strain mice, 3 to 4 weeks old	Xenograft tumors were established in nude mice through subcutaneous injection of human bladder cancer T24 cells.	7 d	This herbal extract inhibited the proliferation of T24 and UMUC3 cells, inducing cell cycle arrest and apoptosis. Moreover, the extract may impede the migration of bladder cancer cells by suppressing EMT and inducing ROS generation, thereby promoting apoptosis.
Zhang 2017 [144]	TSN	Not reported	Male BALB/c athymic nude mice, aged 6 to 8 weeks	IHC analysis, three-dimensional on-top assay, and fluorescent-gelatin degradation assay.	50 d	TSN was well tolerated and exhibited inhibitory effects on both osteosarcoma growth and metastasis. In an additional osteosarcoma PDX model, TSN demonstrates potent inhibitory effects on tumors derived from patients with osteosarcoma.
Zhang 2018 [145]	*Salvia miltiorrhiza*	Root	Male BALB/c nude mice, aged 6 to 8 weeks, and weighing 18–24 g	A xenograft tumor model of human gastric cancer was established, and each mouse received intraperitoneal injections of tanshinone IIA (12.5, 25 or 50 mg/kg) three times a week.	28 d	A nude mouse xenograft model was established, and the results indicated that intraperitoneal treatment significantly inhibited both tumor growth and the activation of STAT3.
Zhao 2017 [146]	*Lavandula angustifolia*	Flower and leaves	SPF male BALB/c nude mice, 6 weeks old	The bleeding and necrosis assessed by hematoxylin-eosin staining, apoptosis in xenograft tumor, and IHC.	30 d	This herb demonstrated antiproliferative, antimigration, anti-invasion and antiapoptotic effects, and induced cell cycle disturbance.
Zhao 2022 [147]	FZKA	Decoction	Female BALB/c nude mice, aged from 4–6 weeks and weighing 18–20 g	An animal model was employed to verify the effect of FZKA-induced ferroptosis in NSCLC in vivo. IHC was conducted to detect the protein-level expression of SLC7A11, SLC3A2 and GPX4.	30 d	The formulation of FZKA induced ferroptosis in NSCLC cells, revealing a novel molecular mechanism through which FZKA may exert its therapeutic effects on NSCLC.

(*continued on next page*)

Table 3 (*continued*)

Study	Botanical name	Part used	Animal model used	Methodology	Duration	Outcome
Zheng 2020 [148]	XIAOPI	Formula of a group of herbs	Female BALB/c mice, aged 5 weeks	Breast cancer xenografts were established by inoculating 4T1 cells into the mammary pads of the mice, and lung metastasis was monitored using luciferase imaging. The impact of the XIAOPI formula on TAM phenotype, hematopoietic stem/progenitor cells, and MDSCs were evaluated using flow cytometry.	6 weeks	The XIAOPI formula demonstrated an inhibitory effect on breast cancer lung metastasis and reduced the proportions of MDSCs and TAMs in the tumor. Furthermore, this formula hindered TAMs-induced PMN formation in mice by suppressing the CXCL1 chemokine-mediated MDSC activation.

AD: Aidi injection; CRC: colorectal cancer; CVB-D: cyclovirobuxine D; CXCL1: chemokine (C-X-C motif) ligand 1; DZXX: Dengzhanxixin injection; ELISA: enzyme-linked immunosorbent assay; EMT: epithelial-to mesenchymal transition; FACS: fluorescence-activated cell sorting; FZKA: Fuzheng Kang'ai Decoction; GPX4: glutathione peroxidase 4; HCC: hepatocellular carcinoma; HE: hematoxylin-eosin; HepG2: hepatoblastoma cell line; IHC: immunohistochemistry; JTT: Juzentaihoto; KA: Kangai injection; LSW: Liushenwan; MDSC: myeloid-derived suppressor cell; MMP: matrix metalloproteinase; NF-κB: nuclear factor κB; NSCLC: non-small cell lung cancer; PaCa: pancreatic cancer; PC-3^{-luc}: luciferase-expressing PC-3; PDX: patient-derived xenograft; PMN: polymorphonuclear; PSEFS: peanut sprout extracts cultivated with fermented sawdust medium; qPCR: quantitative polymerase chain reaction; QKL: Qingkailing injection; RNA-seq: ribonucleic acid sequence; ROS: reactive oxygen species; RT-PCR: reverse transcriptase-polymerase chain reaction; SF: Shenfu injection; SLC3A2: solute carrier family 3 member 2; SLC7A11: solute carrier family 7 member 11; SNKAF: Sinikangai fang; SPF: specific pathogen free; STAT3: signal transducer and activator of transcription 3; SXT: Shuxuetong injection; TAM: tumor-associated macrophage; TKSE: ethanolic extract of *Trichosanthes kirilowii* seeds; TMZ: temozolomide; TRQ: Tanreqing injection; TSN: Toosendanin; TUNEL: terminal deoxynucleotidyl transferase dUTP nick-end labeling; XBJ: Xuebijing injection; XFZYD: Xuefu Zhuyu decoction; XNJ: Xingnaojing injection; XYP: Xiyanping injection; YFSJ: Yi-Fei-San-Jie-pill.

chemotherapy or radiation therapy, which can have severe side effects. However, regardless of whether the anticancer agents are legitimate, the raw mixtures of herbal remedies must be evaluated for safety and efficacy [168]. These mixtures may contain metabolites, in addition to the active pharmaceutical ingredient (API), that can have detrimental consequences, and managing the relative amounts of the API and other components can be challenging [169].

Further high-quality multidisciplinary research is needed to effectively integrate herbal medicine into cancer care, either as an alternative form of medicine or in combination with conventional cancer treatments. This type of research requires adequate funding, and policymakers should advocate for and allocate resources to cancer research involving the use of herbal medicine.

The current systematic review had certain limitations. Firstly, studies specifically related to the toxicity of herbal extracts or isolated hazardous compounds were not included in the review. Secondly, while efforts were made to search and identify relevant papers using common indexing and abstracting online databases, the review was limited to English-language publications, which may have resulted in some papers being missed and not included in the evaluation. Additionally, this study does not provide a comprehensive assessment of all plant-derived compounds with potential anticancer properties, including their mechanisms of action and effectiveness, as it falls outside the scope of this review.

Future studies should focus on integrating personalized medicine approaches with herbal therapies in cancer treatment. This includes identifying biomarkers and genetic profiles to tailor herbal treatments to individual patients. Mechanistic studies should investigate the precise targets and pathways modulated by herbal compounds. Rigorous clinical trials with comprehensive controls are needed to evaluate safety, efficacy and potential interactions. Pharmacokinetic and pharmacodynamic studies will optimize dosing regimens and enhance treatment efficacy. Long-term safety assessments and follow-up studies are crucial to evaluate sustainability and adverse effects. Identifying synergistic combinations with standard treatments or complementary therapies can overcome drug resistance. Pursuing these research directions will advance personalized medicine and maximize the potential of herbal therapies in cancer care.

5. Conclusion

This comprehensive systematic review has provided significant insights into the future of cancer treatment, particularly in the context of personalized medicine and the potential advantages of herbal interventions. The findings from in vitro, in vivo and clinical trial studies have revealed compelling evidence supporting the efficacy and safety of herbal medicine in the management of various types of cancer. The evidence has shown promising results regarding the anti-inflammatory, antiapoptotic, cell regenerative, and antioxidant properties of certain herbal medicines, and the clinical evidence supporting their effectiveness in cancer treatment remains inconclusive. Despite mixed findings, many cancer patients still use herbal remedies due to their perceived natural and safer nature compared to conventional cancer treatments. However, it is crucial to exercise caution and consider potential interactions and side effects, as some herbs may interfere with cancer treatments or have toxic effects on the body. Further research is warranted to better understand the safety, efficacy and mechanisms of action of herbal medicine in cancer care, and to inform evidence-based decision-making for healthcare professionals and patients alike.

Table 4
Anticancer effects of herbal medicinal plant extracts in individualized clinical studies.

Study	Botanical name	Part used	Sample size	Study duration	Design	Jadad score	Outcome
Ballesteros-Ramírez 2020 [50]	*Petiveria alliacea* and *Caesalpinia spinosa*	Leaves and pods	26 cases	Not reported	Peripheral blood and bone marrow samples were procured both before the commencement of the study and upon its conclusion. Flow cytometry was employed to assess immunophenotypic outcomes.	6	Certain patients exhibited a favorable response, while others manifested a suboptimal response, as determined by their respective IC_{50} values. A response was classified as favorable when the IC_{50} values were less than 2 μmol/L.
Chae 2018 [149]	*Rhus verniciflua* Stokes	Not reported	3 cases	9 (case 1), 16 (case 2), and 26 months (case 3)	Distal bile duct cancer was typically managed with a 500 mg capsule twice daily. In the case 2 of hepatocellular carcinoma, a 500 mg capsule was prescribed once daily. For the third person, a dosage of 500 mg three times daily was recommended.	2	The tumor size exhibited a reduction, contributing to an extension of the average survival period to 56 months.
Lee 2015 [150]	Korean medicine therapy	Formula of polyherbal	1 case	16 months	The 46-year-old Korean woman with stage III (T2N3M0) right breast cancer underwent treatment involving intravenous administration of 10 mL each of WGP, CSP, TKP, EAP and AMP on a weekly basis.	4	After treatment, the CT images revealed an absence of recurrent findings, with a notable reduction in lymph node size.
Li 2022 [35]	Atractylodes, Macrocephala, Tuckahoe, Codonopsis, and dried tangerine peel	Chinese medicine formulation	A cohort of 880 patients	4 years	The patients diagnosed with stage IV SCC who were admitted between July 2017 and June 2020.	7	Therapies derived from TCM may potentially contribute to an extension in the survival time.
Tan 2020 [151]	Calycosin (*Astragalus*)	Root	A cohort of ten hospitalized patients diagnosed with osteosarcoma	Not reported	The study involved ten hospitalized patients and collected candidate biotargets of calycosin against OS, utilizing a cell culture approach with the cell line U-2 OS. Immunostaining procedures and RT-PCR test were employed for further analysis.	2	The OS sections demonstrated diminished expressions of TP53 and caspase-3, along with heightened expression of X-linked inhibitor of apoptosis protein when compared to OS-free controls. Furthermore, the application of calycosin led to an increase in apoptotic cells, with treated OS cells displaying intracellular upregulation of TP53 and caspase-3 expressions, along with a decrease in the apoptotic protein expressions.
Tseng 2019 [152]	TCM/CHPs	Formula	A total of 30,294 patients with newly diagnosed NPC (ICD-9-CM 147)	10 years	A retrospective, nationwide, population-based study was conducted, gathering data from the Registry for Catastrophic Illnesses Patient Database spanning the years 2001 through 2011 in Taiwan, China	5	These findings furnish insights into personalized therapeutic approaches and may stimulate additional clinical investigations and pharmacological research pertaining to the utilization of CHPs for the treatment of NPC in the context of Taiwan.
Yutani 2013 [153]	JTT/Kampo	Roots and bark	57 cases	16 months	Patients were randomly allocated to receive personalized peptide vaccination with (n = 28) or without (n = 29) JTT. Evaluation included T-cell responses to the vaccine peptides, humoral immune responses to the vaccine peptides, analysis of laboratory markers, and flow cytometric examination of a suppressive immune cell subset in peripheral blood mononuclear cells	6	JTT did not significantly impact immune responses to vaccine antigens, measured by antigen-specific interferon-γ secretion and antigen-specific immunoglobulin G titers. However, it prevented deterioration in patients' conditions, including anemia, lymphopenia, hypoalbuminemia, elevated plasma interleukin-6, and reduced performance status, commonly seen in advanced cancers.

AMP: *Astragalus membranaceus* pharmacopuncture; CHP: Chinese herbal product; CSP: *Cordyceps sinensis* pharmacopuncture; CT: computed tomography scan; EAP: *Euonymus alatus* pharmacopuncture; IC_{50}: half-maximal inhibitory concentration; JTT: Juzentaihoto; NPC: nasopharyngeal carcinoma; RT-PCR: reverse transcriptase-polymerase chain reaction; SCC: squamous cell carcinoma; TCM: traditional Chinese medicine; TKP: *Trichosanthes kirilowii* pharmacopuncture; TP53: tumor protein p53; U-2 OS: human bone osteosarcoma epithelial cell; WGP: wild ginseng pharmacopuncture.

Table 5
Anticancer activity of herbal medicines and active phytochemicals reported in the included studies.

Plant	Active phytochemical	Molecular targets and/or effect on cancer cells (reference)
Chaetomorpha ligustica algae	AgNP and $AgNO_3$	The algae, featuring nanoparticles, showed cytotoxicity at 10 μg/mL against HCT116 and HT29 human colon cancer cell lines after 48 h. HT29 exhibited increased expression of *ATM*, *ATR*, *CHK1* and *CHK2* genes, while in HCT116, *ATM* expression decreased with a slight increase in the other genes [42].
Commiphora gileadensis	AgNP and $AgNO_3$	*C. gileadensis* extracts showed higher toxicity at higher concentrations than their biogenic AgNPs. Both extracts exhibited dose-dependent cytotoxicity against HT29, HTC116 and SW620. RT-PCR analysis revealed increased expression of *CHK1*, *CHK2*, *ATM* and *ATR* genes [43].
Colchicum boissieri and *Colchicum balansae*	Phenolic, flavonoid and tannin contents	Plant extracts ranging from 0.02 to 1.2 mg/mL were administered to the Caco-2 human cell line for 24 and 48 h. No significant results were observed during these incubation periods. The IC_{50} values for both plant extracts were 0.2 mg/mL at 24 h and 0.1 mg/mL at 48 h. *C. boissieri* extracts exhibited greater antioxidant activity than those of *C. balansae*, with higher levels of total bioactive compounds in *C. boissieri* compared to *C. balansae* [45].
Ocimum	Polyphenols and flavonoids	The IC_{50} values of the extracts ranged from 94.3 to 49.36 μg/mL. Notably, no significant genotoxicity was observed across varying concentrations of distinct *Ocimum* extracts [46].
Eclipta alba	Luteolinl	The plant extracts induced the intrinsic pathway of apoptosis, characterized by the overexpression of HSP60, downregulation of the anti-apoptotic protein XIAP, and the localization of HSP60 within the endoplasmic reticulum [47]. This active compound demonstrated a reduction in the percentage of methylation in sequence 5′ CpG promoter regions and an increase in global DNA methylation in HeLa cells. Moreover, it upregulated the expression of several tumor suppressor genes, including *cadherin1*, *TP73* and *TP53*. Consequently, there was a notable decrease in the expression levels of migration-related genes such as *MMP2*, *MMP9*, snail family transcriptional repressor zinc finger protein 2, and mothers against decapentaplegic homolog-family member 4 [154].
Glycyrrhiza uralensis	Polysaccharides	The ED_{50}, recorded at approximately 100 μg/mL on IEC-6 cells, exhibited a stimulatory effect on cell proliferation. Following a 72-hour incubation, CT26 cells showed an inhibition of around 20%. Additionally, the herb led to the upregulation of the cytokine interleukin-7 after 3 h [48].
Petiveria alliacea and *Caesalpinia spinosa*	Gallic acid, myricetin, and dibenzyl disulfide	Alterations occur in the cellular cytoskeleton, leading to cell cycle arrest and cell death independently of the mitochondria. Additionally, protein expression was analyzed by high-performance liquid chromatography-chip/mass spectrometry, revealing a reduction in β-F1ATPase expression, affecting glycolysis, mitochondrial respiration, and lactate production, as well as a decrease in ATP levels [50].
Ligusticum chuanxiong	Tetra-methylpyrazine	The drug increased G_0/G_1 at 12 h and the sub-G_1 phase from 12 to 48 h, subsequently inducing cell apoptosis by decreasing mitochondrial membrane potential and increasing the release of cytochrome *c*, leading to an increase in cleaved-caspase-3 and cleaved-caspase-9 activation. It also increased caspase activation, p53 expression, and the Bcl-2/Bax protein ratio [155].
Pistacia species (*P. lentiscus* var. Chia, *P. vera*, and *P. integerrima*)	The essential oil's composition includes limonene, cis-ocimene, carene, cadinol, terpinene, phellandrene and terpineol	*P. lentiscus* leaves exhibited higher cell inhibition (IC_{50} ranging from 173.9 to 220.4 μg/mL). It was noted that determining the mechanism of action or molecular targeting of the tested compounds is challenging [52].
Herbaceous peony	Paeoniflorin	PANC-1 and Capan-2 cells were treated with varying concentrations (0, 50, 100, 200 and 300 μmol/L) for 24 h. This resulted in the downregulation of p38 protein within the MAPK signaling cascade. Additionally, there was a decrease in the levels of interleukins 6 and 10 in PANC-1 cells, reducing from approximately 750 to 500 pg/mL and from 80 to 20 pg/mL, respectively ($P < 0.001$) [53].
KangXianYiAi formula	*Astragalus membranaceus*, Rhizoma Dioscoreae, and Sinapis Semen	The formula induced G_2/M cell cycle arrest and triggered apoptosis in HepAD38 cells at a concentration of 500 μg/mL for 48 h ($P < 0.01$). Additionally, elevated mRNA expression was observed for the MAPK8, CREBBP, EGFR, ESR1, hepatocyte nuclear factor 4α, MDM2, nuclear receptor subfamily 3, group C, member 1, and phosphatase and tensin homolog genes [54].
Lychee seeds	Flavonoid	The IC_{50} values for PC-3 and DU145 cells at 48 h were 95.7 and 84.6 μg/mL, respectively, and at 72 h were 61.5 and 55.8 μg/mL, respectively. Overexpression of apoptotic proteins, including Bcl-2 and Bax, was observed after 48 h. The lychee seed flavonoid exhibited a slight regulation of Wnt3a, p-MEK1/2, and p-P44/42 MAPK [56].
Gamboge	Gambogenic acid	Gambogenic acid induced G_2/M cell cycle arrest at 0.51 μmol/L, while also exhibiting a slight regulation of apoptotic proteins such as Bcl-2 and Bax, along with p53 and caspase-3, after 48 h of incubation [57].
Chinese herbal injections	Scutellarin	Scutellarin had the ability to disrupt the interaction between TNF and TNFR2 and inhibit the phosphorylation of p38 MAPK, a downstream signaling component of TNFR2. WEHI-13VAR cells expressed high levels of TNFR2 ($P < 0.001$), and the level of TNFR1 was not detectable by FACS [58].
LSW	Telocinobufagin, bufotaline, cinobufotalin, bufalin, cinobufagin and resibufogenin	The oral administration of LSW resulted in a decrease in nanoDEN-induced COX-2 expression in mice. Additionally, there was a reduction in the expression of β-catenin in both cytoplasmic and nuclear compartments, along with a decrease in PCNA expression in mice ($P < 0.01$) [128].
SH003 formula	*Astragalus membranaceus*, *Angelica gigas* and *Trichosanthes kirilowii* Maximowicz	The H003 formula has significantly suppressed the VEGF-dependent phosphorylation of VEGFR2, focal adhesion kinase, proto-oncogene tyrosine-protein kinase Src, ERK, Akt and STAT3 up to 2 h after VEGF stimulation. Consequently, this formula exerts an anti-angiogenic effect by inhibiting VEGF-stimulated VEGFR2-mediated angiogenic signaling in endothelial cells [59].
Solanum nigrum	Solasonine	Solasonine exhibits the ability to induce apoptosis, as evidenced by a significant decrease in the percentage of cells in the G_0/G_1 phase and an accumulation of cells arrested in the S phase ($P < 0.001$). Furthermore, the inhibition of the ERK/MAPK, p38/MAPK, and PI3K/Akt pathways was observed through Western blotting. Additionally, the expression of neuropilin-1 protein was suppressed [60].

(*continued on next page*)

Table 5 (*continued*)

Plant	Active phytochemical	Molecular targets and/or effect on cancer cells (reference)
Cortex Fraxini	Esculetin	Esculetin at 100 μg/mL induced cell cycle arrest at G_0/G_1 and G_2/M phases, reduced S phase population, and decreased expression of cyclin D1, CDK4, CDK6 and c-Myc. Apoptosis was confirmed by an increase in cleaved caspase-3 expression [61].
Curcumin	Zinc-curcumin Zn(II)-curc compound	This compound induced the NRF2 activation oxidative stress pathway, leading to an increase in NRF2 protein levels and its downstream targets, heme oxygenase-1 and p62/SQSTM1. Simultaneously, it significantly reduced the levels of Kelch-like ECH-associated protein 1 at μg/mL for 24 h. In the analyzed cancer cell lines, the inhibition of NRF2/p62 axis enhanced sensitivity to Zn-curc-induced cell death [62].
SNKAF	SNKAF decoction	The results demonstrated that SNKAF serum induces G_2/M and S checkpoints, leading to cell cycle arrest in liver cancer cells. The application of this decoction also increased the numbers of apoptotic cells. Subsequently, Western blotting analysis revealed the regulatory activity of this decoction on the expression of p-Fox3a/Fox3a, p-PI3K/PI3K, p-Akt/Akt, p-p53/p53, Bax, Bcl-2, cleaved-caspase-9, and cleaved-caspase-3 after indicated treatments in HCCLM3 and MHCC97H cells [130].
Epimedium koreanum Nakai	Aohuoside-1 (flavonoid)	The overexpression of caspase-3, caspase-8, and Bax, coupled with the downregulation of Bcl-2 and p-mTOR, was observed in Huh7 cells after 24 h of treatment with 0.1 μmol/L. Indicating that the apoptotic pathway induced by the treatment is caspase-dependent [64].
Alismatis rhizoma (zexie)	Alisol A	Alisol A demonstrated an attenuation of colorectal cancer through the targeting of the PI3K/Akt signaling pathway. It inhibited Bcl-2 protein expression while increasing Bax, cleaved caspase-3, and cleaved PARP protein expression levels in the cells. The enhanced levels of LDH confirmed the effect of alisol A, indicating cellular damage. Additionally, alisol A repressed the phosphorylation levels of PI3K, Akt and mTOR [65].
Epimedium	Icaritin (flavonol glycoside)	Icaritin enhanced the accumulation and activation of $CD8^+$ T cells within melanoma (B16F10) tumors. It increased the percentage of $Ki67^+CD8^+$ T cells and promoted the proliferation of activated splenic $CD8^+$CD44hiCD62Llow T cells [66].
Clinacanthus nutans	Fatty acids and flavonoids	The IC_{50} concentration of the dichloromethane fraction of *C. nutans* at 48 h was found to be 70 μg/mL on HeLa cells. At 250 μg/mL, there was a notable increase in the population of necrotic cells, accompanied by a significantly higher percentage of late apoptotic cells. Additionally, there was a slight increase in the cell distribution percentage in the G_2/M phase, coupled with a significant decrease in the G_0/G_1 phase ($P < 0.05$) [156].
Annona muricata L. (soursop leaves)	Sir-SM2 belongs to genus *Penicillium*	The extracts from this herb were applied to cancer cells, displaying IC_{50} values of < 30 μg/mL. Furthermore, microscopic examination revealed damage to cell morphology at concentrations ranging from 25 to 400 μg/mL [157].
QYSLD	Calycosin-7-O-β-D-glucoside, curcumol and solamargine	The IC_{50} values of ten batches of QYSLD ranged from 1.59 to 5.50 mg/mL. The number of migrated and invaded cells significantly decreased compared to the control, ranging from 12.00 to 68.67 and 7.67 to 27.00, respectively ($P < 0.01$). Furthermore, the DPPH radical-scavenging ability of calycosin-7-O-β-D-glucoside and deacetyl asperulosidic acid gradually increased [68].
Salvia miltiorrhiza	Tanshinone (diterpenes)	This active compound inhibited expanded myelopoiesis in c-myb hyperactivity. It exhibited a higher affinity for binding and inhibited histone enzymatic activity (methyltransferase), suggesting its role as an inhibitor of the PRC2 complex. This compound directly binds to EZH2, leading to the downregulation of MMP9 and ATP-binding cassette subfamily G member 2 proteins [69].
Elephantopus scaber L.	Deoxyelephantopin	Deoxyelephantopin exhibited the capability to inhibit colon cancer cells and tumor growth by inducing G_2/M phase cell arrest followed by apoptosis. This induction leads to severe DNA damage and a reduction in Bcl-2 expression, promoting colon cancer cell apoptosis. Furthermore, deoxyelephantopin upregulated miR-205, a microRNA complementary to the 3′-UTR of Bcl-2, in response to herbal treatment [70].
Carthamus tinctorius (Safflower)	Hydroxysafflor yellow	This medication induced apoptosis in A549 and H1299 cells after 48 h, as evidenced by flow cytometry with annexin violet-fluorescein isothiocyanate/propidium iodide staining. This effect was associated with increased caspase activity (caspase-3 and -9) and downregulation of Bcl-2 protein. Furthermore, the use of PI3K (LY294002) and ERK (SCH772984) inhibitors markedly inhibited proliferation, migration, invasion and EMT, suggesting the involvement of this compound in the PI3K/Akt/mTOR and ERK/MAPK signaling pathways [71].
Sanguisorba officinalis L.	Betulinic acid and quercetin	There was a significant upregulation of PARP and caspase-3 proteins in HepG2 cells ($P < 0.001$). Additionally, this medication downregulated the expression of p-EGFR, p-PI3K, p-Akt, p-NFκB and p-MAPK proteins in HepG2 cells, as revealed by Western blotting analysis [72].
Silybum marianum	Silibinin and Withaferin-A	It was revealed that silibinin affected the downstream targets of STAT3, including BRCA1, BIRC5 and FOXM1, in a dose–response manner. The silibinin IC_{50} signature across 5 NSCLC cell lines exhibited a significant enrichment in gene regulation associated with cell cycle, G_2/M transition, nuclear localization, DNA replication and repair, as well as related signaling, metabolic processes, and functions [73].
Green tea	Polyphenols	Polyphenon 60 demonstrated highly competitive inhibition against mushroom tyrosinase, displaying an IC_{50} value of (0.697 ± 0.021) μg/mL, compared to kojic acid with an IC_{50} value of (2.486 ± 0.085) μg/mL. The study also showed a significant induction of tyrosinase expression at a dose of 60 μg/mL ($P < 0.001$). Subsequently, at the concentration of 60 μg/mL, there was a notable downregulation of cellular tyrosinase [74,118].
MOL	Sitosterol, quercetin and kaempferol	The expression levels of *BMP2* and *Runx2* genes increased at concentrations of 25 and 50 μg/mL, while declining at 100 and 200 μg/mL of the herbal extract ($P < 0.05$). Cell cycle analysis revealed that this medicine at concentrations of 50 and 100 μg/mL arrested the cells at the G_2/M phase, ranging from 7.26% to 27.6%. Lower doses enhanced alkaline phosphatase levels, mineralization, and the expression of *BMP2* and *Runx2* genes in osteoblast-like SaOS-2 cells. [75].

(*continued on next page*)

Table 5 (*continued*)

Plant	Active phytochemical	Molecular targets and/or effect on cancer cells (reference)
Syzygium alternifolium	Flavonoids (eucalyptin, kaempferol-3-*O*-*β*-d-glucopyranoside, and kaempferol-3-*O*-*α*-L-rhamnopyranoside)	These three phytochemicals have targeted the G_2/M phase of cells. Concentrations at 75 μg/mL have shown a significant decrease in viable cell count at the G_2/M phase, ranging from 7.13% to 4.7%. This suggests that the active compounds may have an effect on receptors responsible for gastric human cancer cells [49].
Rhus verniciflua Stokes extract	Gallic acid	This compound increased the percentage of sub-G_1 phase (apoptotic) cells in a dose-dependent manner ($P < 0.01$). It induced apoptosis ($P < 0.05$ at 200 μg/mL; $P < 0.01$ at 300 and 400 μg/mL), elevated p53 expression, increased p21 expression, elevated the Bax/Bcl-2 ratio, and increased levels of cleaved caspase-3, cleaved caspase-9 and PARP [77].
Cinnamomum zeylanicum L.	Cinnamon essential oil	This oil decreased the ratio of high-/low-grade carcinomas, increased the expression of caspase-3 and Bax, and decreased the Bcl-2, Ki67, VEGF, CD24 and MDA levels [79].
Dendrobium	Gigantol	Gigantol exhibited effects on drug targets and the HSP90/Akt/CDK1 signaling pathway. The expression levels of ESR1, HSP90AA1 and XIAP were significantly and gradually decreased with the increase in drug concentration. Simultaneously, there was a significant decrease in the downstream protein levels of p-Akt, Akt and CDK1. The anti-HCC proliferation activity of gigantol through the PI3K pathway suggests its potential inhibition of HCC progression via the HSP90/Akt/CDK1 pathway [87].
Bulbus *Fritillaria cirrhosa* D. Don	Pumiloside, deoxypumiloside, camptothecin, aknadinine, and β-stigmasterol	These compounds induced dose-dependent G_2/M phase cell cycle arrest, significantly reducing protein expression of G_2/M regulators cyclin B1 and CDK1. They also increased apoptosis rate, fluorescence intensities of nuclei and nuclear condensation, decreased anti-apoptotic protein Bcl-2 expression, and increased pro-apoptotic cleaved caspase-3 expression. Furthermore, they elevated the Bax/Bcl-2 ratio and ROS levels. Moreover, the compounds decreased expression of MMP-9 and MMP-2 migration-associated proteins ($P < 0.05$) and reduced phosphorylation of p65 ($P < 0.001$), indicating their potential to inhibit cancer cell proliferation and motility by inactivating NF-κB signaling [88].
Berberis amurensis Rupr.	Berbamine dihydrochloride	This compound inhibited the PI3K/Akt and MDM2-p53 signaling pathways and downregulated the expression of c-Maf [90].
Polygonum cuspidatum	Polydatin	By applying this compound, a significant induction of cell cycle arrest in the S-phase and enhancement of bone alkaline phosphatase activity were observed. Additionally, the compound activated the Wnt-β-catenin pathway and induced osteogenic differentiation through the secretion of sphingolipids and ceramide. These findings indicate that polydatin promotes osteoblast differentiation and mineralization in Saos-2 cells [93].
Rhizoma Curcumae	Curcumol	Significantly reduced CD133 and Nanog protein levels, decreased the percentage of $CD133^+$ cells, and lowered expression of CD133, Nestin, Nanog and SOX-2. This sensitized TMZ-resistant glioma cells to TMZ, significantly decreasing FOXD2-As1 expression in a time- and dose-dependent manner. Overexpression of FoxD2-As1 attenuated the anti-proliferation, anti-metastasis, and pro-apoptosis effects, as well as the impact of curcumol on TMZ-resistant glioma. Additionally, it abolished the inhibitory effect of curcumol on the self-renewal ability of glioma cells and inhibited the activation of EZH2 through downregulation of FOXD2-As1 [94].
Salia miltiorrhiza	Tanshinones (T1, T2A and CT)	This compound significantly promoted apoptosis, induced G_0/G_1 cell cycle arrest in H1299 cells, and partially suppressed aurora kinase A through upregulating the expression of miR-32 [96].
Uncaria rhynchophylla	Hirsutine	This compound arrested the cell cycle at the G_0/G_1 phase ($P < 0.05$ or $P < 0.01$), upregulated pro-apoptotic proteins including Bax, cleaved-caspase-3, cleaved-caspase-9 and cytochrome *c*, and downregulated Bcl-2 protein. Additionally, it decreased *BCL-2* mRNA expression while increasing mRNA levels of Bax, caspase-3 and caspase-9 [99].
Clinacanthus nutans	Alkaloid, phenol, tannin, flavonoid, terpenoid, glycoside and steroid	The expression of IL-6 cytokine in the media of MDA-MB-231/THP-1 macrophage co-culture was significantly reduced at 25 and 100 μg/mL, but not at 50 μg/mL, compared to the LPS-treated control. IL-1β cytokine expression was significantly reduced at 25 μg/mL [100].
C5E	Glutaric acid, 13S-hydroxyoctadecadienoic acid, and bardoxolone methyl	The results revealed that SHH gene expression levels were downregulated by approximately 20% when treated with C5E compared to the control group. This downregulation in SHH mRNA expression levels was significant compared to the treatment with each individual compound [101,102].
Gnetum montanum Markgr. (Gnetaceae)	1-O-Acetyl-D-arabinofuranose, protocatechuic acid-3-glucoside, vanillic acid, licraside, isorhapontigenin, gnetin D, naringenin, pinosylvin, gnemonol K and gnetumontanin C	The experiments showed a significant increase in apoptotic cells (from 20.8% to 61.5%, $P < 0.01$) and G_2/M phase cells (from 25.76% to 34.93%) with 120 μg/mL GME. This herb downregulated the protein expression of P-Akt, P-GSK-3b, P-PDK1, P-c-Raf, caspase-3 and Bcl-2, while upregulating the expression of cleaved caspase-3, cleaved PARP and Bax. In the in vivo study, GME significantly inhibited the growth and migration of SW480 cells in xenograft zebrafish. GME reduced nude mice tumor weight to approximately 32.19% at 28 mg/(kg·d) and to 53.17% ($P < 0.01$) at 56 mg/(kg·d) [103].
Scutellaria baicalensis Georgi	Baicalein	To assess the effect of baicalein on the expression and activation of caspase-3, it was observed that while caspase-3 expression did not significantly change, the activation of caspase-3 (cleaved-caspase-3) through proteolytic cleavage increased in a dose-dependent manner after baicalein treatment. Cleaved PARP was found to be increased by baicalein treatment [106].
Baliospermum montanum	Propiophenone	The extracted phytochemical demonstrated the highest anti-allergic activity with an IC_{50} value of (4.97 ± 0.43) μg/mL. It exhibited anti-inflammatory effects by inhibiting the production of NO in a concentration-dependent manner. Additionally, the compound showed potent cytotoxic activity against HepG2 and KKU-M156 cells, with an IC_{50} of less than 1 μg/mL [107].
Embelia ribes	Embelin (benzoquinone)	Treatment with embelin resulted in an increase in the sub-G_0/apoptotic fraction from 6.2% in untreated cells to 10.0%, 20.1% and 43.8% in K562 cells treated with 10, 25 and 50 μmol/L of embelin, respectively. Moreover, this compound increased cleaved caspase-8, indicating the activation of caspase-8, which subsequently downregulated the expression of Bcl-2 and Bcl-xL proteins, while upregulating the expression of the proapoptotic Bax protein [108].

(*continued on next page*)

Table 5 (*continued*)

Plant	Active phytochemical	Molecular targets and/or effect on cancer cells (reference)
Baliospermum montanum	Triterpenoid and celastrol	These compounds activated caspase-3 and downregulated B-cell lymphoma-2. CuB demonstrated the potential to enhance the expression of p53 and p21 in the two cell lines. Moreover, CuB exhibited the ability to downregulate the expression of P-glycoprotein. Celastrol significantly inhibited the growth of T/E fusion-expressing prostate cancer cells both in vitro and in vivo by targeting three critical signaling pathways: AR, ERG and NF-κB in these cells. In mice receiving 0.5 mg/kg celastrol 4 times a week, significant growth inhibition was observed without obvious toxicity or significant weight loss [109,114].
Peganum harmala	Harmaline (alkaloid)	Harmaline binds to the substrate-binding pocket of SphK1 with appreciable binding affinity and significantly inhibits the kinase activity of SphK1, exhibiting an IC_{50} value in the micromolar range. In MTT assays, the inhibitory effect of harmaline on NSCLC cells was higher for H1299 compared to A549. Harmaline induces apoptosis in NSCLC cells (H1299 and A549), possibly via the intrinsic pathway, characterized by a gradual increase in caspase-3 [112].
Inula oculus-christi	Gaillardin	Gaillardin revealed an increase in the transcription of Bax and a decrease in the transcription of Bcl-2 in acute promyelocytic leukemia cell lines, leading to induced apoptosis [113].
Rhodiola rosea	Salidroside	The results showed higher expressions of multidrug resistance protein-1, P-gp, lysyl oxidase-like 2 enzyme, survivin, Livin and Bcl-2 but lower expression of Bax in HT-29 than in HT-29/L-OHP ($P < 0.01$). The intervention resulted in more HT-29/L-OHP and HT-29 cells arrested at the G_0/G_1 stage, with fewer at the G_2/M stage ($P < 0.01$), whereas almost the same proportion in the S stage [115].
Solanaceae plants	Solamargine (alkaloid)	Solamargine downregulated the expression of the long noncoding RNAs HOTTIP and TUG1, subsequently increasing the expression of miR-4726-5p. Furthermore, miR-4726-5p directly bound to the 3′ untranslated region of MUC1, leading to a decrease in the expression of MUC1 protein. The overexpression of MUC1 partially reversed the inhibitory effect of solamargine on HepG2 and Huh-7 cell viability, suggesting that MUC1 may be the key target in solamargine-induced growth inhibition of HCC [117].
Pimelea decora	6-Methoxyflavone, genistein and flavonoids	Macromolecular biomarkers, such as phosphorylated protein kinase RNA-like endoplasmic reticulum kinase and phosphorylated eukaryotic translation initiation factor 2α, hold great significance in assessing the therapeutic effects of 6-methoxyflavone. There was a substantial increase in ROS production in the cells, along with an increase in caspase 3 and cleaved PARP proteins. After 48 h of treatment, a significant rise in caspase-3, p53, cytochrome *c* and cleaved PARP proteins was observed, alongside a notable increase in cytokines [111,158].
Ophiopogon japonicus	OP-B	The induction of apoptosis in SGC-7901 cells by OP-B was associated with the loss of mitochondrial membrane potential and increased ROS generation. Western blotting analysis revealed that treatment with OP-B increased the protein expression levels of caspase-3 and Bcl-2-associated X protein. In contrast, the expression levels of Bcl-2 and the phosphorylation levels of ERKs 1/2 and c-Jun N-terminal kinases 1/2 were decreased [123].
Scutellaria baicalensis	Baicalein	Baicalein binds to mismatch repair protein MutSα, causing the dissociation of CHK2 from MutSα, leading to S phase arrest and cell survival. In contrast, sustained replication in the presence of baicalein in MutSα-deficient cells results in a high number of DNA double-strand breaks, ultimately leading to apoptosis. Consistently, baicalein specifically reduces the size of MutSα-deficient xenograft tumors and inhibits the growth of azoxymethane/dextran sodium sulfate-induced colon tumors in colon-specific MSH2 knockout mice [124].
Angelica dahurica	Imperatorin (coumarin) and PCA	Coumarin induced apoptosis in colon cancer cells by upregulating p53 and the caspase cascade. Imperatorin induced G_1 phase cell cycle arrest, and as imperatorin concentration increased, the apoptotic index steadily rose. Moreover, imperatorin affected the intrinsic pathway involving Bcl-2 members, p53, p21, MDM2 and the caspase cascade, leading to significant changes in the expression of Bax, caspase-8, MDM2, p53 and p21 [125,159]. PCA induced apoptosis through caspase-3 activation and reduced Harvey and Kristen rat sarcoma viral oncogene homolog (H-Ras and K-Ras) transcript levels in MCF-7 breast cancer cells. In the presence of PCA, there was a significant dose-dependent increase in *Bax* mRNA levels and late apoptotic cells. Additionally, PCA retarded the relative expression of the antiapoptotic gene *Bcl-2* in treated cells. Overall, PCA inhibits the growth of MCF-7 cells by reducing Ras expression and inducing cell apoptosis [125,159].
Paeonia lactiflora Pall	6-O-galloylpaeoniflorin (gallic acid)	This compound upregulated miR-489 expression in NBM cells by activating AMP-activated protein kinase. MiR-489 demonstrated significant anti-NBM capabilities by directly targeting XIAP. The compound exhibited a pronounced anti-NBM effect dependent on the AMPK/miR-489/XIAP pathway [126].
Buxus microphylla	CVB-D	The compound demonstrated downregulation of p65, a transcriptional suppressor of BNIP3, upon CVB-D treatment. Ectopic expression of p65 inhibited BNIP3 expression, while its knockdown significantly abolished its transcriptional repression on BNIP3 upon CVB-D treatment. The findings suggest that the compound can provoke mitophagy, revealing the involvement of the p65/BNIP3/LC3 axis as one potential mechanism [141].
Nigella sativa	Thymoquinone	Thymoquinone blocked the activation of the Wnt/β-catenin signaling pathway by dose-dependently decreasing the expression of Wnt3α, p-gsk3β (Ser9), and non-phosphorylated (active) β-catenin (Ser33/37/Thr41). Simultaneously, it increased the expression of p-β-catenin (Ser33/37/Thr41), promoting the phosphorylation and degradation of β-catenin [142].
Plumbago scandens L.	Plumbagin	After 24 h of treatment with 0, 0.75 and 1.5 μmol/L plumbagin, the expression of β-catenin, vimentin, MMP-9, and Slug decreased in a concentration-dependent manner, while Zonula occludens 1 increased. In conclusion, plumbagin treatment significantly blocked the migration ability of breast cancer cells by suppressing EMT, downregulating cyclins (CCND1 and CCNE1), and reducing cyclin-dependent kinase (CDK2, CDK4 and CDK6) proteins in a concentration-dependent manner in both T24 and UMUC3 cells. Additionally, Bax, caspase-3, caspase-6 and caspase-9 increased [143].

(*continued on next page*)

Table 5 (*continued*)

Plant	Active phytochemical	Molecular targets and/or effect on cancer cells (reference)
Salvia miltiorrhiza	Tan IIA	This compound effectively inhibited proliferation in three human gastric cancer cell lines (SNU-638, MKN1 and AGS) in a time- and dose-dependent manner. Tan IIA treatment induced increased apoptosis, upregulated Bax expression, elevated cleaved caspase-3 levels, and reduced Bcl-2 expression. Additionally, Tan IIA significantly inhibited STAT3 phosphorylation, influencing apoptosis gene expression. Overexpression of STAT3 mitigated Tan IIA-induced growth suppression and apoptosis. In a nude mouse xenograft model, intraperitoneal Tan IIA treatment for 28 d significantly inhibited tumor growth and STAT3 activation [160].
Lavandula angustifolia	Linalool and linalyl acetate	The IC_{50} values for linalool and linalyl acetate were (7.22 ± 0.28) and (11.74 ± 0.62) μmol/L in DU145, and (3.06 ± 0.22) and (4.98 ± 0.31) μmol/L in PC-3 cells, respectively. These compounds also inhibited cell migration. In the DU145 cell line, both DR4 and DR5 were significantly upregulated in the essential oil and linalool treatment groups [146].

AgNP: algae-mediated silver nanoparticle; $AgNO_3$: silver nitrate ion; AGS: human gastric adenocarcinoma; ATM: ataxia telangiectasia mutated; ATP: adenosine triphosphate; ATR: ataxia telangiectasia and Rad3 related; Bcl-2: B-cell lymphoma 2; BIRC5: baculoviral IAP repeat-containing 5; BMP: bone morphogenetic protein; BNIP3: Bcl-2 interacting protein 3; BRCA: breast cancer gene; C5E: *Ficus carica*, *Inonotus obliquus*, *Pinellia ternata*, rhizome of *Sparganium stoloniferum* Buchanan–Hamilton, *Alpinia galanga*, *Cinnamomum cassia*, *Astragalus membranaceus*, *Psoralea corylifolia* L., *Tetradium ruticarpum* and *Melia azedarach* L.; CDK: cyclin-dependent kinase; CHK: checkpoint kinase; COX-2: cyclooxygenase-2; CREBBP: cAMP response element-binding protein-binding protein; CuB: cucurbitacin B; CVB-D: cyclovirobuxine D; DNA: deoxyribonucleic acid; DPPH: 2,2-diphenyl-1-picrylhydrazyl; DR: death receptor; ED_{50}: median effective dose; EGFR: epidermal growth factor receptor; EMT: epithelial-mesenchymal transition; ERK: extracellular signal-regulated kinase; ESR1: estrogen receptor 1; EZH2: enhancer of zeste homolog 2; β-F1ATPase: β subunit of F1 adenosine triphosphatase enzyme; FACS: fluorescence-activated cell sorting; FOXM1: forkhead box M1; GME: *Gnetum montanum* extract; HCC: human hepatocellular carcinoma; HepG2: human liver cancer cell line; HSP: heat-shock protein; IC_{50}: half-maximal inhibitory concentration; IL: interleukin; LDH: lactate dehydrogenase; LPS: lipopolysaccharide; LSW: Liushenwan; MAPK: mitogen-activated protein kinase; MDM2: mouse double minute 2; MMP: matrix metalloproteinase; MOL: *Moringa oleifera* leaf; mRNA: messenger ribonucleic acid; mTOR: mechanistic target of rapamycin; MTT: 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide; NF-κB: nuclear factor κB; NSCLC: non-small cell lung cancer; NRF2: nuclear factor erythroid 2 p45-related factor 2; OP-B: ophiopogonin B; PARP: poly(ADP-ribose) polymerase; PCA: p-coumaric acid; PCNA: proliferating cell nuclear antigen; PI3K: phosphoinositide-3-kinase; PKB (Akt): protein kinase B; PRC2: polycomb repressive complex 2; QYSLD: Qi-Yu-San-Long decoction; RNA: ribonucleic acid; ROS: reactive oxygen species; RT-PCR: reverse transcriptase-polymerase chain reaction; Runx2: runt-related transcription factor 2; SHH: sonic hedgehog; SNKAF: Sinikangai fang; SphK1: sphingosine kinase-1; SOX-2: sex-determining region Y; STAT: signal transducer and activator transcription; T/E fusion: fusion of the transmembrane protease, serine 2, gene (TMPRSS2) with the erythroblast transformation-specific (ETS)-related gene (ERG); Tan IIA: tanshinone IIA; TMZ: temozolomide; TNF: tumor necrosis factor; TNFR: tumor necrosis factor receptor; TP53: tumor protein p53; VEGF: vascular endothelial growth factor; VEGFR2: vascular endothelial growth factor receptor 2; XIAP: X-linked inhibitor of apoptosis protein.

Funding

No funding was received for this study.

Authors' contributions

RM contributed to the study design and concept development. BAT and IYK conducted a comprehensive literature search and collected relevant articles. AAMO, BAT and IYK undertook the tasks of data extraction and rigorous analysis. BAT drafted the manuscript, which was subsequently critically revised by AAMO and IYK. All authors reviewed and approved the revised version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joim.2024.02.001.

References

[1] National Cancer Institute. Cancer disparities 2016. (2022-03) [2023-01-21]. https://www.cancer.gov/about-cancer/understanding/disparities.

[2] Stein GS, Pardee AB. Cell cycle and growth control: biomolecular regulation and cancer. 2nd ed. (2005-02) [2023-01-21]. https://www.wiley.com/en-us/Cell+Cycle+and+Growth+Control%3A+Biomolecular+Regulation+and+Cancer%2C+2nd+Edition-p-9780471656432.

[3] DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin 2014;64(4):252–71.

[4] Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64(1):9–29.

[5] Akin S, Can G, Aydiner A, Ozdilli K, Durna Z. Quality of life, symptom experience and distress of lung cancer patients undergoing chemotherapy. Eur J Oncol Nurs 2010;14(5):400–9.

[6] Montemurro F, Rossi V, Cossu Rocca M, Martinello R, Verri E, Redana S, et al. Hormone-receptor expression and activity of trastuzumab with chemotherapy in HER2-positive advanced breast cancer patients. Cancer 2012;118(1):17–26.

[7] Debela DT, Muzazu SG, Heraro KD, Ndalama MT, Mesele BW, Haile DC, et al. New approaches and procedures for cancer treatment: current perspectives. SAGE Open Med 2021;9:20503121211034366.

[8] Cagel M, Grotz E, Bernabeu E, Moretton MA, Chiappetta DA. Doxorubicin: nanotechnological overviews from bench to bedside. Drug Discov Today 2017;22(2):270–81.

[9] Desai AG, Qazi GN, Ganju RK, El-Tamer M, Singh J, Saxena AK, et al. Medicinal plants and cancer chemoprevention. Curr Drug Metab 2008;9(7):581–91.

[10] Kanwal U, Bukhari NI, Ovais M, Abass N, Hussain K, Raza A. Advances in nano-delivery systems for doxorubicin: an updated insight. J Drug Target 2018;26(4):296–310.

[11] Grem JL. 5-Fluorouracil: forty-plus and still ticking. A review of its preclinical and clinical development. Invest New Drugs 2000;18(4):299–313.

[12] Macdonald JS. Toxicity of 5-fluorouracil. Oncology (Williston Park) 1999;13(7 Suppl 3):33–4.

[13] Rastogi N, Chag M, Ayyagari S. Myocardial ischemia after 5-fluorouracil chemotherapy. Int J Cardiol 1993;42(3):285–7.

[14] Makovec T. Cisplatin and beyond: molecular mechanisms of action and drug resistance development in cancer chemotherapy. Radiol Oncol 2019;53(2):148–58.

[15] Raudenska M, Balvan J, Fojtu M, Gumulec J, Masarik M. Unexpected therapeutic effects of cisplatin. Metallomics 2019;11(7):1182–99.

[16] Anand U, Dey A, Chandel AKS, Sanyal R, Mishra A, Pandey DK, et al. Cancer chemotherapy and beyond: current status, drug candidates, associated risks and progress in targeted therapeutics. Genes Dis 2022;10(4):1367–401.

[17] Gibson RJ, Keefe DMK, Lalla RV, Bateman E, Blijlevens N, Fijlstra M, et al. Systematic review of agents for the management of gastrointestinal mucositis in cancer patients. Support Care Cancer 2013;21(1):313–26.

[18] McGuire DB, Fulton JS, Park J, Brown CG, Correa MEP, Eilers J, et al. Systematic review of basic oral care for the management of oral mucositis in cancer patients. Support Care Cancer 2013;21(11):3165–77.

[19] Jordan K, Gralla R, Jahn F, Molassiotis A. International antiemetic guidelines on chemotherapy induced nausea and vomiting (CINV): content and implementation in daily routine practice. Eur J Pharmacol 2014;722:197–202.

[20] Hamilton G, Rath B. Role of circulating tumor cell spheroids in drug resistance. Cancer Drug Resist 2019;2(3):762–72.

[21] Longley DB, Johnston PG. Molecular mechanisms of drug resistance. J Pathol 2005;205(2):275–92.

[22] Rottenberg S, Borst P. Drug resistance in the mouse cancer clinic. Drug Resist Updat 2012;15(1–2):81–9.

[23] Uchibori K, Kasamatsu A, Sunaga M, Yokota S, Sakurada T, Kobayashi E, et al. Establishment and characterization of two 5-fluorouracil-resistant hepatocellular carcinoma cell lines. Int J Oncol 2012;40(4):1005–10.

[24] Schnipper LE, Davidson NE, Wollins DS, Tyne C, Blayney DW, Blum D, et al. American Society of Clinical Oncology statement: a conceptual framework to assess the value of cancer treatment options. J Clin Oncol 2015;33(23):2563–77.

[25] Pan SY, Litscher G, Gao SH, Zhou SF, Yu ZL, Chen HQ, et al. Historical perspective of traditional indigenous medical practices: the current renaissance and conservation of herbal resources. Evid Based Complement Alternat Med 2014;2014:525340.

[26] Anonymous. Ruins of the bridge across the lake 2013. (2008-03) [2023-01-22]. https://baike.baidu.com/item/%E8%B7%A8%E6%B9%96%E6%A1%A5%E9%81%97%E5%9D%80.

[27] Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. Environ Health Perspect 2001;109(Suppl 1):69–75.

[28] Leroi-Gourhan A. The flowers found with Shanidar IV, a Neanderthal burial in Iraq. Science 1975;190(4214):562–4.

[29] Falodun A. Herbal medicine in Africa—distribution, standardization and prospects. Res J Phytochem 2010;4(3):154–61.

[30] Buyel JF. Plants as sources of natural and recombinant anti-cancer agents. Biotechnol Adv 2018;36(2):506–20.

[31] Omara T, Odero MP, Obakiro SB. Medicinal plants used for treating cancer in Kenya: an ethnopharmacological overview. Bull Natl Res Cent 2022;46(1):148.

[32] Wu T, Yang X, Zeng X, Eslick GD. Traditional Chinese medicinal herbs in the treatment of patients with esophageal cancer: a systematic review. Gastroenterol Clin North Am 2009;38(1):153–67.

[33] Ying J, Zhang M, Qiu X, Lu Y. The potential of herb medicines in the treatment of esophageal cancer. Biomed Pharmacother 2018;103:381–90.

[34] Zhang YS, Shen Q, Li J. Traditional Chinese medicine targeting apoptotic mechanisms for esophageal cancer therapy. Acta Pharmacol Sin 2016;37(3):295–302.

[35] Li H, Ma C, Chang S, Xi Y, Shao S, Chen M, et al. Traditional Chinese medicine decoctions improve longevity following diagnosis with stage IV esophageal squamous cell carcinoma: a retrospective analysis. Int J Gen Med 2022;15:1665–75.

[36] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

[37] Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169(7):467–73.

[38] O'Connor D, Green S, Higgins JP. Defining the review question and developing criteria for including studies. In: Higgins JP, Green S, editors. Cochrane handbook for systematic reviews of interventions: Cochrane book series. Chichester: John Wiley & Sons Ltd; 2008. p. 81–94.

[39] Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev 2016;5(1):210.

[40] Chien TJ, Liu CY, Fang CJ, Kuo CY. The efficacy of acupuncture in chemotherapy-induced peripheral neuropathy: systematic review and meta-analysis. Integr Cancer Ther 2019;18:1534735419886662.

[41] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1–12.

[42] Al-Zahrani SA, Bhat RS, Al Rashed SA, Mahmood A, Al Fahad A, Alamro G, et al. Green-synthesized silver nanoparticles with aqueous extract of green algae *Chaetomorpha ligustica* and its anticancer potential. Green Process Synth 2021;10(1):711–21.

[43] Al-Zahrani SA, Bhat RS, Al-Onazi MA, Alwhibi MS, Soliman DA, Aljebrin NA, et al. Anticancer potential of biogenic silver nanoparticles using the stem extract of *Commiphora gileadensis* against human colon cancer cells. Green Process Synth 2022;11(1):435–44.

[44] Alim AA, Ghazali WASW, Ali NAM, Ponnuraj KT, Mohamad S, Azlina A. Phytochemical analysis and cytotoxicity of *Clinacanthus nutans* on human gingival fibroblast cell line. Biomed India 2022;42(2):241–6.

[45] Alper M. Antiproliferative and antioxidant potential of methanol extracts of aerial parts of *Colchicum boissieri* and *Colchicum balansae*. Int J Second Metab 2022;9:149–57.

[46] Anusmitha KM, Aruna M, Job JT, Narayanankutty A, Benil PB, Rajagopal R, et al. Phytochemical analysis, antioxidant, anti-inflammatory, anti-genotoxic, and anticancer activities of different *Ocimum* plant extracts prepared by ultrasound-assisted method. Physiol Mol Plant Pathol 2022;117:101746.

[47] Arya RK, Singh A, Yadav NK, Cheruvu SH, Hossain Z, Meena S, et al. Anti-breast tumor activity of *Eclipta* extract in-vitro and in-vivo: novel evidence of endoplasmic reticulum specific localization of Hsp60 during apoptosis. Sci Rep 2015;5:18457.

[48] Ayeka PA, Bian Y, Mwitari PG, Chu X, Zhang Y, Uzayisenga R, et al. Immunomodulatory and anticancer potential of Gancao (*Glycyrrhiza uralensis* Fisch.) polysaccharides by CT-26 colon carcinoma cell growth inhibition and cytokine IL-7 upregulation in vitro. BMC Complement Altern Med 2016;16:206.

[49] Babu TMC, Rammohan A, Baki VB, Devi S, Gunasekar D, Rajendra W. Development of novel HER2 inhibitors against gastric cancer derived from flavonoid source of *Syzygium alternifolium* through molecular dynamics and pharmacophore-based screening. Drug Des Devel Ther 2016;10:3611–32.

[50] Ballesteros-Ramírez R, Aldana E, Herrera MV, Urueña C, Rojas LY, Echeverri LF, et al. Preferential activity of *Petiveria alliacea* extract on primary myeloid leukemic blast. Evid Based Complement Alternat Med 2020;2020:4736206.

[51] Bi C, Zhou S, Liu X, Zhu Y, Yu J, Zhang X, et al. NDDRF: a risk factor knowledgebase for personalized prevention of neurodegenerative diseases. J Adv Res 2022;40:223–31.

[52] Buriani A, Fortinguerra S, Sorrenti V, Dall'Acqua S, Innocenti G, Montopoli M, et al. Human adenocarcinoma cell line sensitivity to essential oil phytocomplexes from *Pistacia* species: a multivariate approach. Molecules 2017;22(8):1336.

[53] Cao C, Zhao W, Chen X, Shen B, Wang T, Wu C, et al. Deciphering the action mechanism of paeoniflorin in suppressing pancreatic cancer: a network pharmacology study and experimental validation. Front Pharmacol 2022;13:1032282.

[54] Cao X, Chen H, Li Z, Li X, Yang X, Jin Q, et al. Network pharmacology and in vitro experiments-based strategy to investigate the mechanisms of KangXianYiAi formula for hepatitis B virus-related hepatocellular carcinoma. Front Pharmacol 2022;13:985084.

[55] Chang E, Pohling C, Natarajan A, Witney TH, Kaur J, Xu L, et al. AshwaMAX and Withaferin A inhibits gliomas in cellular and murine orthotopic models. J Neurooncol 2016;126(2):253–64.

[56] Chang M, Zhu D, Chen Y, Zhang W, Liu X, Li XL, et al. Total flavonoids of *Litchi* seed attenuate prostate cancer progression via inhibiting AKT/mTOR and NF-κB signaling pathways. Front Pharmacol 2021;12:758219.

[57] Chen R, Zhang H, Liu P, Wu X, Chen B. Gambogenic acid synergistically potentiates bortezomib-induced apoptosis in multiple myeloma. J Cancer 2017;8:839–51.

[58] Chen S, Li R, Chen Y, Chou CK, Zhang Z, Yang Y, et al. Scutellarin enhances anti-tumor immune responses by reducing TNFR2-expressing $CD4^+Foxp3^+$ regulatory T cells. Biomed Pharmacother 2022;151:113187.

[59] Choi HS, Kim MK, Lee K, Lee KM, Choi YK, Shin YC, et al. SH003 represses tumor angiogenesis by blocking VEGF binding to VEGFR2. Oncotarget 2016;7(22):32969–79.

[60] Dong Y, Hao L, Shi ZD, Fang K, Yu H, Zang GH, et al. Solasonine induces apoptosis and inhibits proliferation of bladder cancer cells by suppressing NRP1 expression. J Oncol 2022;2022:7261486.

[61] Duan J, Shi J, Ma X, Xuan Y, Li P, Wang H, et al. Esculetin inhibits proliferation, migration, and invasion of clear cell renal cell carcinoma cells. Biomed Pharmacother 2020;125:110031.

[62] Garufi A, Giorno E, Gilardini Montani MS, Pistritto G, Crispini A, Cirone M, et al. P62/SQSTM1/Keap1/NRF2 axis reduces cancer cells death-sensitivity in response to Zn(II)-curcumin complex. Biomolecules 2021;11(3):348.

[63] Guo W, Yao X, Lan S, Zhang C, Li H, Chen Z, et al. Metabolomics and integrated network pharmacology analysis reveal SNKAF decoction suppresses cell proliferation and induced cell apoptosis in hepatocellular carcinoma via PI3K/Akt/P53/FoxO signaling axis. Chin Med 2022;17(1):76.

[64] Guo Y, Zhu H, Weng M, Chen B, Wang C, Sun L. Baohuoside-1 targeting mTOR inducing apoptosis to inhibit hepatocellular carcinoma proliferation, invasion and migration. Biomed Pharmacother 2020;128:110366.

[65] Han W, Xing W, Wang K, Wang B, Bai K. Alisol A attenuates malignant phenotypes of colorectal cancer cells by inactivating PI3K/Akt signaling. Oncol Lett 2022;24(2):249.

[66] Hao H, Zhang Q, Zhu H, Wen Y, Qiu D, Xiong J, et al. Icaritin promotes tumor T-cell infiltration and induces antitumor immunity in mice. Eur J Immunol 2019;49(12):2235–44.

[67] Hassan M, Shafique F, Bhutta H, Haq K, Almansouri T, Asim N, et al. A comparative study to evaluate the effects of antibiotics, plant extracts and fluoride-based toothpaste on the oral pathogens isolated from patients with gum diseases in Pakistan. Braz J Biol 2021;83:e242703.

[68] Huang M, Li R, Yang M, Zhou A, Wu H, Li Z, et al. Discovering the potential active ingredients of Qi-Yu-San-Long decoction for anti-oxidation, inhibition of non-small cell lung cancer based on the spectrum-effect relationship combined with chemometric methods. Front Pharmacol 2022;13:989139.

[69] Huang Y, Yu SH, Zhen WX, Cheng T, Wang D, Lin JB, et al. Tanshinone I, a new EZH2 inhibitor restricts normal and malignant hematopoiesis through upregulation of *MMP9* and *ABCG2*. Theranostics 2021;11(14):6891–904.

[70] Ji H, Zhang K, Pan G, Li C, Li C, Hu X, et al. Deoxyelephantopin induces apoptosis and enhances chemosensitivity of colon cancer via miR-205/Bcl2 axis. Int J Mol Sci 2022;23(9):5051.

[71] Jiang M, Zhou LY, Xu N, An Q. Hydroxysafflor yellow A inhibited lipopolysaccharide-induced non-small cell lung cancer cell proliferation, migration, and invasion by suppressing the PI3K/AKT/mTOR and ERK/MAPK signaling pathways. Thorac Cancer 2019;10(6):1319–33.

[72] Jiang N, Li H, Sun Y, Zeng J, Yang F, Kantawong F, et al. Network pharmacology and pharmacological evaluation reveals the mechanism of the *Sanguisorba*

officinalis in suppressing hepatocellular carcinoma. Front Pharmacol 2021; 12:12618522.
[73] Kaipa JM, Starkuviene V, Erfle H, Eils R, Gladilin E. Transcriptome profiling reveals silibinin dose-dependent response network in non-small lung cancer cells. PeerJ 2020;8:e10373.
[74] Kazi MA, Sahito R, Abbas Q, Ullah S, Majid A, Phull AR, et al. The inhibitory effect of polyphenon 60 from green tea on melanin and tyrosinase in zebrafish and A375 human melanoma cells. Evid Based Complement Alternat Med 2022;2022:7739023.
[75] Khan MI, Siddiqui S, Barkat MA, Alhodieb FS, Ashfaq F, Barkat HA, et al. *Moringa oleifera* leaf extract induces osteogenic-like differentiation of human osteosarcoma SaOS2 cells. J Tradit Complement Med 2022;12(6):608–18.
[76] Kim HJ, Jeong JW, Park C, Choi YH, Hong SH. Naesohwangryeon-tang induced apoptosis and autophagy in A549 human lung cancer cells. J Pharmacopuncture 2019;22(4):269–78.
[77] Kim MS, Lee CW, Kim JH, Lee JC, An WG. Extract of *Rhus verniciflua* Stokes induces p53-mediated apoptosis in MCF-7 breast cancer cells. Evid Based Complement Alternat Med 2019;2019:9407340.
[78] Kocanci FG, Hamamcioglu B, Aslim B. The anti-AChE and anti-proliferative activities of *Glaucium acutidentatum* and *Glaucium corniculatum* alkaloid extracts. J Appl Pharm Sci 2017;7(8):191–200.
[79] Kubatka P, Kello M, Kajo K, Samec M, Jasek K, Vybohova D, et al. Chemopreventive and therapeutic efficacy of *Cinnamomum zeylanicum* L. bark in experimental breast carcinoma: mechanistic in vivo and in vitro analyses. Molecules 2020;25(6):1399.
[80] Lachkar N, Lamchouri F, Toufik H. In vitro antimitotic and hypoglycemic effect study and acute toxicity assessment of the aqueous and organic extracts of *Chamaerops humilis* L. var. argentea Andre. Biomed Res Int 2022;2022:4303506.
[81] Lee HS, Lee IH, Kang K, Park SI, Jung M, Yang SG, et al. A comprehensive understanding of the anticancer mechanisms of FDY2004 against cervical cancer based on network pharmacology. Nat Prod Commun 2021;16(3). https://doi.org/10.1177/1934578X211004304.
[82] Lee HS, Lee IH, Kang K, Park SI, Kwon TW, Lee DY. A network pharmacology analysis of the systems-perspective anticancer mechanisms of the herbal drug FDY2004 for breast cancer. Nat Prod Commun 2021;16(10). https://doi.org/10.1177/1934578X211049133.
[83] Lee HS, Lee IH, Kang K, Park SI, Jung M, Yang SG, et al. A network pharmacology perspective investigation of the pharmacological mechanisms of the herbal drug FDY003 in gastric cancer. Nat Prod Commun 2022;17(1). https://doi.org/10.1177/1934578X211073030.
[84] Lee HS, Lee IH, Park SI, Jung M, Yang SG, Kwon TW, et al. Investigation of anti-liver cancer activity of the herbal drug FDY003 using network pharmacology. Evid Based Complement Alternat Med 2022;2022:5765233.
[85] Li H, Huang N, Zhu W, Wu J, Yang X, Teng W, et al. Modulation the crosstalk between tumor-associated macrophages and non-small cell lung cancer to inhibit tumor migration and invasion by ginsenoside Rh2. BMC Cancer 2018;18(1):579.
[86] Li P, Shi Y, Zhao B, Xu W, Xu Z, Zhang J, et al. Pharmacological evaluation and mechanistic study of compound Xishu Granule in hepatocellular carcinoma. J Tradit Chin Med Sci 2020;7(3):255–64.
[87] Li S, Li H, Yin D, Xue X, Chen X, Li X, et al. Effect of gigantol on the proliferation of hepatocellular carcinoma cells tested by a network-based pharmacological approach and experiments. Front Biosci (Landmark Ed) 2022;27(1):25.
[88] Liu H, Liao W, Fan L, Zheng Z, Liu D, Zhang QW, et al. Ethanol extract of *Ophiorrhiza pumila* suppresses liver cancer cell proliferation and migration. Chin Med 2020;15:11.
[89] Liu J, Chen Y, Cao Z, Guan B, Peng J, Chen Y, et al. Babao Dan inhibits the migration and invasion of gastric cancer cells by suppressing epithelial-mesenchymal transition through the TGF-β/Smad pathway. J Int Med Res 2020;48(6):300060520925598.
[90] Liu L, Xu Z, Yu B, Tao L, Cao Y. Berbamine inhibits cell proliferation and migration and induces cell death of lung cancer cells via regulating c-Maf, PI3K/Akt, and MDM2-P53 pathways. Evid Based Complement Alternat Med 2021;2021:5517143.
[91] Liu Q, Shen JM, Hong HJ, Yang Q, Liu W, Guan Z, et al. Cell metabolomics study on the anticancer effects of *Ophiopogon japonicus* against lung cancer cells using UHPLC/Q-TOF-MS analysis. Front Pharmacol 2022;13:1017830.
[92] Luan Y, Li Y, Zhu L, Zheng S, Mao D, Chen Z, et al. *Codonopis bulleynana* Forest ex Diels inhibits autophagy and induces apoptosis of colon cancer cells by activating the NF-κB signaling pathway. Int J Mol Med 2018;41(3):1305–14.
[93] Luce A, Lama S, Millan PC, Itro A, Sangiovanni A, Caputo C, et al. Polydatin induces differentiation and radiation sensitivity in human osteosarcoma cells and parallel secretion through lipid metabolite secretion. Oxid Med Cell Longev 2021;2021:3337013.
[94] Lv X, Sun J, Hu L, Qian Y, Fan C, Tian N. Curcumol inhibits malignant biological behaviors and TMZ-resistance in glioma cells by inhibiting long noncoding RNA FOXD2-As1-promoted EZH2 activation. Aging (Albany NY) 2021;13 (21):24101–16.
[95] Lv Y, Hou X, Zhang Q, Li R, Xu L, Chen Y, et al. Untargeted metabolomics study of the in vitro anti-hepatoma effect of saikosaponin D in combination with NRP-1 knockdown. Molecules 2019;24(7):1423.
[96] Ma ZL, Zhang BJ, Wang DT, Li X, Wei JL, Zhao BT, et al. Tanshinones suppress AURKA through up-regulation of miR-32 expression in non-small cell lung cancer. Oncotarget 2015;6(24):20111–20.
[97] Machana S, Weerapreeyakul N, Barusrux S. Anticancer effect of the extracts from Polyalthia evecta against human hepatoma cell line (HepG2). Asian Pac J Trop Biomed 2012;2(5):368–74.
[98] Magcwebeba TU, Swart P, Swanevelder S, Joubert E, Gelderblom WCA. In vitro chemopreventive properties of green tea, rooibos and honeybush extracts in skin cells. Molecules 2016;21(12):1622.
[99] Meng J, Su R, Wang L, Yuan B, Li L. Inhibitory effect and mechanism of action (MOA) of hirsutine on the proliferation of T-cell leukemia Jurkat clone E6–1 cells. PeerJ 2021;9:e10692.
[100] Nordin ML, Norpi ASM, Ng PY, Yusoff K, Abu N, Lim KP, et al. HER2/neu-based peptide vaccination-pulsed with B-cell epitope induced efficient prophylactic and therapeutic antitumor activities in TUBO breast cancer mice model. Cancers (Basel) 2021;13(19):4958.
[101] Ou A, Zhao X, Lu Z. Autophagy is involved in *Ficus carica* fruit extract-induced anti-tumor effects on pancreatic cancer. Biomed Pharmacother 2022;150:112966.
[102] Pak PJ, Lee DG, Sung JH, Jung SH, Han TY, Park SH, et al. Synergistic effect of the herbal mixture C5E on gemcitabine treatment in PANC-1 cells. Mol Med Rep 2021;23(5):315.
[103] Pan X, Hou X, Zhang F, Tang P, Wan W, Su Z, et al. *Gnetum montanum* extract induces apoptosis by inhibiting the activation of AKT in SW480 human colon cancer cells. Pharm Biol 2022;60(1):915–30.
[104] Park H, Song JH, Hwang B, Moon B, Yun SJ, Kim WJ, et al. Evaluation of the in vitro and in vivo antitumor efficacy of peanut sprout extracts cultivated with fermented sawdust medium against bladder cancer. Appl Sci 2020;10 (23):8758.
[105] Park SM, Jeon SK, Kim OH, Ahn JY, Kim CH, Park SD, et al. Anti-tumor effects of the ethanolic extract of *Trichosanthes kirilowii* seeds in colorectal cancer. Chin Med 2019;14:43.
[106] Park YG, Choi J, Jung HK, Kim B, Kim C, Park SY, et al. Baicalein inhibits tumor progression by inhibiting tumor cell growth and tumor angiogenesis. Oncol Rep 2017;38(5):3011–8.
[107] Pipatrattanaseree W, Itharat A, Mukkasombut N, Saesiw U. Potential in vitro anti-allergic, anti-inflammatory and cytotoxic activities of ethanolic extract of *Baliospermum montanum* root, its major components and a validated HPLC method. BMC Complement Altern Med 2019;19(1):45.
[108] Prabhu KS, Siveen KS, Kuttikrishnan S, Iskandarani A, Tsakou M, Achkar IW, et al. Targeting of X-linked inhibitor of apoptosis protein and PI3-kinase/AKT signaling by embelin suppresses growth of leukemic cells. PLoS One 2017;12 (7):e0180895.
[109] Qu Y, Cong P, Lin C, Deng Y, Li-Ling J, Zhang M. Inhibition of paclitaxel resistance and apoptosis induction by cucurbitacin B in ovarian carcinoma cells. Oncol Lett 2017;14(1):145–52.
[110] Rahman EY, Kusworini K, Ali M, Purnomo BB, Kania N. The cytotoxic effect of *Eurycoma longifolia* jack root extract on the prostate adenocarcinoma PC-3 cells through apoptosis enhancement. Open Access Maced J Med Sci 2020;8 (A):317–22.
[111] Rendón JP, Cañas AI, Correa E, Bedoya-Betancur V, Osorio M, Castro C, et al. Evaluation of the effects of genistein in vitro as a chemopreventive agent for colorectal cancer—strategy to improve its efficiency when administered orally. Molecules 2022;27(20):7042.
[112] Roy S, Mohammad T, Gupta P, Dahiya R, Parveen S, Luqman S, et al. Discovery of harmaline as a potent inhibitor of sphingosine kinase-1: a chemopreventive role in lung cancer. ACS Omega 2020;5(34):21550–60.
[113] Sayyadi M, Moradabadi A, Noroozi-Aghideh A, Yazdanian M. Effect of gaillardin on proliferation and apoptosis of acute promyelocytic leukemia cell lines, nb4 as cancer treatment. Biointerface Res Appl Chem 2021;11 (1):7445–52.
[114] Shao L, Zhou Z, Cai Y, Castro P, Dakhov O, Shi P, et al. Celastrol suppresses tumor cell growth through targeting an AR-ERG-NF-κB pathway in TMPRSS2/ERG fusion gene expressing prostate cancer. PLoS One 2013;8 (3):e58391.
[115] Shi X, Zhao W, Yang Y, Wu S, Lv B. Salidroside could enhance the cytotoxic effect of L-OHP on colorectal cancer cells. Mol Med Rep 2018;17(1):51–8.
[116] Sun W, Zhang Y, Ren X, Cui L, Wang J, Ni X. In silico studies, biological activities, and anti-human pancreatic cancer potential of 6-hydroxy-4-methylcoumarin and 2,5-dihydroxyacetophenone as flavonoid compounds. J Oleo Sci 2022;71(6):853–61.
[117] Tang Q, Li X, Chen Y, Long S, Yu Y, Sheng H, et al. Solamargine inhibits the growth of hepatocellular carcinoma and enhances the anticancer effect of sorafenib by regulating HOTTIP-TUG1/miR-4726-5p/MUC1 pathway. Mol Carcinog 2022;61(4):417–32.
[118] Ullah MF, Ahmad A, Bhat SH, Abuduhier FM, Mustafa SK, Al-Qirim T. Functional profiling of *Achillea fragrantissima* (a perennial edible herb) against human cancer cells and potential nutraceutical impact in neutralizing cell proliferation by interfering with VEGF and NF-κB signaling pathways. Ital J Food Sci 2022;34(3):35–47.
[119] Wang C, Li P, Peng Y, Liu R, Wu X, Tan S, et al. Integrative RNA-Seq and ATAC-Seq analysis reveals the migration-associated genes involved in antitumor effects of herbal medicine Feiyanning on lung cancer cells. Front Genet 2021;12:799099.
[120] Wihadmadyatami H, Hening P, Kustiati U, Kusindarta DL, Triyono T, Supriatno S. *Ocimum sanctum* Linn. ethanolic extract inhibits angiogenesis in human lung adenocarcinoma (a549) cells. Vet. WORLD 2020;13(9):2028–32.

[121] Xiao Y, Duan Y, Wang Y, Yin X. Resveratrol suppresses malignant progression of oral squamous cell carcinoma cells by inducing the ZNF750/RAC1 signaling pathway. Bioengineered 2021;12(1):2863–73.
[122] Zhang C, Li Z, Wang J, Jiang X, Xia M, Wang J, et al. Ethanol extracts of *Solanum lyratum* Thunb regulate ovarian cancer cell proliferation, apoptosis, and epithelial-to-mesenchymal transition (EMT) via the ROS-mediated p53 pathway. J Immunol Res 2021;2021:5569354.
[123] Zhang W, Zhang Q, Jiang Y, Li F, Xin H. Effects of ophiopogonin B on the proliferation and apoptosis of SGC-7901 human gastric cancer cells. Mol Med Rep 2016;13(6):4981–6.
[124] Zhang Y, Fox JT, Park YU, Elliott G, Rai G, Cai M, et al. A novel chemotherapeutic agent to treat tumors with DNA mismatch repair deficiencies. Cancer Res 2016;76(14):4183–91.
[125] Zheng YM, Lu AX, Shen JZ, Kwok AHY, Ho WS. Imperatorin exhibits anticancer activities in human colon cancer cells via the caspase cascade. Oncol Rep 2016;35(4):1995–2002.
[126] Zhou J, Xie X, Tang H, Peng C, Peng F. The bioactivities of sclareol: a mini review. Front Pharmacol 2022;13:1014105.
[127] Chen T, Yuan SJ, Wang J, Hu W. Mechanism of QHF-cisplatin against hepatocellular carcinoma in a mouse model. World J Gastroenterol 2015;21(35):10126–36.
[128] Chen XZ, Zhang WK, Tang HB, Li XJ, Tian GH, Shang HC, et al. The ethanol supernatant extracts of Liushenwan could alleviate nanodiethylnitrosamine-induced liver cancer in mice. Can J Gastroenterol Hepatol 2018;2018:6934809.
[129] Dai HY, Wang P, Feng LY, Liu LM, Meng ZQ, Zhu XY, et al. The molecular mechanisms of traditional Chinese medicine ZHENG syndromes on pancreatic tumor growth. Integr Cancer Ther 2010;9(3):291–7.
[130] Guo W, Cao P, Wang X, Hu M, Feng Y. Medicinal plants for the treatment of gastrointestinal cancers from the metabolomics perspective. Front Pharmacol 2022;13:909755.
[131] Li M, Yue GGL, Luo L, Tsui SKW, Fung KP, Ng SSM, et al. Turmeric is therapeutic in vivo on patient-derived colorectal cancer xenografts: inhibition of growth, metastasis, and tumor recurrence. Front Oncol 2021;10:574827.
[132] Lin Q, Qu M, Patra HK, He S, Wang L, Hu X, et al. Mechanistic and therapeutic study of novel anti-tumor function of natural compound imperialine for treating non-small cell lung cancer. J Ethnopharmacol 2020;247:112283.
[133] Luo Q, Huang S, Zhao L, Liu J, Ma Q, Wang Y, et al. Chang Qing formula ameliorates colitis-associated colorectal cancer via suppressing IL-17/NF-κB/STAT3 pathway in mice as revealed by network pharmacology study. Front Pharmacol 2022;13:893231.
[134] Ren F, Zhang Y, Qin Y, Shang J, Wang Y, Wei P, et al. Taraxasterol prompted the anti-tumor effect in mice burden hepatocellular carcinoma by regulating T lymphocytes. Cell Death Discov 2022;8(1):264.
[135] Sui H, Zhang L, Gu K, Chai N, Ji Q, Zhou L, et al. YYFZBJS ameliorates colorectal cancer progression in ApcMin/+ mice by remodeling gut microbiota and inhibiting regulatory T-cell generation. Cell Commun Signal 2020;18(1):113.
[136] Sun MY, Sun J, Tao J, Yuan YX, Ni ZH, Tang QF. Zuo Jin Wan reverses DDP resistance in gastric cancer through ROCK/PTEN/PI3K signaling pathway. Evid Based Complement Alternat Med 2018;2018:427856.
[137] Takaku S, Shimizu M, Takahashi H. Japanese Kampo medicine Juzentaihoto enhances antitumor immunity in *CD1d*$^{-/-}$ mice lacking NKT cells. Integr Cancer Ther 2020;19:1534735419900798.
[138] Wang N, Zheng Y, Gu J, Cai Y, Wang S, Zhang F, et al. Network-pharmacology-based validation of TAMS/CXCL-1 as key mediator of XIAOPI formula preventing breast cancer development and metastasis. Sci Rep 2017;7(1):14513.
[139] Wang S, Wu C, Li Y, Ye B, Wang S, Li G, et al. Analysis of the anti-tumor effect of Xuefu Zhuyu decoction based on network pharmacology and experimental verification in *Drosophila*. Front Pharmacol 2022;13 922457.
[140] Yang T, Chen Y, Xu J, Li J, Liu H, Liu N. Bioinformatics screening the novel and promising targets of curcumin in hepatocellular carcinoma chemotherapy and prognosis. BMC Complement Med Ther 2022;22(1):21.
[141] Zeng C, Zou T, Qu J, Chen X, Zhang S, Lin Z. Cyclovirobuxine D induced-mitophagy through the p65/BNIP3/LC3 axis potentiates its apoptosis-inducing effects in lung cancer cells. Int J Mol Sci 2021;22(11):5820.
[142] Zhang M, Du H, Wang L, Yue Y, Zhang P, Huang Z, et al. Thymoquinone suppresses invasion and metastasis in bladder cancer cells by reversing EMT through the Wnt/β-catenin signaling pathway. Chem Biol Interact 2020;320:109022.
[143] Zhang R, Wang Z, You W, Zhou F, Guo Z, Qian K, et al. Suppressive effects of plumbagin on the growth of human bladder cancer cells via PI3K/AKT/mTOR signaling pathways and EMT. Cancer Cell Int 2020;20:520.
[144] Zhang T, Li J, Yin F, Lin B, Wang Z, Xu J, et al. Toosendanin demonstrates promising antitumor efficacy in osteosarcoma by targeting STAT3. Oncogene 2017;36(47):6627–39.
[145] Zhang Y, Wang H, Mao X, Guo Q, Li W, Wang X, et al. A novel gene-expression-signature-based model for prediction of response to tripterysium glycosides tablet for rheumatoid arthritis patients. J Transl Med 2018;16(1):187.
[146] Zhao Y, Chen R, Wang Y, Qing C, Wang W, Yang Y. In vitro and in vivo efficacy studies of *Lavender angustifolia* essential oil and its active constituents on the proliferation of human prostate cancer. Integr Cancer Ther 2017;16(2):215–26.
[147] Zhao YY, Yang YQ, Sheng HH, Tang Q, Han L, Wang SM, et al. GPX4 plays a crucial role in Fuzheng Kang'ai decoction-induced non-small cell lung cancer cell ferroptosis. Front Pharmacol 2022;13:851680.
[148] Zheng Y, Wang N, Wang S, Yang B, Situ H, Zhong L, et al. XIAOPI formula inhibits the pre-metastatic niche formation in breast cancer via suppressing TAMs/CXCL1 signaling. Cell Commun Signal 2020;18(1):48.
[149] Chae J, Lee S, Lee S. Potential efficacy of allergen removed *Rhus verniciflua* Stokes extract to maintain progression-free survival of patients with advanced hepatobiliary cancer. Explore (NY) 2018;14(4):300–4.
[150] Lee DH, Kim SS, Seong S, Kim N, Han JB. Korean medicine therapy as a substitute for chemotherapy for metastatic breast cancer: a case report. Case Rep Oncol 2015;8(1):64–71.
[151] Tan J, Qin X, Liu B, Mo H, Wu Z, Yuan Z. Integrative findings indicate anti-tumor biotargets and molecular mechanisms of calycosin against osteosarcoma. Biomed Pharmacother 2020;126:110096.
[152] Tseng ST, Liu CT, Wu BY, Hung YC, Lin CH, Hsu CY, et al. Chinese herbal products for nasopharyngeal carcinoma: a population-based registry study. Eur J Integr Med 2019;31:100979.
[153] Yutani S, Komatsu N, Matsueda S, Yoshitomi M, Shirahama T, Yamada A, et al. Juzentaihoto failed to augment antigen-specific immunity but prevented deterioration of patients' conditions in advanced pancreatic cancer under personalized peptide vaccine. Evid Based Complement Alternat Med 2013;2013:981717.
[154] Pramodh S, Raina R, Hussain A, Bagabir SA, Haque S, Raza ST, et al. Luteolin causes 5'CpG demethylation of the promoters of TSGs and modulates the aberrant histone modifications, restoring the expression of TSGs in human cancer cells. Int J Mol Sci 2022;23(7):4067.
[155] Bi L, Yan X, Chen W, Gao J, Qian L, Qiu S. Antihepatocellular carcinoma potential of tetramethylpyrazine induces cell cycle modulation and mitochondrial-dependent apoptosis: regulation of p53 signaling pathway in HepG2 cells in vitro. Integr Cancer Ther 2016;15(2):226–36.
[156] Haron NH, Toha ZM, Abas R, Hamdan MR, Azman N, Khairuddean M, et al. In vitro cytotoxic activity of *Clinacanthus nutans* leaf extracts against HeLa cells. Asian Pac J Cancer Prev 2019;20(2):601–9.
[157] Hasan AEZ, Julistiono H, Bermawie N, Riyanti EI, Arifni FR. Soursop leaves (*Annona muricata* L.) endophytic fungi anticancer activity against HeLa cells. Saudi J Biol Sci 2022;29(8):103354.
[158] Zhang C, Quan Y, Bai Y, Yang L, Yang Y. The effect and apoptosis mechanism of 6-methoxyflavone in HeLa cells. Biomarkers 2022;27(5):470–82.
[159] Saremi S, Kolahi M, Tabandeh MR, Hashemitabar M. Induction of apoptosis and suppression of Ras gene expression in MCF human breast cancer cells. J Cancer Res Ther 2022;18(4):1052–60.
[160] Zhang Y, Guo S, Fang J, Peng B, Zhang Y, Cao T. Tanshinone IIA inhibits cell proliferation and tumor growth by downregulating STAT3 in human gastric cancer. Exp Ther Med 2018;16(4):2931–7.
[161] Zoi V, Galani V, Lianos GD, Voulgaris S, Kyritsis AP, Alexiou GA. The role of curcumin in cancer treatment. Biomedicines 2021;9(9):1086.
[162] Pucci B, Kasten M, Giordano A. Cell cycle and apoptosis. Neoplasia 2000;2(4):291–9.
[163] Li K, Liu J, Wu L, Xiao Y, Li J, Du H, et al. Genomic correlates of programmed cell death ligand 1 (PD-L1) expression in Chinese lung adenocarcinoma patients. Cancer Cell Int 2022;22(1):138.
[164] Lichota A, Gwozdzinski K. Anticancer activity of natural compounds from plant and marine environment. Int J Mol Sci 2018;19(11):3533.
[165] Liu HC, Ku MK, Chung FY, Lin CC, Lin SR. Effectiveness of great burdock essence compounds in the adjuvant treatment of gastric ulcer patients infected with *Helicobacter pylori*. Genomic Med Biomark Health Sci 2012;4(3):81–4.
[166] Koga N, Moriya F, Waki K, Yamada A, Itoh K, Noguchi M. Evaluation of immunological efficacy of Japanese herbal medicine, hochu-ekki-to and keishi-bukuryo-gan, in patients with castration-resistant prostate cancer under personalized peptide vaccination. J Clin Oncol 2017;35(15 suppl):e16584.
[167] Josefson D. St John's wort interferes with chemotherapy, study shows. BMJ 2002;325(7362):460.
[168] Kwon SB, Kim MJ, Yang JM, Lee HP, Hong JT, Jeong HS, et al. *Cudrania tricuspidata* stem extract induces apoptosis via the extrinsic pathway in SiHa cervical cancer cells. PLoS One 2016;11(3):e0150235.
[169] Ruthrotha Selvi B, Pradhan SK, Shandilya J, Das C, Sailaja BS, Shankar GN, et al. Sanguinarine interacts with chromatin, modulates epigenetic modifications, and transcription in the context of chromatin. Chem Biol 2009;16(2):203–16.