

## The use of phytotherapy in hepatocellular carcinoma – a systematic review

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### Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignant tumours and the second most frequent cause of cancer-related death worldwide. The aim of this review is to identify whether phytotherapy has an effect over the treatment of HCC or if it is suitable as a combination with chemotherapy. A systematic review was performed in order to offer current information over the use of phytotherapy in HCC. We conducted an electronic search of articles published in English in peer reviewed journals between 2012-2022. After keywords were associated, 302 articles were found. After the exclusion of articles which did not meet the inclusion criteria, there were 77 articles eligible for abstract evaluation. The following were discarded: two case report, one systematic review, 36 *in vitro* studies and nine studies which discussed other pathologies or with no regard to phytotherapy. The remaining articles encompassed 27 *in vivo* studies of phytotherapy in hepatocellular carcinoma and two randomized control trials. This selection process is illustrated in the Prisma Flow Diagram. Amongst the evaluated articles, two of them researched the effect of phytotherapy over human subjects in two randomized control trials, while the others illustrated the outcomes of phytotherapy over hepatocellular carcinoma cells and murine specimens. To sum up, phytotherapy has proven its usefulness in hepatocellular carcinoma, especially throughout the following mechanisms: anti-inflammatory effect, suppressing malignant cell proliferation, inhibiting angiogenesis, stimulating apoptosis, and even sensitizing cells to chemotherapy.

**Keywords:** hepatocellular carcinoma; medicinal herbs; traditional Chinese medicine; traditional Korean medicine

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## Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumours and the second most frequent cause of cancer-related death worldwide. Hepatocellular carcinoma acts as the most common type of primary liver neoplasm, the majority of cases are developing in the context of chronic liver damage and inflammation, especially due to chronic hepatitis B virus or hepatitis C virus infections and chronic alcohol intake. The incidence of nonviral HCC is increasing, notably in developed countries. Non-alcoholic fatty liver disease or metabolic associated fatty liver disease leads to non-alcoholic steatohepatitis (NASH), resulting in liver cirrhosis and lastly, in HCC (Boyer *et al.*, 2012; Tang *et al.*, 2017).

Early-stage clinical symptoms of this pathology are nonspecific; therefore, patients were usually diagnosed at an intermediate or advanced stage. Latter advances in early diagnosis and treatment have improved the short-term prognosis of patients with HCC, but there are still limited treatment options available. At the present moment the main therapies for HCC encompass liver resection (LR), radiofrequency ablation (RFA), liver transplantation (LT), trans arterial chemoembolization (TACE), Sorafenib and also symptomatic treatment for stage D, according to Barcelona Clinic Liver Cancer staging system (BCLC) (Reig *et al.*, 2022). Surgical resection is an optimal option for very early stage or early-stage HCC patients with preserved liver function, whilst patients who present with severe liver dysfunction may be considered for LT. The European Association for the Study of the Liver (EASL) Guidelines provides recommendations regarding liver transplant for BCLC 0, A and even the first subgroup of B stage patients, laying out specific criteria for each category. In spite of these treatment possibilities, early-stage diagnosis of HCC is difficult and it has a poor prognosis, thus explaining the extensive research for new methods of diagnosing and treating this pathology (Bishayee *et al.*, 2012; Zamora-Valdes *et al.*, 2017; Reig *et al.*, 2022).

In view of the above-mentioned treatment paths, there is a critical need for searching for alternative approaches, as the use of phytochemicals obtained from dietary sources which offers a preventive and therapeutic approach over HCC (Bishayee *et al.*, 2012; Yang *et al.*, 2022). Phytochemicals have antioxidant, anti-inflammatory and anti-proliferative effects, which can combat the oxidative stress and inflammation involved in liver cancer (Bishayee *et al.*, 2012; Yang *et al.*, 2022). There are many herbal medicines which have proven their efficiency as anti-inflammatory agents and therefore have the capacity of suppressing the development of hepatocellular carcinoma. Clinical trials and reviews are warranted in order to explore the effectiveness of herbal medicine in both prevention and treatment of HCC (Rino *et al.*, 2015; Farazuddin *et al.*, 2019).

Traditional Chinese Medicine (TCM) possesses curative effects in hepatocellular carcinoma. As for example Fuzheng Jiedu Xiaoji formulation (FZJDXJ) is composed of modified Chinese classical blends, such as *Angelicae sinensis* decoction or Dang-gui-bu-xue-tang (DGBX) and Si-jun-zi decoction (SJZ), *Paris polyphylla* Sm and *Pinellia ternata* Makino, commonly prescribed for hepatoma treatment in Beijing Ditan Hospital. These mixtures inhibit apoptosis induced by Ang-II, have antioxidant effects, induce cell cycle arrest in human gastric cancer, and HepG2 cell apoptosis, especially *Pinellia ternata* Makino (Yang *et al.*, 2021).

Traditional Korean Medicine (TKM) carries out benefits for patients with HCC by improving their quality of life and maintaining tumour size. Lately, TKM has been highly used in cancer treatment. Jang *et al.* (2018) published a case report describing a 62-years old Korean woman with HCC and lung metastases, who went under associated treatment with TKM and Sorafenib after going under surgery and six cycles of adjuvant chemotherapy and treated afterwards only with Sorafenib, but with no regression and also experiencing most of the side effects of the treatment. Following 8 weeks of TKM treatment, the size of the metastatic nodules decreased and the tolerance for Sorafenib's side effects improved, thus endorsing the advantages of using TKM in combination with standard treatment for HCC and extrahepatic metastasis (Jang *et al.*, 2018).

Newly identified or recurrent HCC patients, who cannot meet criteria for curative therapies, are in need of further adjuvant methods of treatment. Western medicine has its demonstrated advantages over treating

subjects who suffer from hepatocellular carcinoma, but still the five-year survival rate is somber. Chinese Herbal Medicine (CHM) for example, has been used in the treatment of HCC patients for many years, and have been proven to be an efficacious and safe option for cirrhosis and chronic hepatitis. Moreover, there is a lot of experience in using CHM in preventing and treating HCC, proven in a series of *in vitro* studies. For this reason, we propose a systematic review of the existing literature regarding the efficacy of herbal medicine in hepatocellular carcinoma, in both *in vitro* and *in vivo* studies (Bishayee *et al.*, 2012; Xu *et al.*, 2016; Zamora-Valdes *et al.*, 2017; Yang *et al.*, 2021; Reig *et al.*, 2022).

#### *Aim of the review*

The aim of this review is to identify whether herbal medicine has an effect over the treatment of hepatocellular carcinoma or if it is suitable as a combination with the standardized treatment used for this pathology.

#### Research questions:

1. Which is/are the herbal medication/ herbs used in the treatment of hepatocellular carcinoma?
2. What effects does herbal medicine have over hepatocellular carcinoma cells?

### **Materials and Methods**

A systematic review was performed in order to offer current information over the use of phytotherapy in hepatocellular carcinoma.

#### *Search strategy:*

We conducted an electronic research of articles published in English in peer reviewed journals between 2012-2022. The research process took place in October 2022. A combination of the following search terms was used: phytotherapy, hepatocellular carcinoma, herbal medicine, and *in vivo* studies. The search strategy was limited to the following electronic databases: PubMed, PsycINFO, CINAHL.

#### *Inclusion criteria*

This research includes all the articles which show the use of at least one herbal substance/ formulation in hepatocellular carcinoma studies.

#### *Exclusion criteria*

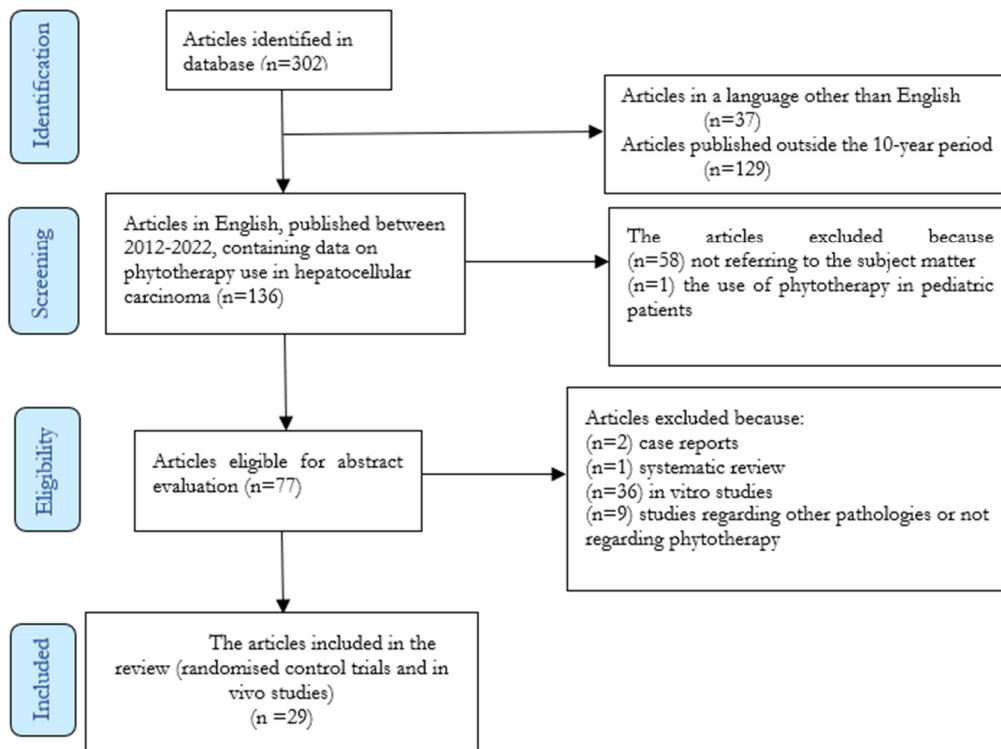
The articles excluded from the present research were published earlier than 2012, in other languages than English, not referring to the subject, studies referring to paediatric patients or studies which have not used at least one herbal substance or medicine in order to treat or influence the prognosis of hepatocellular carcinoma. Literature reviews were as well discarded.

#### *Data extraction*

The abstracts of these articles were read to detect duplicates and identify articles for full copy retrieval. The articles were then reviewed independently by different members of the team. In addition, the medicinal herbs were categorized according to their clinical or molecular implications. The process for this entailed: identifying the herbs referred to by each article and determining the effects of these in hepatocellular carcinoma. After the initial data collection phase, the reviewers' reports were independently cross-checked and items for clarification were discussed and resolved at a face-to-face meeting.

## Results

After keywords were associated, 302 articles were found. Articles published in other language than English were excluded (n=37), as well regarding articles issued outside a 10-year period (n=129). Afterwards, articles which were not referring to the subject matter (n=58) or concerning paediatric patients (n=1) were excluded. There were 77 articles eligible for abstract evaluation, from which the following were discarded: two case reports, one systematic review, 36 *in vitro* studies and nine studies which discussed other pathologies or with no regard to phytotherapy. The remaining 29 articles encompassed 27 *in vivo* studies of phytotherapy in hepatocellular carcinoma and two randomized control trials. These articles were included in the final analysis. This selection process is illustrated in the Prisma Flow Diagram (Figure 1).



**Figure 1.** Prisma Flow Diagram for the selected studies included in the systematic review (records identified from PubMed, Embase and Cochrane database)

The list of articles and associated selected information from the data extraction process is presented in Table 1.

**Table 1.** Author name and year of publication, title of the article from which we extracted information, botanical substance, the aim of the study presented in the articles and the effects of the plants stated before

Author name, year	Title of article	Botanical substance/ name of plants	The aim of study	Effects
Yang <i>et al.</i> , 2021 [1]	Fuzheng Jiedu Xiaoji formulation (FZJDXJ) inhibits hepatocellular carcinoma progression in patients by targeting the AKT/ CyclinD1 /p21/p27 pathway	FZJDXJ contains: <i>Codonopsis pilosula</i> <i>Astragalus mongholicus</i> <i>Astratylodes membranaceus</i> <i>Poria cocos</i> <i>Adenophora stricta</i> <i>Radix ophiopogonis</i> <i>Angelica sinensis</i> <i>Rehmannia glutinosa</i> <i>Paris polyphylla</i> <i>Curcuma phaeocaulis</i> <i>Pinellia ternata</i>	To explore the effectiveness of FZJDXJ in HCC A randomized controlled clinical trial 1:1	<ul style="list-style-type: none"> <li>✓ Prolonged OS and reduced the overall mortality rate in patients especially with BCLC A and B stage</li> <li>✓ Reduced the incidence of HCC complications including abdominal infection, hepatic encephalopathy, multiple metastases, and rupture and hemorrhage of HCC</li> <li>✓ For patients with BCLC stage B, had a significant effect on PFS extension</li> <li>✓ In combination therapy with TACE inhibited HCC tumor progression and proliferation</li> </ul>
Wang <i>et al.</i> , 2021 [2]	Calundulose E (CE) inhibits HepG2 cell proliferation and migration via p38/JNK-HMGB1 signaling axis	CE is the major natural pentacyclic triterpenoid saponin <i>Aralia</i> plants such as <i>Panax japonica</i> and <i>Aralia elata</i>	To explore the effects of CE on HepG2 cell proliferation and migration	<ul style="list-style-type: none"> <li>✓ Anti-inflammatory effect</li> <li>✓ Significantly suppressed Hep G2 cell proliferation and migration in a dose dependent manner by activating p38 and JNK signaling pathways</li> <li>✓ Reduced the expression of Cyclin D1, E, MMP-2, MMP-9 and EMT dose dependently</li> </ul>
El-Saied <i>et al.</i> , 2018 [3]	<i>Rheum palmatum</i> root (RPR) extract inhibits hepatocellular carcinoma in rats treated with diethylnitrosamine	RPR (Chinese rhubarb) – 16 compounds to anthraquinones, flavonoids, and tannins	To investigate the potential anticancer properties of RPR against HCC-induced in adult male rats	<ul style="list-style-type: none"> <li>✓ Exhibited antimutagenic activity</li> <li>✓ Decreased the numbers and areas of putative foci</li> <li>✓ The potential anticancer properties</li> <li>✓ Beneficial effect in prevention of HCC</li> </ul>
Song <i>et al.</i> , 2021 [4]	Ganoderma lucidum spore polysaccharide (GLSP) inhibits the growth of hepatocellular carcinoma cells by altering macrophage polarity and induction of apoptosis	<i>Ganoderma lucidum</i> spore polysaccharide (GLSP)	To reveal the specific biological mechanism of GLSP to enhance immunity and to inhibit the growth of hepatocellular carcinoma cells	<ul style="list-style-type: none"> <li>✓ Promoting the secretion of various inflammatory factors and cytokines</li> <li>✓ Reshapes the tumor microenvironment by activating macrophages</li> <li>✓ Regulating the polarization of macrophages</li> <li>✓ Can block HCC tumor cells</li> </ul>
Farazuddin <i>et al.</i> , 2014 [5]	Chemotherapeutic potential of curcumin-bearing microcells against hepatocellular carcinoma in model animals	<i>Curcuma longa</i>	To assess the anticancer efficacy of curcumin against DEN-induced HCC in model animals	<ul style="list-style-type: none"> <li>✓ Demonstrated that curcumin-bearing microcells and PLGA microparticles were non-toxic to living cells</li> <li>✓ PLGA microparticles reduced liver enzymes</li> <li>✓ Reduced animal mortality</li> <li>✓ Exhibited notable antiproliferative activity toward HepG2 cells</li> <li>✓ Reduced expression inflammatory cytokines, including TNF-<math>\alpha</math></li> </ul>
Sadek <i>et al.</i> , 2017 [6]	The chemo-prophylactic efficacy of an ethanol <i>Moringa oleifera</i> leaf extract (MOLEE) against hepatocellular carcinoma in rats	<i>Moringa oleifera</i> leaf extract	To assess the chemo-prophylactic proficiency and other likely activities of MOLEE against DEN-induced HCC	<ul style="list-style-type: none"> <li>✓ MOLEE contains fundamental antioxidant and phenolic compounds that ensure intensification against oxidative changes</li> <li>✓ Decreased AFP and CEA levels</li> <li>✓ The expression of Bcl-2, Bcl-x1 and <math>\beta</math>-arrestin-2 were fundamentally diminished</li> <li>✓ Had chemoprotective effect against DEN-induced HCC</li> <li>✓ Improved the antioxidant activity and the enlistment of apoptosis</li> </ul>
Joseph <i>et al.</i> , 2013 [7]	Anti-cancerous efficacy of Ayurvedic milk extract of <i>Semecarpus anacardium</i> (SA) nuts on hepatocellular carcinoma in Wistar rats	<i>Semecarpus anacardium</i> (SA) (Varnish tree)	To determine the anti-cancerous efficacy of Ayurvedic preparation made of SA nuts	<ul style="list-style-type: none"> <li>✓ Reduced AST and ALT</li> <li>✓ Reduced the activity of AKP and GGT</li> <li>✓ The reduction in LDH activity owes to controlled glycolysis and renders the protection of the membrane integrity</li> <li>✓ Reduced the concentration of A2M indicating curing action</li> <li>✓ Flavonoids play a role in cancer prevention and treatment including free radical scavenging, antimutagenic and antiproliferative properties, and inhibitors of angiogenesis</li> </ul>
Song <i>et al.</i> , 2015 [8]	Protective Effects of Total Glucosides of Paeony (TGP) on N-nitroso-diethyl-amine-induced Hepatocellular Carcinoma in Rats via	TGP is extracted from the root of <i>Paeonia lactiflora</i> and contains hydroxyl-paeoniflorin, paeonin, albiflorin and benzoyl-paeoniflorin	To determine the anti-tumor effect of TGP against DEN-induced HCC in rats, and to find the related mechanism	<ul style="list-style-type: none"> <li>✓ Decreased the mortality rate and the number of nodules and index of liver and spleen</li> <li>✓ The hepatic pathological lesions were markedly improved</li> </ul>

	Down-regulation of Regulatory B Cells			<ul style="list-style-type: none"> <li>✓ The levels of AST, ALT, ALP and AFP were significantly decreased</li> <li>✓ The level of BAFF was decreased significantly positively correlated with IL-10</li> </ul>
<b>Wu <i>et al.</i>, 2018 [9]</b>	Effects of Dahuang zhechong pill (DHZCP) on doxorubicin-resistant SMMC-7721 xenografts in mice	DHZCP contains 12 traditional Chinese medicinal herbs: Eupolyphaga Seu Steleophaga, <i>Rheum palamatum</i> L., <i>Scutellaria baicalensis</i> Georgi, <i>Glycyrrhiza glabra</i> L., <i>Prunus persica</i> Batsch., <i>Armeniaca dasycarpa</i> Borkh., <i>Paeonia officinalis</i> L., <i>Rehmannia glutinosa</i> DC., <i>Toxicodendron vernicifluum</i> F.A. Barkley., 10 <i>Tabanus bivittatus</i> Matsumurea Hirudo, and <i>Holotrichia diomphalia</i> Bates	To investigate the ability of DHZCP to reverse doxorubicin resistance of SMMC-7721 cell in a xenograft mouse model, and to explore the underlying mechanism	<ul style="list-style-type: none"> <li>✓ Had significant anticancer effect</li> <li>✓ Reduced tumor size and weight</li> <li>✓ Enhanced apoptosis of hepatoma cells, and reversed the resistance to DOX</li> <li>✓ DHZCP reverses the drug resistance of hepatocellular carcinoma not only by direct regulation of apoptosis-related and angiogenesis-related protein expression, but also by inhibiting ATP energy metabolism, affecting various biological functions, increasing the accumulation of DOX in tumor tissue</li> </ul>
<b>Chang <i>et al.</i>, 2021 [10]</b>	Microalgal extract from thermotolerant <i>Coelastrrella</i> sp. F50 retards the liver tumor progression by targeting hepatic cancer stem cells	Thermotolerant green microalga <i>Coelastrrella</i> sp. F50	To elucidate the antitumor activity and mechanism of microalgal extract from thermotolerant <i>Coelastrrella</i> sp F50 (F50) in HCC	<ul style="list-style-type: none"> <li>✓ A relatively high dose of F50 extract was required to inhibit the invasiveness and anchorage-independent growth of HCC cells</li> <li>✓ Possesses a unique inhibitory function on hepatic cancer stemness</li> <li>✓ Decreased the protein level of CD133 and ABCG2 and contributed to F50-mediated CSCs suppression</li> <li>✓ AST/ALT ratio was significantly diminished</li> <li>✓ Induced apoptosis and inhibited proliferation and CD133/ABCG2 expression in hepatoma tissues</li> <li>✓ Repressed COX-2/prostaglandin E2 axis <i>in vitro</i> and <i>in vivo</i></li> </ul>
<b>Abdel-Hamid <i>et al.</i>, 2013 [11]</b>	Can methanolic extract of <i>Nigella sativa</i> (NS) seed affect glycoregulatory enzymes in experimental hepatocellular carcinoma?	<i>Nigella sativa</i> (NS)	To investigate the modulating role of NS on premalignant perturbations in three glycolregulatory enzymes in an experimental rat model of HCC	<ul style="list-style-type: none"> <li>✓ Significantly decreased the serum AFP level and the activities of HK, GAPDH and G6PD</li> <li>✓ Animals pre-treated with NS showed minimal changes in hepatocyte morphology and histology</li> </ul>
<b>Thoppil <i>et al.</i>, 2012 [12]</b>	Black currant anthocyanins abrogate oxidative stress through Nrf2- mediated antioxidant mechanisms in a rat model of hepatocellular carcinoma	Black currant skin extract (BCSE)	To elucidate the underlying antioxidant mechanism of black currant anthocyanins implicated in the previously observed chemo-preventive effects against experimental hepatocarcinogenesis	<ul style="list-style-type: none"> <li>✓ Upregulated the gene expression of several hepatic antioxidants and carcinogen detoxifying enzymes</li> <li>✓ Exert chemo-preventive actions by attenuating oxidative stress through activation of Nrf2 signaling pathway</li> </ul>
<b>Tang <i>et al.</i>, 2020 [13]</b>	Epigallocatechin gallate induces chemo-preventive effects on rats with diethylnitrosamine-induced liver cancer via inhibition of cell division cycle 25A	Epigallocatechin gallate (EGCG), the most active monomer in green tea	To investigate the anti-tumor and preventive effect of EGCG on HCC via the inhibition of CDC25A	<ul style="list-style-type: none"> <li>✓ Inhibited cell viability in human hepatoma cell lines</li> <li>✓ Caused cell cycle arrest in HepG2 cells</li> <li>✓ Induced CDC25A downregulation in HepG2 cells</li> <li>✓ Induced p21waf1/cip1 upregulation in HepG2 cells</li> <li>✓ Chemopreventive effects against HCC <i>in vivo</i></li> <li>✓ Reduced significantly GGT level</li> <li>✓ Reversed HCC-induced elevation of CDC25A and reduction of p21waf1/Cip1</li> </ul>
<b>Chou <i>et al.</i>, 2017 [14]</b>	Exploration of anti-cancer effects and mechanisms of Zuo-Jin-Wan and its alkaloid components <i>in vitro</i> and in orthotopic HepG2	Zuo-Jin-Wan (ZJW) is composed by two herbs: <i>Coptis chinensis</i> (CC) and <i>Evodia rutaecarpa</i> (ER)	To investigate the anti-cancer effects and mechanisms of ZJW, CC, ER, berberine, and evodiamine <i>in vitro</i> and <i>in vivo</i> .	<ul style="list-style-type: none"> <li>✓ Significantly displayed cytotoxicity in a dose- and time-dependent manner</li> <li>✓ Potential anti-tumor promoting agent in liver</li> <li>✓ Oral administration of ZJW exhibited anti-cancer effects by decreasing the weight of tumor</li> </ul>

	xenograft immunocompetent mice			mass and the accumulation of ascites in an orthotopic intrahepatic xenograft model
<b>Man et al., 2015 [15]</b>	Turmeric enhancing anti-tumor effect of <i>Rbizoma paradisi</i> saponins by influencing their metabolic profiling in tumors of H22 hepatocarcinoma mice	Turmeric belonging to <i>Curcuma longa</i> (RT) and <i>Rbizoma paradisi</i> saponins (RPS) extracted from <i>Paris polyphyllin</i> (RSP)	To investigate the progression of the biochemical response to RT and capture metabolic variations during intragastric administration of their compatibility.	<ul style="list-style-type: none"> <li>✓ RT had a synergic effect on RSP's antitumor activity and reduced toxicity of RSP alone</li> <li>✓ Ameliorated histopathological alterations</li> <li>✓ RT enhanced anti-tumor effect of RSP through mediating the tumor microenvironment to promote anti-tumor immunity of mice</li> <li>✓ RT combination increased anti-tumor effect of RSP through inhibiting signals of organic acids like acetate, amino acids containing alanine, asparagine, glutamine, putrescine, and saponin, lipid compounds, and carbohydrates like myoinositol and arabinose in the tumor tissue</li> </ul>
<b>Liu et al., 2014 [16]</b>	Pulsatilla saponin A, an active molecule from <i>Pulsatilla chinensis</i> , induces cancer cell death and inhibits tumor growth in mouse xenograft models	<i>Pulsatilla</i> saponin A is an active compound from <i>Pulsatilla chinensis</i>	To investigate the inhibiting growth effect on hepatocellular carcinoma	<ul style="list-style-type: none"> <li>✓ Has an antiproliferative activity toward cultured cancer cells</li> <li>✓ Inhibited tumor growth in mouse xenograft models</li> <li>✓ Treated cells were likely arrested in the G2/M phase and that these cells may undergo apoptosis</li> <li>✓ Induced apoptosis in a dose-dependent manner</li> </ul>
<b>Chen et al., 2015 [17]</b>	Anti-tumor effect of $\alpha$ -pinene on human hepatoma cell lines through inducing G2/M cell cycle arrest	Alpha-pinene	To assess the inhibitory effect of alpha-pinene on hepatocellular carcinoma and investigate the molecular mechanism	<ul style="list-style-type: none"> <li>✓ Showed inhibitory effect on BEL-7402 cell growth in a dose-and time-dependent manner</li> <li>✓ Caused marked accumulation of a G2/M population in BEL-7402 cells</li> <li>✓ Significantly suppressed growth of tumor cells in the tumor-bearing mice</li> <li>✓ Upregulated Chk1 and Chk2 protein level and downregulated Cyclin B, CDC25 and CDK1 protein level</li> </ul>
<b>Darweish et al., 2013 [18]</b>	Chemopreventive and hepatoprotective effects of Epigallocatechin-gallate against hepatocellular carcinoma: role of heparan sulfate proteoglycans pathway	Epigallocatechin-gallate, polyphenolic catechin, abundant in green tea	To determine the chemopreventive and hepatoprotective effects of Epigallocatechin-gallate	<ul style="list-style-type: none"> <li>✓ Restoration of heparan-sulfate proteoglycans (HSPGs)</li> <li>✓ Inhibition of vascular invasion markers, by reduced expression of (matrix metalloproteinase-9) MMP-9, syndecan-1 and (fibroblast growth factor) FGF-2 <i>in vivo</i> and <i>in vitro</i></li> <li>✓ Activation of caspase-3 apoptotic pathway</li> </ul>
<b>Abdelmoneem et al., 2018 [19]</b>	Decorating protein nanospheres with lactoferrin enhances oral COX-2 inhibitor/herbal therapy of hepatocellular carcinoma.	Diosmin or diosmetin 7-O-rutinoside, a natural flavone glycoside (DSN) and berberine chloride (BRB), an isoquinolone alkaloid	To prove antitumor superiority of the combined drug nanocarriers compared with free drugs	<ul style="list-style-type: none"> <li>✓ Enhanced cytotoxicity against HepG2 cells</li> <li>✓ Activate apoptotic enzyme, caspase 3 and inhibit VEGF, TNF-alpha, NF-kappa B, and COX-2</li> <li>✓ Reducing the expression of tumor proliferation marker Ki67</li> </ul>
<b>Shi et al., 2016 [20]</b>	Evodiamine exerts anti-tumor effects against hepatocellular carcinoma through inhibiting $\beta$ -catenin-mediated angiogenesis.	Evodiamine, a bioactive alkaloid isolated from dried and nearly ripe fruits of <i>Euodia rutaeacarpa</i> (Rutaceae)	Evodiamine inhibits cellular invasion and migration and blocks angiogenesis, therefore could be a potential therapeutic agent for HCC	<ul style="list-style-type: none"> <li>✓ Reduces expressions of <math>\beta</math>-catenin thus lowering VEGFa expression in order to suppress angiogenesis</li> </ul>
<b>Zhong et al., 2018 [21]</b>	Ellagic acid synergistically potentiates inhibitory activities of chemotherapeutic agents to human hepatocellular carcinoma.	Ellagic acid, a natural polyphenolic compound, produced especially in nut galls and pomegranate	To investigate the anticancer activity of Ellagic acid, focusing on its stimulating effects on doxorubicin hydrochloride (DOX) and cisplatin (DDP)	<ul style="list-style-type: none"> <li>✓ Sensitized HCC cells to DOX treatment <i>in vivo</i></li> <li>✓ Reduced Ki67 signal thus reducing tumor cell proliferation and promoting apoptosis in the xenograft mouse model</li> </ul>
<b>Bu et al., 2015 [22]</b>	The herbal compound Songyou Yin (SYY) inhibits hepatocellular carcinoma growth and improves survival in models of chronic fibrosis via paracrine inhibition of activated hepatic stellate cells.	SYY is a herbal Chinese medicine combined of five herbs	Songyou Yin (SYY), herbal compound, has the ability to attenuate hepatoma cell invasion and metastasis via down-regulation of cytokine secretion by hepatic stellate cells (aHSCs)	<ul style="list-style-type: none"> <li>✓ Prolonged survival of mice model by inducing caspase-3-dependent tumor cell apoptosis</li> <li>✓ Inhibited HCC invasiveness by down-regulations of enzyme matrix metalloproteinase-2 (MMP-2)</li> <li>✓ <i>In vitro</i>, HCC cells incubated in conditioned media from SYY treated aHSCs showed a decreased proliferation, reduced colony formation and lower invasive potential</li> </ul>
<b>Lin et al., 2014 [23]</b>	<i>Livistona chinensis</i> seeds inhibit hepatocellular carcinoma angiogenesis	<i>Livistona chinensis</i> , belongs to the monocotyledonous Palmaceae family, being a	To investigate the role of <i>Livistona chinensis</i> seeds in cancer treatment, especially	<ul style="list-style-type: none"> <li>✓ Promoting cancer cell apoptosis in hepatocellular carcinoma</li> <li>✓ Suppressing the expression of VEGF-A and</li> </ul>

	<i>in vivo</i> via suppression of the Notch pathway.	medicinal herb widely spread across Eastern Asia	regarding the effects over tumor angiogenesis	<ul style="list-style-type: none"> <li>✓ VEGFR-2 in tumor tissues, more exactly inhibiting tumor angiogenesis</li> <li>✓ Inhibiting the expression of Notch, D114 and Jagged1</li> </ul>
<b>Wang <i>et al.</i>, 2013 [24]</b>	Steroidal saponin of <i>Trillium tschonoskii</i> reverses multidrug resistance of hepatocellular carcinoma.	<i>Trillium tschonoskii</i> (TTS) is a traditional Chinese medicine, also called Yan Ling Chao	TTS has the potential ability of reversing the multidrug resistance in hepatocellular carcinoma cells and enhance chemosensitivity	<ul style="list-style-type: none"> <li>✓ TTS was found to suppress colony-formation dose-dependently, thus inhibiting HCC cells proliferation</li> <li>✓ TTS reserved the MDR of R-HepG2, increasing the sensitivity of these cells to chemotherapeutic agents <i>in vitro</i> and <i>in vivo</i></li> <li>✓ TTS stopped tumor cells proliferation and enhanced toxicity of DOX in HCC cells, by considerably reducing Ki67 positive rate</li> </ul>
<b>Xiao Li <i>et al.</i>, 2018 [25]</b>	Ginsenoside Rg3 decreases NHE1 expression via inhibiting EGF-EGFR-ERK1/2-HIF-1 alpha pathway in hepatocellular carcinoma: a novel antitumor mechanism	Ginsenoside Rg3 is the main pharmacologically bioactive compound extracted from China's herb ginseng	Ginsenoside Rg3 could inhibit HCC cells proliferation, induce apoptosis and inhibit angiogenesis.	<ul style="list-style-type: none"> <li>✓ Rg3 significantly decreased NHE1 mRNA expression in a concentration-dependent manner compared with the controls in Bel-7402 and HCCLM3 cells</li> <li>✓ Rg3 treatment significantly decreased EGF protein expression compared with the controls</li> <li>✓ Rg3 blocked NHE1 expression through inhibiting EGF-ERK1/2-HIF-1<math>\alpha</math> pathway</li> </ul>
<b>Wang <i>et al.</i>, 2015 [26]</b>	Inhibition of eukaryotic elongation factor-2 confers to tumor suppression by an herbal formulation Huanglian-Jiedu Decoction (HLJDD) in human hepatocellular carcinoma	Huanglian-Jiedu Decoction is an ancient herbal formula with multiple purposes, such as: anti-ulcer, anti-trypanosomal, anti-inflammation, anti-oxidation, reduces neutrophil infiltration and suppresses pre-adipocyte differentiation	HLJDD has a possible ability of liver protection and anti-cancer effects therefore is thought to be useful in treatment of liver diseases and cancer. A recent study has shown that this formulation inhibits human liver cancer <i>in vitro</i> .	<ul style="list-style-type: none"> <li>✓ HLJDD could suppress the proliferation, angiogenesis, and invasiveness of HCC cells both <i>in vitro</i> and <i>in vivo</i></li> <li>✓ HLJDD suppresses mTOR pathway which reduces phosphorylation of eEF2K, activating it, and this way eEF2 is revealed as a novel target for this decoction in treating HCC</li> <li>✓ Inhibits nascent protein synthesis</li> </ul>
<b>Nanda <i>et al.</i>, 2017 [27]</b>	Hepatoprotective Mongolian prescription II (MPIO) enhances the antitumor effects of chemotherapeutics in hepatocellular carcinoma xenografts	Hepatoprotective Mongolian prescription II is a mixture of 18 different medicinal herbs ( <i>Terminalia chebula</i> , <i>Carthamus tinctorius</i> , <i>Radix glycyrrhizae</i> are the primary ingredients)	MPIO can induce apoptosis and cell cycle arrest thus becoming an anticancer agent.	<ul style="list-style-type: none"> <li>✓ MPIO inhibits HepG2 and Huh-7 cell proliferation</li> <li>✓ MPIO improves sensitivity of chemotherapeutics and decreases the toxicity and dose of chemotherapeutics</li> <li>✓ In combination with 5-FU has higher sensitization than either drug alone</li> <li>✓ Inhibits tumor growth in H22 and MHCC97H cell transplantable tumors <i>in vivo</i></li> </ul>
<b>Shu <i>et al.</i>, 2015 [28]</b>	Antitumor immunostimulatory activity of polysaccharides from <i>Salvia chinensis</i> Benth	<i>Salvia chinensis</i> Benth is a traditional Chinese medicine, found in the South-Central China. <i>S. chinensis</i> consists of flavonoids and polysaccharides. Flavonoids can induce HCC cell apoptosis.	To evaluate the antitumor activity of PSSC against H22 HCC cells and the toxicity of PSSC on tumor-bearing animals.	<ul style="list-style-type: none"> <li>✓ Suppressing tumor transplantation induced PGE2 production thus having an anti-tumor immunostimulatory activity</li> <li>✓ Activating JAK3/STAT5 anti-apoptotic pathway in CD4+ T cells</li> <li>✓ Downregulation of COX-2 expression in TAMs</li> </ul>
<b>Xu <i>et al.</i>, 2016 [29]</b>	Jian Pi Li Qi decoction alleviated postembolization syndrome following transcatheter arterial chemoembolization for hepatocellular carcinoma	Jian Pi Li Qi decoction is an often-used formulation in China. It is known to improve liver function and immune function impairment <i>in vivo</i> caused by chemotherapy.	Because of previous research that showed the efficiency of JPLQ in improving the effects and lower the side effects of TACE, it is thought that JPLQ could prevent and treat Postembolization Syndrome.	<ul style="list-style-type: none"> <li>✓ Patients receiving PLQ experienced a relieve regarding to the following symptoms: fever, pain, fatigue, lack of appetite, drowsiness, dry mouth, constipation, but without statistical difference among the 3 groups during 3 days after TACE besides drowsiness and dry mouth</li> <li>✓ After TACE, both TB and AST/ALT levels were lower in the herbal medicine group</li> </ul>

Abbreviations: FZJDXJ-Fuzheng Jiedu Xiaoji formulation; AKT-Protein kinase B pathway; OS-one-year overall survival; PFS-progression-free survival; TACE-transcatheter arterial chemoembolization; CE-Calundulose E; HepG2-; RPR- *Rheum palmatum* root; TGF- $\beta$ 1-transforming growth factor beta 1; DEN-induced HCC- diethylnitrosamine-induced HCC; PLGA- a non-enzymatically-degradable polymer; TNF- $\alpha$ -tumor necrosis factor-alpha; MOLEE- *Moringa oleifera* leaf ethanol extract; AFP-Alpha fetoprotein; CEA-Carcinoembryonic antigen; SA- *Semecarpus anacardium*; AST-aspartate aminotransferase; ALT-alanine aminotransferase; AKP-alkaline phosphatase; GGT-gamma-glutamyl transferase; TGP- Total Glucosides of Paeony; BAFF- B-cell activating factor; DOX-doxorubicin; GAPDH-glyceraldehyde-3-phosphate dehydrogenase; G6PD- glucose-6-phosphate dehydrogenase.

Amongst the evaluated articles, two of them (6.89%) researched the effect of phytotherapy over human subjects in two randomised control trials, while the other 27 articles (93.10%) illustrated the outcomes of phytotherapy over hepatocellular carcinoma cells and rodents (mice, rats). In 20 of the situations above mentioned the studies used active compounds extracted from one plant, with 9 articles describing the use of a formulation based on more than one plant. Within the latter category there are 6 articles which show the use of specific formulations, which are registered as traditional medicine.

After analysing the articles aforementioned, a series of outcomes was observed. These effects can be divided into two major categories: molecular effects (Table 2) and then both clinical and paraclinical results (Table 3).

The molecular effects demonstrated through the use of herbal medicine in HCC are: inhibiting tumour cells proliferation, anti-inflammatory effect, induced or enhanced apoptosis and reducing angiogenesis (Table 2).

**Table 2.** Molecular effects and the plants responsible for them

Inhibiting tumor cells proliferation	Anti-inflammatory effect	Induced/ Enhanced apoptosis	Reducing angiogenesis
Fuzheng Jiedu Xiaoji Calunduloside E <i>Ganoderma lucidum</i> spore polysaccharide <i>Curcuma longa</i> <i>Semecarpus anacardium</i> <i>Paeony lactiflora</i> Dahuang zhenchong pill <i>Coelastrella</i> sp F50 Epigallocatechin gallate (green tea) Zuo-Jin-Wan <i>Curcuma longa</i> & <i>Rhizoma paridis</i> <i>Pulsatilla saponin A</i> $\alpha$ - pinene Diosmin & berberine choride <i>Euodia rutaecarpa</i> Ellagic acid Songyou Yin <i>Trilium tschonoskii</i> Chinese herb gindeng Huanglian-Jiedu Decoction Mongolian prescription II <i>Salvia chinensis</i> Benth	Calunduloside E <i>Ganoderma lucidum</i> spore polysaccharide <i>Curcuma longa</i> <i>Paeonia lactiflora</i> <i>Coelastrella</i> sp F50 $\alpha$ - Pinene <i>Salvia chinensis</i> Benth	<i>Curcuma longa</i> Dahuang zhechong pill <i>Coelastrella</i> sp F50 <i>Pulsatilla saponin A</i> Diosmin&berberine chloride Ellagic acid Songyou Yin <i>Livistona chinensis</i> <i>Salvia chinensis</i> Benth	<i>Semecarpus anacardium</i> <i>Euodia rutaecarpa</i> <i>Livistona chinensis</i> Huanglian-Jiedu Decoction

**Table 3.** Clinical and paraclinical effects and the plants responsible for these outcomes

Prophylaxis	Reducing complication	Reducing mortality	Reducing hepatocytolisis	Lowering tumor markers	Sensitizing cells to chemotherapy
<i>Rbeum palmatum</i> <i>Moringa oleifera</i> <i>Semecarpus anacardium</i> Black currant skin Epigallocatechin gallate (Green tea)	Fuzheng Jiedu Xiaoji Zuo-Jin-Wan	Fuzheng Jiedu Xiaoji <i>Curcuma longa</i> <i>Paeony lactiflora</i>	<i>Curcuma longa</i> <i>Semecarpus anacardium</i> <i>Paeonia lactiflora</i> <i>Coelastrella</i> sp F50 <i>Nigella sativa</i> Epigallocatechin gallate Jian Pi Li Qi Decoction	<i>Moringa oleifera</i> leaf <i>Paeonia lactiflora</i> <i>Nigella sativa</i>	Dahuang zhenchong pill Ellagic acid <i>Trilium tschonoskii</i> Mongolian prescription II

As for clinical and paraclinical outcomes, these are as follows: prophylaxy, reducing complications rate, reducing mortality rate, reducing liver enzymes, decreased levels of tumoral markers and raising sensitivity to chemotherapeutic agents (Table 3).

Inhibiting malignant cell proliferation was proven in almost all 29 studies, except for three situations: *Moringa oleifera* leaf, Black currant skin extract, both possessing an anti-oxidation effect and *Livistona chinensis* expressing an important inhibitory effect over angiogenesis.

The suppression of cell proliferation was demonstrated in almost all the studies on HepG2 cells, because of an enhanced cytotoxicity against these cells. The herbs which showed such an effect are: Canduloside E, *Curcuma longa*, Mongolian prescription II. Other type of malignant cells on which the studies were conducted are H22 cell lines, in murine subjects, where GLSP inhibited cell proliferation with the help of activated macrophages and MPII inhibited tumour growth. Moreover, MPII inhibited the proliferation of Huh-7 cells. In addition, cell growth was ceased in BEL-7402 cells by Alpha-pinene.

The anti-inflammatory effect was proven in the studies using the following herbs: Calunduloside E, Ganoderma lucidol, *Curcuma longa*, *Paeonia lactiflora*, *Coelastrella*, alpha-pinene and *Salvia chinensis*. There is a list of herbs, that have proven their influence in decreasing inflammation through cyclines, inhibiting TNF, reducing cytokines and prostaglandins activity thus reducing the peritumoral edema.

Apoptosis is induced by the following medicinal herbs: *Curcuma longa*, *Coelastrella*, *Pulsatilla* saponin A, Diosmin and Berberine, Ellagic acid *Livistona* and *Salvia chinensis*. The same outcome was observed for the formulations containing 12 plants as is Dahuang zhechong or including 5 herbs as Songyou Yin. *Rheum palmatum* and *Paeonia*, found in DHZCP have shown their effect in both inducing apoptosis and inhibiting tissular proliferation.

A major advantage for the uptake of medicinal herbs during therapy for hepatocellular carcinoma is reducing the level of transaminase, which was shown while using *Curcuma longa*, *Semercarpus anacardium*, *Paeonia lactiflora*, *Coelastrella* sp F50, *Nigella sativa*, *Epigallocatechin gallate*. Jian Pi Li Qi decoction is a formulation used in the Traditional Chinese Medicine for having positive effects over liver function, especially after chemotherapy, therefore being useful in the treatment of HCC.

There are a few concoctions used in the TCM, such as Fuzheng Jiedu Xiaoji and Zuo-Jin-Wan, which reduce the rate of complications for this pathology. Fuzheng Jiedu Xiaoji also proved it's efficiency in reducing HCC mortality. Other herbs that attested a positive outcome regarding the mortality rate where *Curcuma longa* and *Paeonia lactiflora*.

*Moringa oleifera* leaf, *Paeonia lactiflora*, *Nigella sativa* have a favourable effect reducing the level of tumor markers.

*Rheum palmatum*, *Moringa olifeira*, *Semercarous anacardium*, Black currant skin, Epigallocatechin gallate (green tea) had shown major prophylactic benefits concerning several actions: antioxidation, antimutagenic and also throughout carcinogen detoxifying enzymes or activation of capsase-3-apoptotic pathway and restoration of proteoglycans.

## Discussion

The use of phytotherapy provides multiple benefits for patients diagnosed and treated for hepatocellular carcinoma. Taking into consideration the fact that this illness is still imposing difficulties in early diagnosis thus patients having either treatment option issues or an impaired quality of life, herbal medicine has shown its advantages. (Bishayee *et al.*, 2012; Reig *et al.*, 2022) There are several effects of phytotherapy that will be discussed at length: the useful combination between TACE and herbal medication, important for reducing the incidence of complications in HCC, enhancing performance status in B stage patients and inhibiting tumour cell proliferation, or ameliorating postembolisation syndrome; reducing oxidative stress; antimutagenic effects

and increasing tumour cells' sensitivity for chemotherapeutic drugs (Yang *et al.*, 2021; Xu *et al.*, 2015; Thoppil *et al.*, 2012; Sadek *et al.*, 2017; El-Saied *et al.*, 2018; Wu *et al.*, 2018).

TACE is one of the standardized treatments of hepatocellular carcinoma, widely used due to its benefits. Most patients with HCC are diagnosed while at an intermediate or advanced stage, with few therapeutic options available, thus being the reason for using TACE, in accordance with BCLC. The chemotherapeutics commonly used for TACE are Cisplatin, for inhibiting DNA replication and transcription and Pirarubicin, which inhibits DNA polymerase, prevents nucleic acid synthesis and as well, cell transition from G2 to M phase. Despite these benefits, recurrence and metastasis after TACE are possible, therefore the combination of this type of therapy and effective drugs, such as TCM, may improve the process of blocking the tumour progression (Galle *et al.*, 2017; Yang *et al.*, 2022). The results of a randomized clinical trial using FZJDXJ treatment were a prolonged overall survival and reduced overall mortality rate in patients, especially those included in BCLC A and B stages. The mortality analysis proved that patients in stages A and B had a reduced incidence of HCC complications, including abdominal infection, encephalopathy, multiple metastases, rupture, or haemorrhage of HCC. This Traditional Chinese concoction had a significant effect on performance status lengthening in B stage patients and inhibited tumour cell proliferation for the same category of individuals. All in all, FZJDXJ inhibited tumour progression (Yang *et al.*, 2021).

Postembolization syndrome (PES) is a complication of TACE which appears in 60-80% of cases and includes the following symptoms: fever, nausea, vomiting, abdominal pain, lack of appetite and impaired liver function. An effective approach to prevent this syndrome is necessary, especially because a combination of antipyretic agents, analgesics, antiemetics and cytoprotective drugs will accentuate the metabolic charge of the liver (Leung *et al.*, 2001; Xu *et al.*, 2015). Jian Pi Li Qi decoction is a frequently used prescription in TCM. A randomized, double-blind, placebo-controlled trial was performed to confirm if this therapy option is capable to prevent and treat TACE related PES, Chen *et al.* found that Jian Pi Bu Qi improves prevention and reduction of PES syndrome. Other herbs as Qingre Jiedu Decoction associated with Western medicine has shown benefits in preventing and treating symptoms after TACE. JPLQ decoction improves the efficacy of chemotherapy and can also improve liver function and relieve the side effects brought on by TACE. (Leung *et al.*, 2001; Xu *et al.*, 2015) This study enrolled 150 patients receiving TACE therapy. The patients were randomly allocated to three groups: A, (subjects received neither herbal medication or placebo) containing in the end 50 patients, group B (placebo treatment group), including 40 patients and C (JPLQ decoction treatment group) with 50 individuals. The number of patients studied was lower than the number enrolled due to their consent withdrawal. The patients were admitted in the hospital for 4 days and supervised during therapy. The study compared the percentage of patients facing severe levels of the most important symptoms (pain, disturbed sleep, distress, fatigue, lack of appetite, drowsiness, dry mouth, nausea, vomiting, bloating, constipation), 1 day before TACE to 3 days after the procedure. The result was that for each symptom, the percentage was higher in the first day after TACE than in the following ones. The instrument to assess postembolization syndrome was M.D. Anderson Symptom Inventory module for use in patients with gastrointestinal cancer (MDASI-GI) (Wang *et al.*, 2010; Xu *et al.*, 2015). On the first day after the procedure there were no statistical differences found among the three groups of subjects. However, the patients in group C faced an attenuation of drowsiness and dry mouth on the first day and they had these symptoms significantly relieved on the second day after TACE: pain, fatigue, lack of appetite, drowsiness, dry mouth, and constipation. It is important to state that although this decoction could provide overall relief for some symptoms, it could not ameliorate severe pain, fatigue, constipation, or the lack of appetite. The post-procedure fever had a peak on the first and second day after TACE and gradually decreased on the third day. The incidence of fever was lower in group C, than in the other groups during the supervision, but the differences were not statistically significant. Regarding liver function after TACE, the results have demonstrated that there is a protective effect over liver function while using JPLQ decoction after this therapy, according to the fact that total bilirubin level (TB) in group C was lower than in group A and B, and the values of aspartate transaminase and alanine

transaminase were lower in group C than A, but like the ones expressed by the subjects in group B. The results of this trial also demonstrated that JPLQ can improve the quality of life of patients classified as moderate to advanced stages of HCC. The quality of life and the burden that is expressed by lowering it through symptoms and therapy side effects can be modified using herbal medicine (Leung *et al.*, 2001; Xu *et al.*, 2015; Pop *et al.*, 2022).

Chinese rhubarb, *Moringa oleifera*, ayurvedic milk extract of Varnish tree, Black currant and an active monomer from green tea gave prophylactic actions in HCC. This effect is due to the attenuation of oxidative stress, the growth of antioxidant enzymes, lowering the lactate dehydrogenase (LDH) activity which interferes with glycolysis therefore protecting the integrity of hepatocytes membrane, having also antimutagenic effects (Thoppil *et al.*, 2012; Joseph *et al.*, 2013; Sadek *et al.*, 2017; El-Saied *et al.*, 2018; Tang *et al.*, 2020).

Raising sensitivity of hepatocellular carcinoma cells to chemotherapeutic agents is an important effect that increases the efficacy of this therapy (Wang *et al.*, 2013; Nanda *et al.*, 2017; Wu *et al.*, 2018; Zhong *et al.*, 2018). DHZCP is composed out of 12 plants known for their therapeutic effects in TCM. This formulation inhibits ATP energy metabolism and improves accumulation of Doxorubicin in the tumour tissue, while Ellagic acid increases the sensitivity of tumour cells for the above-mentioned chemotherapeutic drug (Wu *et al.*, 2018; Zhong *et al.*, 2018). Phytotherapy has impressive effects in hepatocellular carcinoma, and even in preventing the occurrence of such a pathology, although there are studies that request caution when it comes to associating phototherapeutics and biliary diseases that have a high risk of malignant degeneration (Bishayee *et al.*, 2012; Puia *et al.*, 2013; Sadek *et al.*, 2017; Tang *et al.*, 2020).

Curcumin represents a natural compound, widely investigated and with multiple therapeutic actions, such as anticancer, anti-virus, anti-arthritis, anti-amyloid, anti-oxidative and anti-inflammatory. Regarding liver diseases, curcumin inhibits HBV gene expression and replication via down-regulation of PGC-1 $\alpha$ . Studies have demonstrated that curcumin significantly ameliorated non-alcoholic fatty liver disease, while other papers exhibit curcumin's effects over hepatic stellate cells, inactivating them, and protection against liver steatosis and fibrosis (Farazuddin *et al.*, 2019; White *et al.*, 2019; Yang *et al.*, 2022). Moreover, this compound can suppress stromal cell-derived factor-1/CXCR4 signalling, thus reducing the incidence of circulating gastric cancer cells and decreasing the risk of liver metastases. Thereby, curcumin might show advantages in the therapy of HCC. Unluckily, curcumin has a poor bioavailability and hydrophobicity, which imposes a major issue as for using it as a potent anticancer agent (Duvoix *et al.*, 2005; Farazuddin *et al.*, 2019; Yang *et al.*, 2022). To avoid these problems, Farazuddin *et al.* (2019) developed a novel, dual-core microcell formulation of curcumin by encapsulating this element in microcells, facilitating its kinetics. Analysis revealed that these microcells helped regression of HCC and maintenance of liver tissue architecture. In addition, free curcumin had a modest effect on neoplastic suppression (Farazuddin *et al.*, 2019; Yang *et al.*, 2022).

Tang *et al.* (2020) described the effects of Epigallocatechin gallate over HCC. EGcG is the most rich and bioactive catechin found in green tea. The results of this study proved that eGcG can inhibit the proliferation of HepG2 and Huh7 cells, reduce the expression of cdc25a and elevate the expression of p21waf1/cip1 in HepG2. Moreover, *in vivo* eGcG reduced tumour volume and increased survival rates of diethylnitrosamine (DEN)-induced HCC in rats. Although, the findings of Tang's *et al.* (2020) are the first to show that eGcG possesses chemopreventive properties, there was no significant difference regarding this outcome between GTe (Green Tea extract) and eGcG. Previous studies have shown that GTe at an eGcG-equivalent biological concentration exhibits a stronger inhibition concerning squamous cell carcinoma and another study described that EGCG and GTE can be immune checkpoint inhibitors in lung cancer evolution. Concerning the study of Tang *et al.* (2020) the results have demonstrated that EGCG expresses chemopreventive properties, which can be explained by the reduction in CDC25A, as an important liver cancer gene. Moreover, EGCG and GTE reduced tumour volume, improved the survival rates of HCC subjects, and inhibited the proliferation of hepatoma cells (Huang *et al.*, 2009; Liu *et al.*, 2011; Rawangkan *et al.*, 2018; Tang *et al.*, 2020). Altogether, considering its poor stability and low bioavailability, eGcG can be used as an

association with other antitumor medication, thus having a synergistic effect of HCC prevention and treatment (Tang *et al.*, 2020).

### **Conclusions**

This review aimed to explore whether herbal medicine has any beneficial effects for hepatocellular carcinoma patients and if so, which are the herbs that provide such outcomes. From the reviewed articles it has been shown that herbal medicine provides a large series of benefits for patients that were diagnosed with HCC, especially concerning the following mechanisms: anti-inflammatory and anti-oxidative effects, suppressing malignant cell proliferation, inhibiting angiogenesis, stimulating apoptosis, and even sensitizing cells to chemotherapy therefore expressing outstanding results. Moreover, phytotherapy expresses favourable outcomes regarding the quality of life of patients included in advanced stages of the disease or that are experiencing side effects of certain therapies, as for patients receiving TACE. To obtain all these results, studies used either single herbs or a mixture of medicinal herbs, for example: FZJDXJ formulation, Jian Pi Li Qi decoction, Curcumin, Black currant, Chinese rhubarb, Ellagic acid, obtained from nut galls or pomegranate, or one bioactive catechin found in green tea and many more, which were successful in obtaining favourable results. All in all, regardless of the use of only one herb or a concoction, phytotherapy has proven its usefulness in hepatocellular carcinoma.

### **Authors' Contributions**

Conceptualization, C.P.U., R.P. and F.G.; Methodology, E.M., A.P., L.F., Validation, F.G. and N.A.H.; Resources, A.C., Ş.U., D.S. and F.Z.; Data curation, C.P.U.; Writing-original draft preparation, C.P.U. and R.P.; Writing-review and editing, C.P.U. and F.G., Visualization C.P.U., Ş.U. and F.G.; Supervision, F.G. and N.A.H. All authors read and approved the final manuscript.

### **Ethical approval** (for researches involving animals or humans)

Not applicable.

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### **Conflict of Interests**

The authors declare that there are no conflicts of interest related to this article.

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