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CLINICAL TRIAL

Reviewing Clinical Trials and Meta-Analyses to Assess the Efficacy and Safety of Huachansu in Cancer Treatment

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Abstract

Traditional Chinese Medicine (TCM), including herbal remedies and animal secretions like HuaChansu, also called Cinobufacini, has gained attention for its therapeutic efficacy in cancer treatment. HuaChansu, extracted from the skin of toads from the genus Bufo, has been used traditionally for various diseases and recently explored for its anti-cancer properties attributed to bufadienolides like bufalin, resibufogenin, and cinobufagin. Clinical studies and meta-analyses have evaluated its efficacy and safety across various cancers. For hepatocellular carcinoma, non-small cell lung cancer, and pancreatic cancer, pilot studies and clinical trials showed HuaChansu's potential for disease stabilization with minimal toxicity. In breast cancer, a meta-analysis suggested that HuaChansu combined with chemotherapy improves response rates and quality of life. Studies on gallbladder and gastric cancers indicated similar benefits, enhancing therapeutic effects and reducing side effects. In lung cancer, HuaChansu improved survival rates and quality of life when combined with chemotherapy, though placebo-controlled trials are needed. For liver cancer, meta-analyses and randomized controlled trials demonstrated improved survival rates and reduced recurrence when HuaChansu was used with transarterial chemoembolization. These findings underscore HuaChansu potential as a complementary cancer treatment, warranting further research to optimize its dosage and administration for enhanced efficacy.

Introduction

Traditional Chinese Medicine (TCM) is widely utilized in China and is based on plants and animal secretions. Its cost-effectiveness and therapeutic efficacy have drawn attention to this alternative medicine in Europe and the United States [1]. HuaChansu, also known as Cinobufacini, is the most common TCM and has been approved by Chinese NMPA since the 1990s. This water-soluble preparation, extracted from the skin and parotid venom glands of Bufo bufo gargarizans, a subspecies of the common

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toad found primarily in East Asia, is mainly composed of indole alkaloids (bufotenine, bufotenidine, cinobufotenine and serotonin) and steroidal cardiac glycosides [2], and was first used as an adjuvant for heart failure treatment [3]. Subsequently, it has been used as a detoxicant, analgesic, diuretic, hemostatic, anti-inflammatory, and cardiotonic agent. Recently, anti-cancer properties such as inhibition of cell proliferation, induction of cell differentiation, of apoptosis, and inhibition of cancer angiogenesis have been discovered and attributed to the action of bufadienolides [4,5] and cardiac glycosides, enabling them to be redirected towards cancer treatment [6]. Among these molecules, the cardiac glycosides bufalin, resibufogenin, and cinobufagin are the three main active components [7], demonstrating anti-cancer activities, as we previously reported in melanoma cell lines [5,8,9] (Figure 1).

Article Search Strategy

We conducted a search in PubMed and reviewed references from relevant articles to identify studies on the use of HuaChansu in cancer treatment. Only publications written in English between 2003 and 2024 were included, with a particular focus on the last five years. Clinical studies were screened based on the presence of a database entry, abstract, available full text, or title referring to these conditions. The following keywords were used: HuaChansu, Cinobufacini, cancer, clinical study, and trial. After a critical analysis of the publication content, the final selection of articles was included in this review. The study was conducted according to the PRISMA checklist for reviews and meta-analyses. Institutional review board approval was not required.

Initial study

A pilot study by the Fudan University Cancer Hospital (Shanghai, China) and the MD Anderson Cancer Centre (Houston, Texas, USA) explored the efficacy and side effects of HuaChansu in treating hepatocellular carcinoma, non-small cell lung cancer, and pancreatic cancer. The study enrolled 15 patients who received intravenous HuaChansu for 14 days followed by 7 days off. Six patients had stable disease (median duration = 6.0 months; range 3.5-11.1 months), and one hepatocellular carcinoma patient experienced a 20% reduction in tumor mass

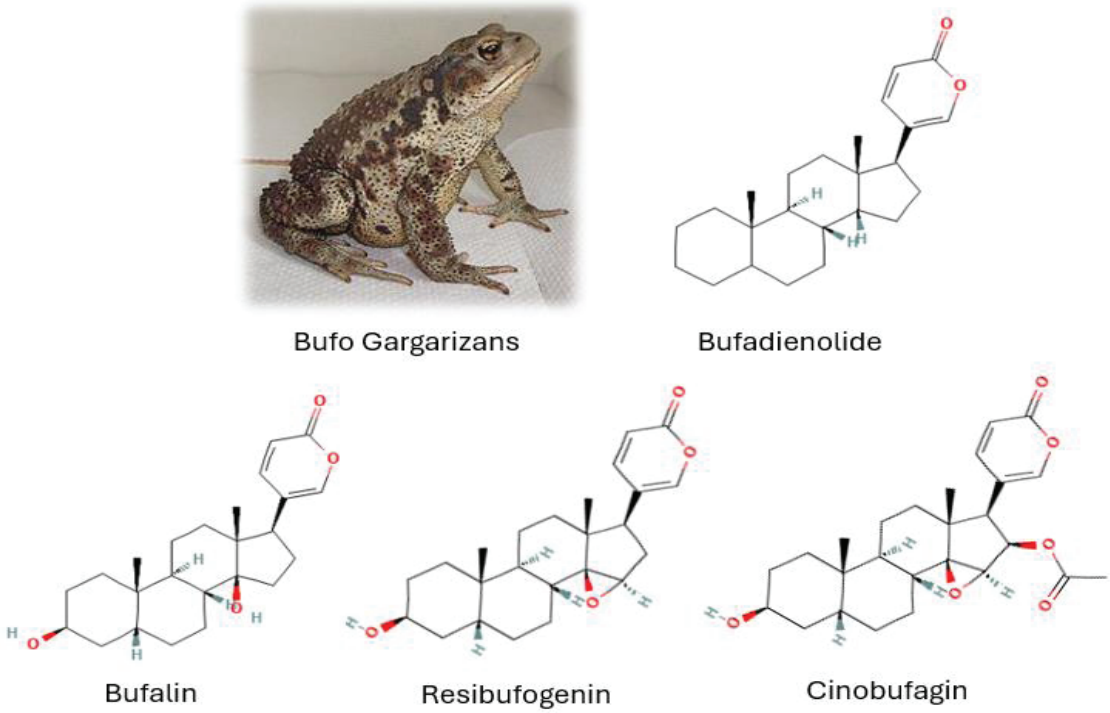

Figure 1 Bufo bufo gargarizans, the East Asian subspecies of the common toad, and the chemical structures of the bufadienolides and cardiac glycosides isolated from its skin and parotid venom glands. The main active components include bufalin, resibufogenin, and cinobufagin which have demonstrated significant anti-cancer activities.

lasting over 11 months. In addition, 73% of patients had no toxicities greater than grade I, with no grades III and IV observed, despite using doses eight times higher than conventional doses in China. Grade I toxicities included hematological (leukopenia, thrombocytopenia), mucocutaneous (oral ulcer, rash), gastrointestinal (loss of appetite, constipation, diarrhoea), cardiovascular (premature ventricular contraction, hypertension), and respiratory (dyspnoea) effects. Electrocardiograms showed no cardiac dysfunction. This study highlighted that HuaChansu is well tolerated at higher concentrations and results in disease stabilization when used as a single agent [7].

Following this first observation, a phase II/III clinical trial (NCT00837239) was conducted to study the intravenous combination of gemcitabine and HuaChansu in pancreatic cancer. The study compared the effects of gemcitabine and HuaChansu versus gemcitabine and placebo in 76 patients with locally advanced or metastatic pancreatic adenocarcinoma (39 in the experimental group *vs.,* 37 in the control group). No additional toxicity was induced by the combination, but no benefit was observed in terms of objective radiographical response rate, Progression-Free Survival (PFS), and time to progression. The lack of effectiveness could be due to several factors: the difficulty in treating advanced pancreatic cancer, a possibly too low dose of HuaChansu, potentially too short exposure time, and the type of administration [10].

Breast cancer

A meta-analysis of 16 studies involving 1331 patients evaluated the safety and efficacy of HuaChansu combined with chemotherapy. Most studies indicated that the combination improved the Objective Response Rate (ORR) and clinical benefit rate. The quality of life was enhanced by decreasing pain and side effects such as kidney damage. The tumor markers CA 15-3, CA 125 and CEA were also reduced with the combination compared to chemotherapy alone. However, attention must be paid to the quality of the meta-analysis, as patient pathological stages, HuaChansu dosages, and chemotherapy treatments varied across the studies [11].

Gallbladder cancer

Gallbladder carcinoma, often diagnosed at an advanced stage, is conventionally treated with surgery and chemotherapies [12]. The 5-year survival rate is less than 5%, with high risks of relapse [13]. A study analysed the efficacy and safety of combining Gemcitabine and Oxaliplatin (GEMOX) with HuaChansu, administered three days before chemotherapy cycles. Out of 23 patients, 8 (34.8%) showed a partial response, and 7 (30.4%) had stable disease. This combination was well tolerated, with myelosuppression being the main adverse effect, and improved patient quality of life with reduced pain [12].

Gastric cancer

China accounts for 43% of new gastric cancer cases worldwide, with a poor prognosis and a 5-year survival rate lower than 20% [14,15]. Two meta-analyses (12 studies, 853 patients, and 14 studies, 976 patients) investigated the combination of HuaChansu and chemotherapy versus chemotherapy alone. They found improved response rates and quality of life, with increased Karnofsky Performance Scale (KPS) scores and reduced cancer-related pain [16,17]. Another meta-analysis (27 studies, 1939 patients) showed that combining HuaChansu with chemotherapy improved therapeutic effects and alleviated side effects such as nausea, vomiting, leukopenia, anemia, and gastrointestinal effects [18].

A Bayesian network meta-analysis, comparing Oxaliplatin and Tegafur (SOX) chemotherapy regimens with the combination of SOX and TCM, indicates that HuaChansu is the TCM that demonstrates the highest clinical effectiveness (Surface Under the Cumulative Ranking curve (SUCRA): 78.71%) compared to other TCM by significantly decreasing leukopenia (SUCRA: 93.35%), thrombocytopenia (SUCRA: 80.19%), nausea and vomiting (SUCRA 95.15%) incidence induced by SOX chemotherapy [19].

Lung cancer

Lung cancer is the leading cause of cancer-related death in China, with rates projected to increase by 40% by 2030 [15]. A clinical trial involving 121 patients (65 in the treatment group *vs.,* 56 in the control group) investigated the efficacy of HuaChansu combined with chemotherapy across different stages of lung cancer. Stage III patient survival significantly improved in the experimental group (19.3 months *vs.,* 12.7 months) [20]. However, the absence of a placebo control warrants caution. Another study with 80 patients found that combining chemotherapy with HuaChansu injection reduced leukopenia incidence, however no differences were observed for other adverse effects like diarrhoea and vomiting [21].

Two additional clinical trials explored HuaChansu as maintenance therapy post-chemotherapy [19]. The first study indicated improved 1-year survival (78.1% *vs.*, 53.1%) and quality of life, with reductions in fatigue, nausea, vomiting, appetite loss, and alopecia [22]. The second one showed a reduction in CTLA-4 concentration in serum after two HuaChansu cycle treatment [23].

Two meta-analyses of HuaChansu combined with platinum-based chemotherapy reported improvements in 1- and 2-year survival rates, objective tumor response rates, and quality of life by reducing side effects (27 studies, 2125 patients [24] and 19 studies, 1564 patients [25]). Another meta-analysis (32 studies, 2753 patients) found that administering HuaChansu before chemotherapy could enhance survival rates and quality of life by reducing alopecia, thrombocytopenia, and gastrointestinal effects [26].

Cinobufatolin was also assessed for the treatment of non-small cell lung cancer in meta-analyses [27,28]. One analysis indicates that intravenous infusion of Cinobufatolin improved the therapeutic effects of chemotherapy [27]. Indeed, the 1-2-3-year survival rates and quality of life were enhanced with Cinobufatolin injection [27]. The latest analysis (21 studies, 1735 patients) evaluated the safety and effectiveness of Cinobufatolin injection as an adjunctive treatment [28]. The findings suggest that the injection was safe, with 73% of patients experiencing no drug-related toxicity greater than grade I [28]. Moreover, chemotherapy efficacy was enhanced, as evidenced by improved ORR, disease control, and quality of life, achieved by reducing chemotherapy-related adverse effects [28].

Finally, a recent overview of systematic reviews and meta-analyses assessed the efficacy and safety of HuaChansu as an adjuvant therapy for non-small cell lung cancer based on Systematic Reviews (SRs) and Meta-Analyses (MAs) [29]. The results indicate generally low quality of the included SRs/MAs with significant shortcomings in reporting and risk of bias. In this context, while HuaChansu shows promise, higher quality SRs/MAs and randomized control trials are necessary to confirm its effectiveness and safety [29].

Liver cancer

Liver cancer, the sixth most common cancer and third leading cause of cancer-related death worldwide [15], is often treated with Transarterial Chemoembolization (TACE) at advanced stage [30]. This treatment reduces tumor blood supply by blocking hepatic arteria and gives high doses of chemotherapies to the tumor [30]. A meta-analysis (15 studies, 1225 patients) indicated that HuaChansu combined with TACE improved short-term effectiveness rates, quality of life, and 1- and 2-year survival rates compared to TACE alone [31]. This combination improves also the ORR and the 2-year survival rate in middle and advanced liver cancer stages [32]. A single-center randomized controlled trial (NCT01715532) compared HuaChansu combined with TACE versus TACE alone in unresectable hepatocellular carcinoma [33]. Results indicated significantly improved median PFS (6.8 months *vs.*, 5.3 months; $p = 0.029$) and Overall Survival (OS) (14.8 months *vs.*, 10.7 months; $p = 0.025$) with HuaChansu treatment [33]. Of note, the limitations of this trial include the non-blinded study design, data from a single center, and all patients having preserved liver functions [33].

Chemotherapeutic agents can also be replaced by HuaChansu in TACE [31]. Its effectiveness was reported in a meta-analysis (7 studies, 360 patients) where the authors found that HuaChansu could improve the quality of life and lower the grade I hepatotoxicity compared with traditional chemotherapeutic agent used during TACE [31]. A retrospective study (56 patients; 31 patients in HuaChansu TACE group *vs.*, 25 patients in Epirubicin TACE group) indicates also that HuaChansu could improve the efficacy of TACE by improving ORR in large hepatocellular carcinoma, better than Epirubicin as chemotherapeutic agent [34].

HuaChansu role in preventing recurrence post-surgery and TACE was also studied [35]. A multicenter randomized controlled trial (ChiCTR-TRC-07000033) with 379 patients across five Chinese hospitals compared HuaChansu treatment (intravenous injection) and TACE after small hepatocellular carcinoma resection [35]. HuaChansu treatment reduced recurrence risk by 30.5%, prolonged median recurrence-free survival, and reduced adverse effects like fatigue, fever, upper abdominal pain, and nausea compared to TACE alone [35]. A retrospective case-controlled study found that intravenous HuaChansu for 15 days increased PFS rates ($p < 0.01$) and OS rates ($p < 0.045$), indicating longer times before recurrence and metastasis after surgery compared to TACE alone [36].

A retrospective study analysed also the benefits of using versus Cisplatin and 5-Fluorouracil (CF) with Hepatic Arterial Infusion (HAI). The latter one allows to directly deliver drugs in hepatic arteria and reduces systemic toxicities due to first-pass metabolism in liver. This study including 130 patients (69 patients in HuaChansu group *vs.*, 61 patients in CF group) indicates that ORR increased by 17% while the OS and PFS decreased by 39% and 42%, respectively, for patients treated with HuaChansu [37].

Discussion

The impact of HuaChansu and its active components, bufadienolides, in cancer treatment, particularly through data from clinical trials and meta-analyses, has yielded promising results across various types of cancers, including hepatocellular carcinoma, non-small cell lung cancer, breast cancer, gallbladder cancer, gastric cancer, and liver cancer [7-34]. HuaChansu, as an additional treatment or used alone, has demonstrated potential in stabilizing disease, improving survival rates, enhancing quality of life, and reducing chemotherapy-related side effects. Table 1 reviews the effects of HuaChansu and HuaChansu in clinical studies.

The pilot study conducted in 2009 by the Fudan University Cancer Hospital and the MD Anderson Cancer Centre highlighted the tolerability and efficacy

Table 1: Overview of the effects of HuaChansu treatments on clinical parameters across different cancer types in clinical trials.

Cancer Type	Treatment	Overall Response Rate	Quality of Life	Side Effects	References
Hepatocellular carcinoma, Non-small cell lung cancer, Pancreatic cancer	HuaChansu (IV)	Disease stabilization (6 out of 15 patients), 20% reduction in tumor mass in 1 hepatocellular carcinoma patient	Improved (reduced toxicities greater than grade I)	Mainly Grade I toxicities observed (hematological, mucocutaneous, gastrointestinal, cardiovascular, respiratory effects)	[7]
Pancreatic cancer	HuaChansu (IV) + Gemcitabine	No benefit in ORR, PFS, and time to progression	Not reported	No additional toxicity induced by the combination	[10]
Breast cancer	HuaChansu (IV) + Chemotherapy (Docetaxel, Pirarubicin, Cyclophosphamide, Epirubicin, Vinorelbine, Capecitabine, 5-FU)	Improved ORR and clinical benefit rate	Enhanced (reduced tumor markers)	Not reported	[11]
Gallbladder cancer	HuaChansu (IV) + GEMOX	Partial response in 34.8% of patients, stable disease in 30.4% of patients	Improved (reduced pain, improved quality of life)	Mainly myelosuppression	[12]
Gastric cancer	HuaChansu (IV) + Chemotherapy (Oxaliplatin, Epirubicin, Floxuridine, Etoposide, Cisplatin, Capecitabine, Leucovorin, Paclitaxel)	Improved response rates, quality of life, KPS scores, and reduced cancer-related pain	Enhanced (reduced side effects such as nausea, vomiting, leukopenia, anemia, and gastrointestinal effects)	Not reported	[16-18]
Lung cancer	HuaChansu (PO and IV) + Chemotherapy (Docetaxel, Gemcitabine, Permetrexed, Cisplatin, Etoposide, Vinorelbine, Paclitaxel)	Improved survival in Stage III patients	Enhanced	Reduced leukopenia incidence, no differences observed for adverse effects like diarrhea and vomiting	[20-28]
Liver cancer	HuaChansu (PO or IV) + TACE	Improved short-term effectiveness rates, quality of life, 1-2 year survival rates, ORR	Not reported	Not reported	[31-35]

IV: Intravenous injection, PO: Per Os administration, RCT: Randomized Controlled Trial; [7]:Phase I; [10]: Phase II; [11,16-18,20-22,24,25,27,28,31-33,35]: Phase III.

of HuaChansu at higher doses, showing significant disease stabilization and manageable toxicity levels in patients with hepatocellular carcinoma, non-small cell lung cancer, and pancreatic cancer [7]. This paved the way for a phase II clinical trial which, despite not showing significant improvement in objective response rates or PFS, pointed out areas for further research, including dose optimization and administration methods.

Meta-analyses on breast cancer and gastric cancer revealed that combining HuaChansu with chemotherapy improved ORR, clinical benefit rates, and quality of life, underscoring the potential synergistic effects of this component [11]. The studies on gallbladder and lung cancer further support the use of HuaChansu in combination with conventional chemotherapy, showing improved survival rates and reduced side effects, but the lack of placebo controls in some studies necessitates cautious interpretation [10,17-26].

The extensive research on liver cancer, involving combinations of HuaChansu with TACE and other treatments, has shown significant improvements in short-term effectiveness rates, survival rates, and quality of life [29-32]. These studies emphasize HuaChansu's role in enhancing the efficacy of TACE and reducing adverse effects, highlighting its potential in managing advanced liver cancer stages and preventing post-surgery recurrence [33,34].

While these findings are encouraging, several limitations must be addressed. The variability in study designs, patient populations, dosages, and treatment protocols across different trials necessitates standardization for more definitive conclusions. Furthermore, the absence of placebo controls and the need for longer follow-up periods in some studies indicate areas for improvement in future research.

Conclusion

The clinical trials and meta-analysis studies reviewed demonstrate the promising role of HuaChansu and bufadienolides in cancer treatment (Figure 1). The combination of HuaChansu with conventional therapies has shown potential in improving survival rates, stabilizing disease progression, and enhancing the quality of life for patients with various types of cancer. However, further research is necessary to optimize dosages, administration methods, and treatment protocols. Standardizing study designs and including placebo controls will enhance the reliability of future findings. Overall, HuaChansu represents a valuable addition to the arsenal of cancer treatments, warranting continued investigation and integration into clinical practice.

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