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Review

# Therapeutic Role of Phytochemicals in Gallbladder Cancer: Pharmacological Activity and Associated Molecular Mechanisms

Kanika Patel, Dinesh Kumar Patel

Department of Pharmaceutical Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Prayagraj, Uttar Pradesh, India

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**Corresponding author:** Dinesh Kumar Patel, e-mail: dkp.itbhu@gmail.com

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**Abstract**

Gallbladder cancer (GBC) is a relatively rare but highly lethal malignancy. It is the most aggressive biliary tract carcinoma and the sixth most common gastrointestinal cancer worldwide. Over 90% of patients are diagnosed at an advanced stage due to the absence of symptoms in the early stages. The primary clinical treatment for GBC is surgical resection, while chemotherapy and postoperative radiation therapy can improve prognosis. This study compiles and analyzes scientific data from PubMed, Google Scholar, Google, Scopus, and ScienceDirect to evaluate the biological potential of phytochemicals in medicine and their efficacy in treating gallbladder cancer. Additional scientific evidence has been gathered from books, journals, and scientific reports to assess the therapeutic effectiveness of phytochemicals against GBC. This article also discusses the biological significance of gallbladder cancer in medicine. Scientific data analysis highlights the biological potential of numerous phytochemicals, including oxymatrine, baicalein, stigmasterol, icariin, dihydrotanshinone I, ursolic acid, emodin, garcinol, wogonin, pterostilbene, fangchinoline, isoliquiritigenin, cirsimaritin, ponicidin, oridonin, magnolol, and ginsenoside Rg3, in targeting gallbladder cancer. Additionally, this study examines the molecular mechanisms underlying their efficacy. Scientific analysis confirms the therapeutic potential of phytochemicals in GBC treatment. However, further research is needed to validate their clinical applicability, elucidate precise molecular mechanisms, and ensure their safety profiles.

**Keywords:** Phytochemicals, gallbladder cancer, cancer, herbal medicine, pharmacology

## INTRODUCTION

Herbal medicine, derived from plants and various natural sources, has long served as a vital foundation for prescription drugs. Globally, more than 80% of people continue to rely on herbal preparations for their primary healthcare needs. Herbal remedies, composed of plant-derived substances and the phytochemicals they produce, play a crucial role in primary healthcare systems.[1–3] These remedies may consist of single herbs or a combination of plant-based compounds and their derivatives. The widespread use of herbal medicine in modern healthcare is largely due to its significant therapeutic benefits compared to traditional allopathic drugs.[4–6] Phytochemicals, which are pure bioactive compounds found in plants, are responsible for the diverse pharmacological properties of plant materials. These compounds contribute to the colors, flavors, and structural organization of plant materials at different levels. Plant-based products have been widely utilized in medicine, nutraceuticals, cosmetics, beverages, and perfumes. Many essential products used in daily life, including pharmaceuticals, originate from natural sources.[7–9] Additionally, research has demonstrated that phytochemicals are responsible for various physiological processes within living tissues.[10–12]

## METHODOLOGY

This study aims to examine the pharmacological activity and biological potential of phytochemicals in medicine, as well as their effectiveness in treating gallbladder cancer. It also explores the molecular mechanisms underlying the pharmacological actions of these phytochemicals and their therapeutic efficacy against gallbladder cancer. Using the keywords herbal medicine, phytochemicals, and gallbladder cancer, this review collected 135 research papers from various scientific databases, including PubMed, Google Scholar, Google, Scopus, and ScienceDirect. Among these, 55 publications were selected for a comprehensive analysis of their scientific findings. Additionally, this review provides a concise explanation of the molecular mechanisms that contribute to the therapeutic efficacy of phytochemicals in gallbladder cancer. The findings presented in this article further support the therapeutic potential of phytochemicals in the treatment of gallbladder cancer.

## GALLBLADDER CANCER

Gallbladder cancer (GBC) is the most common bile duct cancer and a highly aggressive malignancy with a poor prognosis and high mortality rate. The only potentially curative treatment for GBC is surgical resection.[13] Although the exact cause of GBC remains unknown, it is frequently associated with gallstones and chronic gallbladder inflammation. Due to the gallbladder's anatomical location beneath the liver, early detection is challenging, leading to most diagnoses occurring at advanced stages.[14] Gallbladder carcinoma accounts for 1.7% of all cancer-related deaths. With a

male-to-female ratio of 1:5, it is a serious condition that predominantly affects older women in their 70s.[15] GBC ranks sixth among digestive system malignancies worldwide and is the most prevalent biliary tract cancer, comprising 80–95% of all biliary tract cancers.[16] It is characterized by early lymph node invasion and distant metastases. Approximately 90% of GBC patients are diagnosed at an advanced, incurable stage, as the tumor is typically aggressive and spreads rapidly.[17] Many patients who undergo surgery remain at risk of recurrence or metastasis.[18] Northern India's Indo-Gangetic belt has the highest incidence of GBC, with a rate of 21 per 100,000.[19] According to GLOBOCAN 2020, GBC is the 20th most common cancer in India, accounting for 1.7% of all cancer-related deaths, with an incidence rate of 1.5%. The prevalence of GBC varies by region and ethnic group, with high rates reported in Pakistan, Northern India, East Asia, and South America.[20] Surgery is considered the only effective treatment for GBC; however, fewer than 20% of patients are eligible for surgery at the time of diagnosis.[21] Various factors, including lifestyle, infections, and genetics, have been linked to gallbladder cancer.[22] The incidence rate for women in Northern India is 22 per 100,000, while in Pakistan and among North American Indians (New Mexico), it is 11 per 100,000. In contrast, the overall prevalence in Europe is low, ranging from 0 to 4 per 100,000. However, certain Eastern European countries, including Poland, have reported relatively high incidence rates, reaching 14 per 100,000.[23]

## AVAILABLE THERAPY

Currently, there are limited treatment options for advanced GBC. The first-line chemotherapy regimen of gemcitabine and cisplatin has a low five-year survival rate.[14] However, combination chemotherapy with gemcitabine and cisplatin has shown some benefit as a first-line palliative treatment, offering a slightly improved one-year survival rate.[19] For patients with incurable GBC, treatment options include systemic chemotherapy and radiation therapy. Since the late 1990s, gemcitabine has been recognized as an effective anticancer treatment for various malignancies.[24] Although radical resection remains the most effective treatment for GBC, overall survival rates remain low. Chemotherapy is the most commonly used treatment for this cancer.[25] Systemic chemotherapy remains the primary option for patients with advanced GBC. However, regimens such as gemcitabine with cisplatin or FOLFOX have limited efficacy, and their severe side effects remain a significant concern.[26] Surgical resection is the only potentially curative treatment for GBC. Palliative treatments, such as chemotherapy and radiation therapy, are commonly used to improve prognosis in patients with recurrent or incurable disease. However, these treatments rarely yield satisfactory results.[27]

According to research, consuming phytochemicals may help prevent cancer and improve the quality of life for cancer patients. Understanding the molecular mechanisms underlying the effects of these bioactive compounds may enable the scientific community to develop or refine novel therapeutic approaches for devastating diseases such as cancer.[28] The active components of Traditional Chinese Medicine (TCM), including dihydroartemisinin, magnolol, and ponicidin, have shown promise in the treatment of GBC. Dihydroartemisinin significantly suppresses GBC cell motility and invasion by targeting translationally controlled tumor protein-dependent signaling pathways, specifically by inhibiting the activation of cell division control protein 42 (CDC42). Magnolol, a bioactive compound extracted from *Magnolia officinalis*, also exhibits notable anti-tumor activity against GBC. By upregulating p53 and p21 while downregulating cyclin D1, CDC25A, and cyclin-dependent kinase 2 (CDK2), it inhibits GBC cell proliferation, induces cell cycle arrest at the G0/G1 phase, and promotes mitochondria-dependent apoptosis. Similarly, ponicidin, a diterpenoid compound derived from *Rabdosia rubescens*, demonstrates significant anti-tumor efficacy against GBC cells.[14] Wogonin has been shown to inhibit tumor growth by inducing cell cycle arrest, promoting apoptosis, and preventing metastasis, according to several preclinical studies.[28] Plant sterols have demonstrated strong anti-proliferative and apoptosis-inducing effects against various carcinomas.[29] Sanguinarine, a DNA intercalator, shares a molecular structure with known polyaromatic hydrocarbon carcinogens. Additionally, sanguinarine induces endoplasmic reticulum and oxidative stress, leading to the unfolded protein response and the formation of genetic lesions involving 8-hydroxyguanine. Sanguinarine has also been implicated as an etiological factor in gallbladder carcinoma.[30] Emodin, a reactive oxygen species (ROS) generator, enhances the sensitivity of gallbladder cancer SGC-996 cells to cisplatin by producing ROS and downregulating multidrug-resistance-associated protein 1 (MRP1).[31]

## PHYTOCHEMICALS EFFECTIVE AGAINST GALLBLADDER CARCINOMA

### Oxymatrine

This study aims to investigate the anti-tumor activities of oxymatrine and its underlying mechanisms in gallbladder carcinoma cells both *in vitro* and *in vivo*. The findings indicate that oxymatrine inhibits cell viability and metastatic potential in a dose-dependent manner while inducing apoptosis. Additionally, the results reveal that oxymatrine upregulates PTEN expression in GBC cells, while significantly downregulating phosphorylated protein kinase B (p-AKT), matrix metalloproteinase (MMP)-2, MMP-9, and the Bcl-2/Bax ratio. Furthermore, the oxymatrine-mediated suppression of GBC-SD cells was markedly reversed by pretreatment with a specific PI3K/AKT activator (IGF-1). Oxymatrine administration also led to a significant, dose-dependent reduction in tumor growth. These findings suggest that oxymatrine may serve as a promising new chemotherapeutic agent for GBC.[27]

### Baicalein

The anti-proliferative and anti-metastatic effects of baicalein, along with its underlying mechanisms in gallbladder carcinoma, have been investigated. Treatment with baicalein significantly inhibited proliferation and promoted apoptosis in GBC-SD and SGC996 cells, two widely used gallbladder cancer cell lines. Additionally, baicalein treatment suppressed the metastatic potential of GBC cells. The findings indicate that baicalein inhibits GBC cell growth and metastasis by downregulating the expression of Zinc Finger Protein X-linked (ZFX). Baicalein may serve as a potential phytochemical flavonoid for GBC treatment, while ZFX could act as a molecular marker or predictive target for the disease.[17]

### Stigmasterol

Researchers have investigated the role of stigmasterol in inducing apoptosis in human gallbladder cancer cells by downregulating the Jab1 protein. Stigmasterol downregulated the Jab1 gene while upregulating the expression of p27. These gene modifications may be mediated through the mitochondrial apoptotic signaling pathway. The induction of apoptosis leads to the activation of caspase-3. An increase in apoptotic cells and DNA fragmentation was demonstrated using Annexin V staining, Hoechst staining, and cell cycle analysis. Stigmasterol may serve as a promising anti-cancer treatment for gallbladder cancer by specifically targeting Jab1.[29]

### Icariin

Researchers have explored the biological potential of icariin, a fla-

vonoid derived from *Epimedium* (*Herba Epimedii*), in enhancing the anticancer effects of gemcitabine in gallbladder cancer. In both GBC-SD and SGC-996 cells, icariin (40–160 μg/mL) induced apoptosis and reduced cell proliferation in a dose-dependent manner, with SGC-996 cells showing lower susceptibility to the treatment. Additionally, icariin (40 μg/mL) significantly enhanced the anticancer activity of gemcitabine (0.5 μmol/L) in both cell lines. In a gallbladder cancer xenograft model, mice treated with a combination of gemcitabine and icariin developed significantly fewer tumors compared to those treated with either drug alone. Icariin exerts anticancer effects and enhances gemcitabine antitumor activity in gallbladder cancer by inhibiting NF-κB activity. The combined administration of gemcitabine and icariin may offer a more effective treatment option for individuals with gallbladder cancer.[24]

**Dihydrotanshinone I**

The anti-tumor effects of dihydrotanshinone I on gallbladder carcinoma have been studied, along with its possible molecular mechanisms. Dihydrotanshinone I anti-tumor activity was effectively counteracted by the overexpression of nuclear factor erythroid 2-related factor 2 (Nrf2), while Nrf2 knockdown significantly enhanced its inhibitory effects on GBC. Additionally, GBC cells became more sensitive to dihydrotanshinone I treatment when protein kinase C (PKC) and nuclear import inhibitors were used. Conversely, dihydrotanshinone I-induced apoptosis and reactive oxygen species (ROS) production in NOZ and SGC-996 cells were inhibited by Nrf2 activators, proteasome inhibitors, antioxidants, and PKC activators. By regulating Nrf2 phosphorylation and the Keap1-Nrf2 signaling pathway, dihydrotanshinone I suppressed GBC cell growth. These findings provide strong justification for further research on dihydrotanshinone I as a potential therapeutic agent for GBC.[14]

**Ursolic Acid**

Ursolic acid, derived from *Isodon excisoides*, has been tested for its antiproliferative and anti-invasive properties in gallbladder carcinoma, along with its underlying mechanisms. In a dose-dependent manner, ursolic acid induced apoptosis in GBC-SD cells while inhibiting their invasion and proliferation. PCR array analysis revealed that 24 genes were differentially expressed in ursolic acid-treated groups compared to the untreated group. These gene expression changes indicated that ursolic acid activated the extrinsic apoptotic pathway, leading to apoptosis in GBC-SD cells. Further analysis using the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database confirmed that ursolic acid suppressed the Nuclear factor kappa B (NF-kB) and protein kinase B (AKT) signaling pathways. These findings suggest that ursolic acid may offer a promising approach for the chemoprevention or chemotherapy of GBC.[21]

**Emodin**

Side population (SP) cells, a model of cancer stem cell-like cells, have been used to determine whether emodin affects the cancer stem cells of gallbladder carcinoma. Emodin not only reduced the SP cell ratio, effectively inhibited clone formation, and eliminated sphere formation by suppressing the function of ATP-binding cassette super-family G member 2 (ABCG2)—a protein associated with the Hoechst dye efflux activity of SP cells—but also significantly increased the intracellular accumulation of doxorubicin, the primary substrate of the ABCG2 efflux pump, through a mechanism related to reactive oxygen species (ROS). Emodin, either alone or in combination with chemotherapy, is a potent drug that targets the cancer stem-like SP cells of gallbladder carcinoma.[31] In a ROS-dependent manner, emodin promotes the death of gallbladder cancer cells stimulated by cisplatin. Further research revealed that cisplatin suppresses the expression of survivin, a protein involved in apoptosis inhibition, when assessed after drug treatment. Additionally, studies demonstrated that emodin downregulated survivin expression without causing detectable harm to healthy tissues, thereby enhancing the anticancer effects of cisplatin *in vivo*.[25]

**Garcinol**

Gallbladder carcinoma cells (GBC-SD and NOZ) were treated with garcinol and assessed using the Cell Counting Kit-8 (CCK-8) assay. GBC-SD cells were then selected for further transwell chamber assays, Western blot analysis, and quantitative real-time polymerase chain reaction (qRT-PCR). The results indicated that garcinol significantly inhibited GBC cell proliferation in a dose- and time-dependent manner. Additionally, garcinol treatment suppressed GBC-SD cell invasion in a dose-dependent manner. By downregulating mRNA expression levels, garcinol reduced the activity of two key enzymes involved in tumor invasion: MMP2 and MMP9.[32]

**Wogonin**

This study aimed to investigate the effects and mechanisms of wogonin on the invasion and motility of human gallbladder cancer GBC-SD cells. At doses of 1–10 μM, wogonin significantly reduced the mobility and invasive activity of human gallbladder cancer GBC-SD cells without inducing apoptosis. Furthermore, wogonin decreased the production of MMP-2, MMP-9, and phosphorylated extracellular signal-regulated protein kinase 1/2 (ERK1/2) in a concentration-dependent manner but did not affect phosphorylated Akt. Additionally, it was determined that the metastasis suppressor maspin is a downstream target of wogonin. Wogonin increased both maspin protein and mRNA levels. By upregulating the metastasis suppressor maspin, wogonin inhibits cell invasion and motility. Overall, these findings provide new insights into the chemoprotective properties of wogonin, a key component of the traditional Chinese medicine *Scutellaria baicalensis*.[33]

**Pterostilbene**

This study examined the potential application of pterostilbene *in vitro* and *in vivo* for the treatment of gallbladder cancer. Pterostilbene effectively inhibited the proliferation, migration, and invasion of gallbladder cancer cells. Additionally, it demonstrated the ability to induce apoptosis *in vitro*. Consistent with these *in vitro* findings, tumor xenograft models showed that pterostilbene exhibited low toxicity while suppressing tumor growth *in vivo*. Because pterostilbene inhibits the PI3K/AKT signaling pathway, which regulates cell proliferation, it represents a potential therapeutic agent for gallbladder cancer.[34]

**Fangchinoline**

Fangchinoline, a bisbenzylisoquinoline alkaloid, was found to have a dose-dependent inhibitory effect on GBC cell proliferation and colony formation. Furthermore, Hoechst staining, TUNEL assays, and flow cytometry demonstrated that fangchinoline effectively induced apoptosis in GBC cells. Lastly, we confirmed that fangchinoline suppressed the formation of xenograft tumors *in vivo*. These findings suggest that fangchinoline may be a potential therapeutic agent for the treatment of gallbladder cancer.[35]

**Isoliquiritigenin**

A range of methods, including cytotoxicity testing, RNA sequencing, quantitative real-time polymerase chain reaction, ROS detection, lipid peroxidation detection, ferrous ion detection, glutathione disulfide/glutathione (GSSG/GSH) detection, lentivirus transfection, tumorigenesis

experiments in nude mice, and immunohistochemistry, were used to evaluate the effects of isoliquiritigenin on GBC cells both *in vitro* and *in vivo*. *In vitro*, isoliquiritigenin significantly inhibited GBC cell growth. The primary mechanism underlying this inhibition was ferroptosis, with HMOX1 and GPX4 identified as key molecules in the process. HMOX1 knockdown or GPX4 overexpression significantly increased GBC cell survival and reduced sensitivity to isoliquiritigenin-induced ferroptosis. Furthermore, isoliquiritigenin markedly altered the GSSG/GSH ratio, ROS levels, lipid peroxidation levels, and iron concentration in GBC cells. Lastly, by regulating HMOX1 and GPX4, isoliquiritigenin controlled ferroptosis in GBC and significantly suppressed tumor proliferation *in vivo*.[36]

**Cirsimaritin**

Research on the biological effects of cirsimaritin on the human gallbladder cancer cell line GBC-SD has demonstrated that it induces mitochondrial apoptosis in GBC-SD cells and inhibits tumor cell proliferation. Additionally, cirsimaritin downregulated Akt phosphorylation and triggered endoplasmic reticulum stress, further supporting its potential efficacy against human gallbladder cancer.[37]

**Ponicidin**

The effects of ponicidin on GBC cell growth were examined using CCK-8, colony formation, and EdU-488 DNA synthesis assays. The impact of ponicidin on the invasion and migration of GBC cells was assessed using wound healing, cell invasion, and migration assays. To explore the underlying mechanisms, mRNA sequencing was performed. Protein expression levels were determined through immunohistochemical labeling and Western blot analysis. The binding motif was validated using the dual-luciferase assay and the ChIP assay. To evaluate the anti-tumor efficacy and safety of ponicidin, a nude mouse model of GBC was employed. *In vitro*, ponicidin inhibited the proliferation, invasion, and migration of GBC cells. Furthermore, in the nude mouse model, ponicidin effectively and safely suppressed tumor growth. These findings suggest that ponicidin holds promise as a safe and effective treatment for GBC.[26]

**Oridonin**

This study examined the effects of oridonin on GBC cell motility, apoptosis, proliferation, and the cell cycle both *in vitro* and *in vivo*. Additionally, the fundamental mechanisms underlying oridonin function in hypoxia-induced cell migration were investigated in GBC. Oridonin treatment increased cell apoptosis, induced cell cycle arrest at the G0/G1 phase, and significantly reduced GBC-SD cell proliferation and metastatic potential in a dose-dependent manner. Furthermore, in a GBC-SD cell xenograft model, oridonin inhibited GBC cell proliferation and decreased HIF-1α and MMP-9 expression levels. Oridonin exhibits antitumor effects in GBC.[38] The primary objectives of this study were to explore the mechanisms behind oridonin-induced apoptosis and cell cycle arrest, as well as to evaluate the inhibitory effects of oridonin, a diterpenoid derived from *Rabdosia rubescens*, on gallbladder cancer both *in vitro* and *in vivo*. Oridonin exhibited strong growth suppression, S-phase arrest, apoptosis, and colony formation inhibition in SGC996 and NOZ cells in a dose-dependent manner. In athymic nude mice, NOZ xenograft growth was significantly suppressed after three weeks of intraperitoneal injections of oridonin at doses of 5, 10, or 15 mg/kg. Western blot analysis revealed that oridonin regulated proteins associated with the cell cycle in response to S-phase arrest. Oridonin potent anti-gallbladder cancer effects are linked to its regulation of the mitochondrial pathway, which plays a crucial role in S-phase arrest and apoptosis. Consequently, oridonin may serve as a novel antitumor drug for the treatment of gallbladder cancer.[13]

**Magnolol**

This study investigated the effects of magnolol on the development of human GBC cell lines. Magnolol significantly inhibited GBC cell line growth in a dose- and time-dependent manner. When cells were pretreated with a p53 inhibitor (pifithrin-α) before magnolol treatment, pifithrin-α blocked magnolol-induced apoptosis and G0/G1 arrest. The same mechanisms activated *in vitro* were also observed *in vivo*, where magnolol suppressed tumor growth. Magnolol effectively inhibits the proliferation of GBC cells and may represent a promising therapeutic agent for GBC treatment.[39]

**Ginsenoside Rg3**

The biological potential of ginsenoside Rg3 in gallbladder cancer treatment has been evaluated in both *in vitro* and *in vivo* studies. Ginsenoside Rg3 activated the ER stress-mediated signaling pathway, leading to apoptosis in the gallbladder cancer cell line GBC-SD. Additionally, ginsenoside Rg3 treatment resulted in a significant upregulation of long intergenic non-protein coding RNA-p21. By upregulating the ER stress-mediated signaling pathway, ginsenoside Rg3 effectively suppressed tumor growth in a GBC-SD xenograft model. These findings suggest that the antitumor activity of ginsenoside Rg3 in gallbladder cancer is mediated by ER stress activation.[18] This study also explored the underlying signaling pathways and the potential impact of ginsenoside Rg3 on gallbladder cancer cells. Rg3 exhibited strong cytotoxic and pro-apoptotic effects on both primary and established human gallbladder cancer cells. However, Rg3-induced cytotoxicity was significantly diminished by CHOP shRNA knockdown, the ER stress inhibitor salubrinal, and the caspase-12 inhibitor z-ATAD-fmk. *In vivo*, oral administration of Rg3 significantly reduced the growth of GBC-SD xenografts in nude mice. However, its efficacy was weakened when co-administered with salubrinal, an ER stress inhibitor. These results indicate that ginsenoside Rg3-induced antitumor activity in gallbladder cancer is mediated through ER stress activation.[40]

## DISCUSSION

In modern medicine, medicinal plants have been used to treat a wide range of health conditions in both industrialized and developing nations.[41] In several countries, including China, India, Korea, and Japan, medicinal plants are an integral part of the healthcare system.[42] In recent decades, medicinal herbs have also been widely utilized in North America and Europe, primarily as functional and nutritional products.[43–45] Each year, Americans spend $30 billion on approximately 55,000 over-the-counter nutritional supplements. Herbal products are commercially available in the U.S., Europe, Canada, and Australia for various medical purposes.[46–48] For centuries, medicinal plants have been used in the food, pharmaceutical, and medical industries.[49,50] Herbal medicines have a long history of traditional use and are widely favored due to their accessibility, pharmacological activity, biological potential, lower incidence of side effects, and affordability compared to synthetic drugs.[51–54] These advantages contribute to their widespread popularity. To combat both infectious and non-infectious diseases, new pharmaceutical compounds are being developed using herbal medicines and their phytochemical constituents.[55] Scientific information on these phytochemicals has been collected from PubMed, Google Scholar, Google, Scopus, and Science Direct and analyzed in this study to assess their biological potential in medicine and their effectiveness in treating gallbladder cancer. The efficacy of phytochemicals in gallbladder cancer treatment has also been extensively reviewed using data from books, journals, and scientific reports. This article further explores the biological significance of gallbladder cancer in medicine. An analysis of

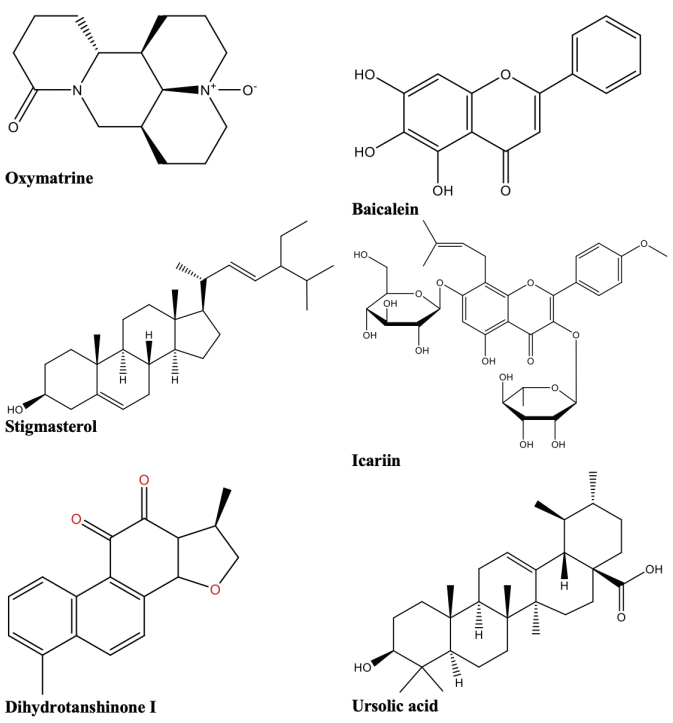


**Figure 1.** Chemical structure of phytochemicals having effectiveness on gallbladder cancer.

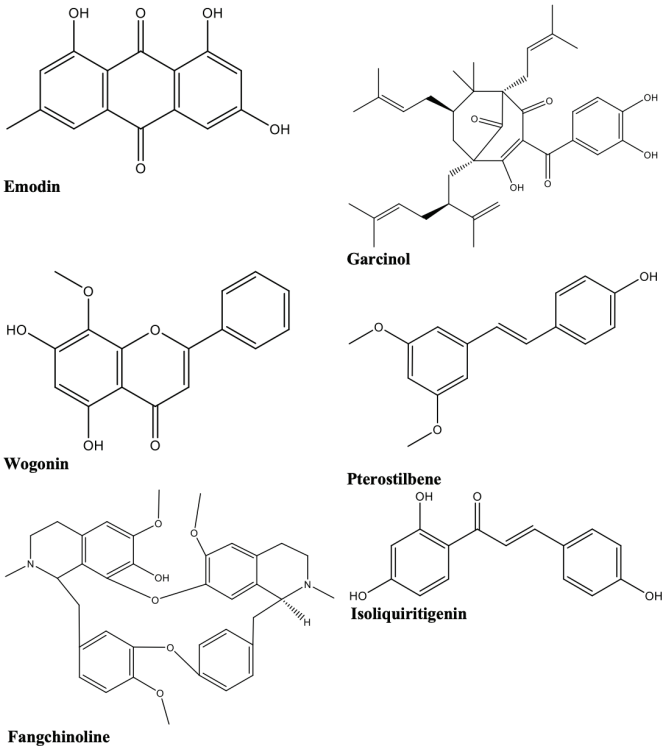


**Figure 2.** Chemical structure of phytochemicals having effectiveness on gallbladder cancer.

scientific data has demonstrated the biological potential of oxymatrine, baicalein, stigmasterol, icariin, dihydrotanshinone I, ursolic acid, emodin, garcinol, wogonin, pterostilbene, fangchinoline, isoliquiritigenin, cirsimaritin, ponicidin, oridonin, magnolol, and ginsenoside Rg3 in the treatment of gallbladder cancer (Figures 1–3). Additionally, the molecular mechanisms underlying their therapeutic effects are examined in this study and summarized in Table 1. Further scientific research should be conducted to investigate the biological sources of these phytochemicals in medicine, as data analysis has demonstrated their efficacy against gallbladder cancer. Although these phytochemicals have shown promise in treating gallbladder cancer, additional studies are needed to explore their effects on other malignancies and to determine their broader therapeutic potential. To better understand their biological applications in medicine, the healthcare sector should also evaluate their effectiveness in treating different human diseases. Furthermore, comprehensive clinical studies should be conducted to determine each phytochemical's plasma profile, ensuring its safety for clinical use.

## FUTURE PERSPECTIVE

The use of phytochemicals to enhance the physical, chemical, and biological properties of food, as well as to treat human diseases, has recently garnered increased attention from the scientific community. This review examined the effectiveness of phytochemicals in gallbladder cancer, highlighting their biological significance, therapeutic efficacy, and key molecular mechanisms. However, further pharmacological research and deeper investigations into their molecular mechanisms are necessary for their clinical application in modern medicine.

Additional studies should be conducted to determine the natural sources of these phytochemicals and confirm their presence in nature. Scientific research, supported by both *in vitro* and *in vivo* studies, should explore the metabolic pathways and mechanisms of action of these

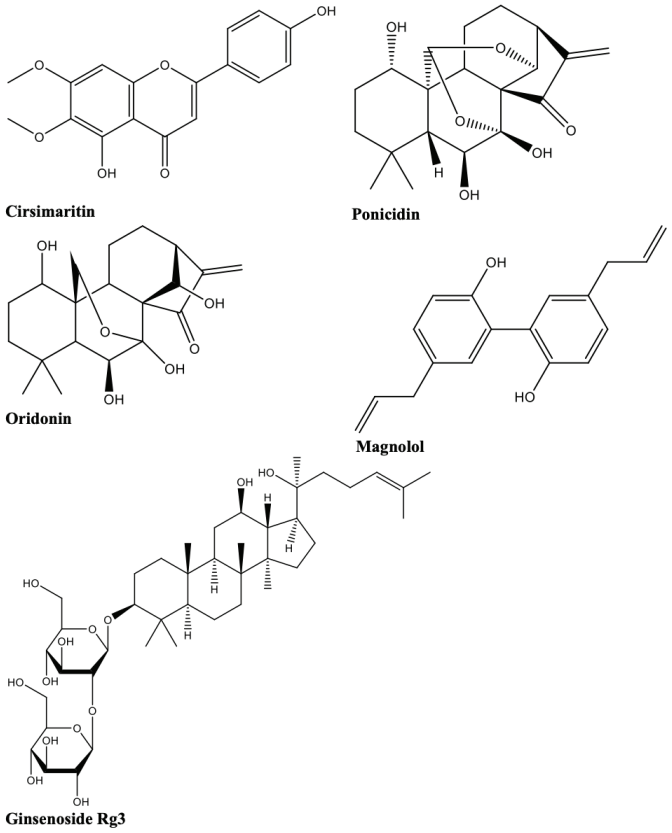


**Figure 3.** Chemical structure of phytochemicals having effectiveness on gallbladder cancer.

**Table 1.** Molecular mechanism of phytochemicals having effectiveness on gallbladder cancer.

| S. No. | Phytochemical | Molecular Mechanism | Reference |
|---|---|---|---|
| 1. | **Oxymatrine** | The reduction of the PTEN/PI3K/AKT pathway, which was thought to be the key signaling route in controlling carcinogenesis, is responsible for the decrease of cell proliferation, migration, invasion, and the induction of apoptosis in response to oxymatrine in GBC cells. | [27] |
| 2. | **Baicalein** | Zinc finger protein X-linked (ZFX) expression was down-regulated by baicalein, which prevented GBC cell proliferation and metastasis. | [17] |
| 3. | **Stigmasterol** | Genes may be altered through the signaling route of mitochondrial apoptosis. The apoptotic induction triggers the activation of caspase-3 growth in DNA and apoptotic cells. | [29] |
| 4. | **Icariin** | Icariin caused G(0)-G(1) phase arrest, increased caspase-3 activity, lowered the expression of Bcl-2, Bcl-xL, and survival proteins in GBC-SD cells, and greatly reduced both constitutive and gemcitabine-induced NF-κB activity. | [24] |
| 5. | **Dihydrotanshinone I** | Dihydrotanshinone I, by encouraging Keap1-mediated Nrf2 degradation and preventing protein kinase C (PKC)-induced Nrf2 phosphorylation, mainly targeted Nrf2. As a result, Nrf2 nuclear translocation is suppressed, and the expression of its target gene is decreased. | [14] |
| 6. | **Ursolic acid** | Ursolic acid suppresses the NF-κB and Akt signaling pathways, which may be linked to the apoptosis and invasion inhibition of GBC-SD cells. | [21] |
| 7. | **Emodin** | By inhibiting ABCG2 expression, emodin may sensitize cisplatin to overcome SP cells' chemoresistance. Crucially, emodin/cisplatin co-treatment *in vivo* inhibited tumor growth produced from SP cells by downregulating ABCG2 expression, just like the experiment *in vitro* did. | [25,31] |
| 8. | **Garcinol** | In GBC-SD cells, garcinol treatment also reduced Stat3 and Akt activity. When combined, garcinol actions on GBC-SD cells may be linked to the inhibition of the Stat3 and Akt signaling pathways, which may help to block their downstream targets, including MMP2 and MMP9 mRNA levels. | [32] |
| 9. | **Wogonin** | Maspin deletion nearly entirely eliminated wogonin-induced suppression of MMP-2, MMP-9, and phosphorylated ERK1/2, as well as GBC-SD cell invasion and motility. | [33] |
| 10. | **Pterostilbene** | Pterostilbene reversed EMT with a correlated inhibition of PI3K/Akt activation. | [34] |
| 11. | **Fangchinoline** | The PI3K/Akt/XIAP axis, was significantly inhibited in GBC cells after treating with fangchinoline. | [35] |
| 12. | **Isoliquiritigenin** | Isoliquiritigenin mostly caused ferroptosis in GBC by downregulating GPX4 both *in vitro* and *in vivo* and activating the p62-Keap1-Nrf2-HMOX1 signaling pathway. | [36] |
| 13. | **Cirsimaritin** | Cirsimaritin inhibited the growth of tumor cells and induced mitochondrial apoptosis in GBC-SD cells. | [37] |
| 14. | **Ponicidin** | Ponicidin inhibited the expression of MAGEB2 to have anti-tumor actions. Ponicidin inhibited the MAGEB2 transcript by upregulating FOXO4 expression and encouraging its accumulation in the nucleus. | [26] |
| 15. | **Oridonin** | By focusing on the HIF-1α/MMP-9 signaling pathway, oridonin can inhibit cell migration and the transition of tumor epithelial cells into mesenchymal cells. | [13,38] |
| 16. | **Magnolol** | Magnolol also inhibited the advancement of the cell cycle at the G0/G1 phase and caused apoptosis associated to mitochondria by upregulating the levels of the proteins p53 and p21 and downregulating those of cyclin D1, CDC25A, and Cdk2. | [39] |
| 17. | **Ginsenoside Rg3** | Elevated expression of lipocalin 2, CCAAT/enhancer-binding protein homologous protein, activating transcription factor 4 (ATF4), and phosphorylation of eukaryotic translation-initiation factor 2α (eIF2α) | [18] |

compounds. Furthermore, comprehensive pharmacokinetic data, including absorption, distribution, metabolism, and excretion (ADME) profiles, should be established by comparing these phytochemicals with other known drugs to underscore their medicinal significance. To provide scientific evidence regarding the specific safety and toxicity of these phytochemicals, data from future preclinical and clinical studies must be collected. Additionally, researchers should investigate the potential synergistic effects of combining these phytochemicals with other drugs and treatments. The scientific insights presented in this review will be valuable for researchers exploring the potential health benefits of these phytochemicals in medicine, particularly in the treatment of gallbladder cancer.

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