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REVIEW

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Molecular mechanisms of action and chemosensitization of tumor cells in ovarian cancer by phytochemicals: A narrative review on pre-clinical and clinical studies

Josianne Rocha Barboza[1] | Francisco Assis Nascimento Pereira[1] | Cleydlenne Costa Vasconcelos[1] | Maria Nilce de Sousa Ribeiro[1] | Alberto Jorge Oliveira Lopes[1,2]

[1]Laboratório de Farmacognosia, Departamento de Farmácia, Campus Bacanga, Universidade Federal do Maranhão, São Luís, Brazil

[2]Postgraduate Program in Chemistry, Instituto Federal de Educação, Ciência e Tecnologia do Maranhão, Campus Monte Castelo, São Luis, Brazil

Correspondence
Alberto Jorge Oliveira Lopes, Josianne Rocha Barboza and Maria Nilce de Sousa Ribeiro
Universidade Federal do Maranhão. Laboratório de Farmacognosia, Departamento de Farmácia, Campus Bacanga, Av. dos Portugueses, 1966, São Luís 65080-805, Maranhão, Brazil.
Email: lopesajo@gmail.com; josi.anne.r@hotmail.com; mnsousaribeiro@gmail.com

Abstract

Ovarian cancer is the second-leading cause of death among women with cancer of the genital tract. Currently, drugs derived from platinum and taxanes constitute the majority of ovarian cancer treatments. Patients undergoing this chemotherapy are susceptible to cumulative toxic effects and resistance to chemotherapy. Therefore, it is crucial to identify treatment options that are both more effective and better tolerated by patients. Phytochemicals in this context are plant-derived chemicals with antitumor activity that can be used as therapeutic or adjuvant agents in the treatment of ovarian cancer. Consequently, the purpose of this literature review is to demonstrate through existing pre-clinical and clinical trials the potential of phytochemicals in the treatment of ovarian cancer, the mechanisms of action involved, and to contribute to the development of new therapeutic options for ovarian cancer. For this review, the databases PubMed, Scopus, Science Direct, and ClinicalTrials.gov were queried between 2010 and 2022 using terms such as "ovarian cancer," "phytochemicals," "phenolic compounds," "terpenes," and "alkaloids." The present review summarized the possible molecular mechanisms of action by which phytochemicals, such as phenolic acids, flavonoids, diterpenes, triterpenes, saponins, and alkaloids, inhibit this type of cancer, specifically the ability of phytochemicals to induce cell growth regulation, apoptosis, oxidative stress reduction, anti-angiogenesis, and chemosensitization of tumors in ovarian cancer. As their action and cellular mechanism have already been demonstrated in several pre-clinical trials, the

Abbreviations: Akt, protein kinase B; ASK1, Apoptosis signal-regulating kinase 1; ATG, autophagy related proteins; Bax, pro-apoptotic BCL-2 associated protein X; Bcl-2, B-cell lymphoma protein 2; BRCA1 and BRCA2, Breast Cancer types 1 and 2; CARL, Calreticulin; CAT, catalase; CDKs, D-type cyclins, and cyclin-dependent kinases; CHK2, Checkpoint kinase 2; CisR, Cisplatin resistant; COF1, Cofilin-1; ENPL, endoplasmin; EpCAM, epithelial cell adhesion molecules; Erk, extracellular signal-regulated kinase pathway; FDA, Food and Drug Administration; FOXP3, forkhead box protein 3; GPx, glutathione peroxidases; GRP78, 78 kDa glucose-regulated protein; GSH, potentiators of the redox status of glutathione; HIF-1α, hypoxia-inducible factor 1-alpha; JNK, c-Jun N-terminal kinases; LC3II, Light chain 3 protein; MAPK, mitogen-activated protein kinase; MDM2, Murine Doble Minute 2; MDR-1, multidrug resistance protein 1; MIC-1, micronemal protein; MMP-2 and MMP-9, matrix metalloproteinases 2 and 9; mTOR, mammalian-target of rapamycin signaling pathway; NACA, Nascent polypeptide associated complex; NF-κB, Nuclear factor-κB; NRF2, nuclear factor related to erythroid 2; PARP, poly-ADP-ribose polymerase; PEG, poly (ethylene glycol).; PI3K, Phosphoinositide 3-kinases; PPIA, Peptidylprolyl Isomerase A; PPIA, positive regulation of Peptidylprolyl Isomerase A; PTEN, promoting tensin homologous phosphatase; ROS, reactive oxygen species; RSSA, 40 S ribosomal subunit A; S6K, Ribosomal protein S6 kinase; SOD, superoxide dismutase; TNF-α, tumor necrosis factor alpha; TRAIL, R1 and 2, TNF-related apoptosis inducing ligand receptor 1 and 2; VEGF, vascular endothelial growth factor; VIME, vimentin.

phytochemicals identified in our study have the potential to be investigated for the treatment of ovarian cancer. Through pre-clinical and clinical trials, our study demonstrates the potential of phytochemicals in the treatment of ovarian cancer, contributing to the development of novel therapeutic options for ovarian cancer.

KEYWORDS
clinical, ovarian cancer, phytochemicals, preclinical

1 | INTRODUCTION

After cervical cancer, ovarian cancer is the second most common type of gynecological neoplasm. It is the type of gynecological cancer with the highest death rate because it is typically diagnosed late, making it more difficult to treat (Torre et al., 2018).

In 2020, there will be 313,959 new cases and 207,252 deaths from ovarian cancer worldwide (Sung et al., 2021). Several risk factors, including genetic mutations of the BRCA1 and BRCA2 genes ("breast cancer 1 and 2" genes that encode tumor suppressor proteins), a family history of ovarian or breast cancer, late menopause, endometriosis, nulliparity, hormone replacement therapy, obesity, a lack of physical activity, and smoking, are associated with its occurrence (Kuroki & Guntupalli, 2020).

Histologically, the ovary can develop three types of malignant tumors: epithelial ovarian cancers (subtypes: serous, endometriosis, mucinous, and clear cell), germ cells, and sex-cord stromal. About 95% of ovarian neoplasms are derived from epithelial cells, and their incidence increases in women over 40 (Stewart et al., 2017). Moreover, ovarian cancers are typically characterized by the presence of type-1 and type-2 ovarian cancer cells. Type-1 cells are characterized by a slow-growing phenotype, and the 5-year survival rate for women diagnosed with type-1 cells is high. In contrast, type-2 cells predominantly express a mutated or null isoform of the gene TP53 (60%–80% of cases) or aberrations in the BRCA1 (30%–50%) and BRCA2 (15%–30%) genes, and the majority of ovarian cancers with type-2 have a poor prognosis (Pistollato et al., 2017).

Despite advances in available therapies for ovarian carcinoma, its treatment is restricted to cytoreductive surgery and chemotherapy with platinum derivatives (cisplatin and carboplatin) and taxanes (paclitaxel and docetaxel) that, despite being the first choices, pose the greatest barrier to its effectiveness and the development of resistance after long-term chemotherapy (Radu et al., 2021). This resistance to chemotherapy is a result of molecular changes such as increased oxidative stress (reactive nitrogen species and reactive oxygen species), reduced apoptosis, endogenous factors such as IL-1, IL-6, and TNF, and genetic changes such as mutations in tumor suppressor genes PTEN, BRCA1, BRCA2, and p53 in the cancer ovarian cells that contribute to a lower therapeutic response to platinum derivatives and taxanes, increasing the challenge in the treatment strategy aims to improve the prognosis of ovarian cancer patients (Grunewald & Ledermann, 2017; Rezaei-Tazangi et al., 2021).

In addition, the tumor microenvironment, which consists of immune cells, fibroblasts, extracellular matrix, and proteolytic enzymes such as matrix metalloproteinase (MMP), vascular endothelial growth factor (VEGF), transforming growth factor beta, and platelet-derived growth factor, influences the growth of ovarian cancer tumors (Radu et al., 2021). This microenvironment promotes tumor cell proliferation, migration, and invasion, and therapeutic options for ovarian carcinoma aim to inhibit these factors (Shafabakhsh & Asemi, 2019).

In this context, in vitro and in vivo experimental studies have shown that phytochemicals from the classes of phenolic compounds (phenolic acids and flavonoids), terpenes (diterpenes, triterpenes, and saponins), and alkaloids can be used alone or in conjunction with chemotherapies as a therapeutic alternative since they exert antitumor properties against ovarian cancer in different types of pathways, mainly through inhibition of apoptosis, oxidative stress and inflammation; improve the effectiveness of conventional chemotherapy by acting as chemosensitizing agents, decrease chemoresistance; and reduce the toxicity induced by conventional chemotherapy (Althurwi et al., 2020; Efferth & Oesch, 2021; Ibrahim et al., 2019; Islam, 2017; C.-Y. Sun et al., 2019; Q. Sun et al., 2015; Varela-Rodríguez et al., 2020).

Phytochemicals are chemicals that are produced naturally by plants during secondary metabolism and have a variety of biological activities, including anti-inflammatory, antioxidant, and anti-tumor effects, while being less toxic to normal cells (Yan et al., 2020). The antitumor effect of phytochemicals in ovarian cancer is correlated with their ability to induce cell growth regulation, apoptosis, oxidative stress reduction, anti-angiogenesis, and sensitization (Woźniak et al., 2021).

In this review, we examined the antitumor effects of phytochemicals in ovarian cancer, how they can be useful as alternatives or adjuvant treatments, and the possible molecular mechanisms by which these compounds inhibit this type of cancer. Our objective was to analyze preclinical (in vitro and in vivo) and clinical studies to demonstrate how these models can contribute to the development of alternative ovarian cancer treatment strategies.

2 | METHODS

This narrative review was composed after searching PubMed, SCOPUS, Science Direct, and ClinicalTrials.gov with the following keywords: "ovarian cancer," "phytochemicals," "phenolic compounds," "terpenes," and "alkaloids," using Boolean AND/OR, as well as the truncation (*) and adjacency (adj or N or NEAR) functions to achieve

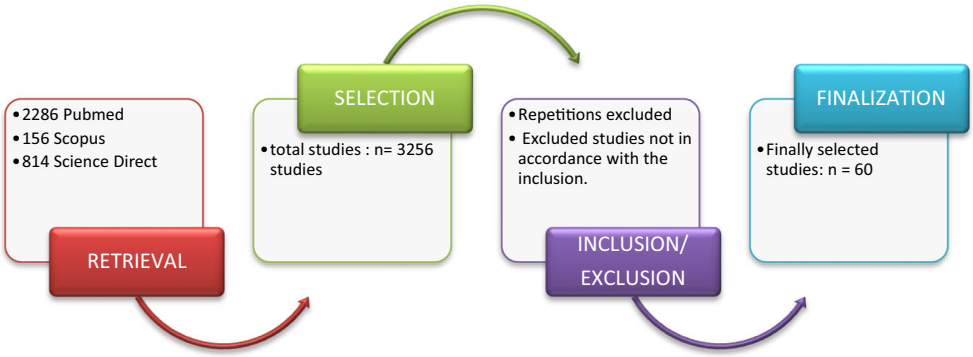


FIGURE 1 Flow chart of literature research.

greater breadth when searching for keywords. The search was limited in time (2010–2022) and language (English only). In addition, we selected trials based on the inclusion criteria listed below: original articles with pre-clinical trials; articles with keywords in the title, abstract, or full text; articles with chemical substances isolated or identified in the extract or identifying the class of secondary metabolites; and articles that described the mechanism of action in ovarian cancer. The primary search yielded 3256 articles, of which 2286 were retrieved from Pubmed, 156 from Scopus, and 814 from Science Direct. Articles that were indexed in two or more databases were only considered once. Sixty articles were chosen after the initial screening of titles, abstracts, and keywords, as the others did not meet the inclusion criteria. For the selection of manuscripts, three researchers selected articles based on their titles, abstracts, and full-text publication analyses, in that order. Consensus was used to resolve any disagreements among the investigators. The resultant articles were manually examined to identify and exclude studies that did not meet the aforementioned criteria. The analysis was conducted as a narrative review in accordance with Gasparyan's criteria (Gasparyan et al., 2011). Then, a search was conducted on the ClinicalTrials.gov database using the phytomolecules identified in this manuscript that have also been approved by the Food and Drug Administration (FDA, USA) and are currently undergoing clinical trials. Standardized coding tables for data extraction from individual trials, key characteristics, and the level of evidence for each study have been developed (Figure 1).

3 | RESULTS AND DISCUSSION

Sixty articles that met the inclusion criteria were selected from the literature search, and the chemical constituents with activity against ovarian cancer were primarily phenolic compounds (43%), terpenes (22%), saponins (14%), and alkaloids (17%). In vitro studies using the cell lines A2780 (human ovarian cancer cells derived from untreated patient tumor tissue), SKOV3 (ovarian adenocarcinoma resistant to multiple substances, such as tumor necrosis factor, adriamycin, and cisplatin, with high proliferation and invasion potential), and OVCAR3 were more prevalent in the scientific literature. Primarily xenograft tumor models and, to a lesser extent, native tumor models are used in in vivo studies. The selected articles on phytochemicals, classes of secondary metabolites, and antitumor mechanisms of action in ovarian cancer are summarized in Table 1. Most of the selected articles (49 articles, or 83%) were published between 2015 and 2022, indicating that the use of phytochemicals and elucidation of their molecular targets in ovarian cancer is a relatively new field of study. Only curcumin, genistein, quercetin, resveratrol, betulinic acid, artemisinin, and berberine (Table 2) have been evaluated in phase I and phase II clinical trials for safety and efficacy.

3.1 | Antitumor effects of phytochemicals on ovarian cancers

Ovarian cancer is the leading cause of death among women with reproductive cancers (Bray et al., 2018; Sung et al., 2021). Chemotherapy is the primary treatment, but patients who receive it for an extended period often develop resistance, which causes the cancer to progress (Sun et al., 2019). Therefore, resistance to chemotherapeutic agents, particularly platinum derivatives and taxanes, which are the drugs of first choice for treating ovarian cancer, is a problem that makes it more difficult to treat the tumor. To increase patient survival, we require alternative treatments that can be used individually or in combination (Woźniak et al., 2021).

In addition, the current ovarian cancer treatments are extremely toxic to healthy cells. (Achkar et al., 2018). Several natural products and phytochemicals, on the other hand, have shown selective cytotoxicity in ovarian cancer cell lines while causing minimal toxicity in normal cells (Barboza et al., 2020; Sun et al., 2019).

In this context, phytochemicals belonging to the classes of phenolic compounds (flavonoids, phenolic acids, coumarins, tannins, and stilbenes), terpenes (diterpenes, triterpenes, saponins), and alkaloids represent potential candidates for the development of new therapeutic agents for ovarian cancer, as they are recognized as safe, easy to obtain, and often cytotoxic to cancer cells but not normal cells (Althurwi et al., 2020; Ibrahim et al., 2019; Tavsan & Kayali, 2019; Varela-Rodríguez et al., 2020).

3.1.1 | Phenolic compounds

Phenolic compounds are plant secondary metabolites with an aromatic ring directly attached to one or more hydroxyl groups. On the

TABLE 1 Literature data concerning phytochemicals with antitumor activity in ovarian cancer cell lines.

Chemical substance(s)	Class of compounds	Natural occurrence	Ovarian cancer cell lines	Assay In vitro/ In vivo	Main effects and mechanism of action	IC_{50}	References
Ellagic acid	Phenolic compounds	Blackberries, grape seed, pomegranate, raspberries, tea, vanilla	ES-2 PA-1	In vitro	Inhibition of Bcl-2 level; Activation of caspase 3; Cell cycle arrest in G1 phase; Elevation of p53 and Cip1/p2 levels; Suppression of cyclin D1 and E levels	IC_{50} 25 to 100 μM in both cell lines.	(Chung et al., 2013)
Protocatechuic acid	Phenolic compounds	Grapes, rice, olives	SKOV3 OVCAR3 A2780	In vitro	Induction of apoptosis, autophagy, and cell cycle arrest in G2/M phase. Activation of cleaved PARP, caspase 3 and Bax; Inhibition of Bcl-2.	IC_{50} values for OVCAR3, SKOV3, and A2780 were 10.7, 14.8, and 14.9 μM, respectively.	(Xie et al., 2018)
10-Gingerol	Phenolic compounds	Ginger	HEY OVCAR3 SKOV3	In vitro	Cell cycle arrest in the G2 phase and decreased expression of cyclins A, B1, and D3.	IC_{50} 100 to 200 μM in both cell lines.	(Rasmussen et al., 2019)
Gallic acid	Phenolic compounds	Blackberries, grape seed, pomegranate, raspberries, tea, vanilla	OVCAR3 A2780/CP-70	In vitro	Inhibition of VEGF and regulation of the PTEN/AKT/HIF-1α pathway is responsible for the suppression of angiogenesis.	IC_{50} 20 and 40 μM in both cell lines	(He, Wang, et al., 2016)
		isolated from *Caesalpinia mimosoides*	A2780 A2780AD	In vitro	Association of gallic acid with paclitaxel (PTX) decreased proliferation and cycle arrest G2/M; Sensitization of PTX-resistant ovarian carcinoma cells by ROS-mediated ERK inactivation.	IC_{50} 50 nM PTX + 50 μM GA in the A2780 cell cultures; and 200 nM PTX + 100 μM GA in the A2780AD cell cultures.	(Sánchez-Carranza et al., 2018)
Gallic acid, Myricetin	Phenolic compounds	Black tea, green tea, or wine	SKOV3 OVCAR3	In vitro In vivo In silico	Induction of apoptosis; Cell cycle arrest; Inhibition of the carbonic anhydrase IX and PI3K protein.		(Varela-Rodríguez et al., 2020)
Apigenin, Luteolin, Myrecetin	Phenolic compounds	Clery, herbs, parsley, chamomile, rooibos tea, *Capsicum* pepper, black tea, green tea, or wine.	A2780 OVCAR3 SKOV3	In vitro	Activation of the extrinsic apoptotic pathway by caspase 3 and 9.	IC_{50} values were 8 μM (Apigenin), 30 μM (Luteolin) and 3.3 μM (Myrecetin) in SKOV3 cells which are platinum-resistant ovarian cancer cells,	(Tavsan & Kayali, 2019)

TABLE 1 (Continued)

Chemical substance(s)	Class of compounds	Natural occurrence	Ovarian cancer cell lines	Assay In vitro/ In vivo	Main effects and mechanism of action	IC_{50}	References
Flavonoids from chinese bayberry leaves: Myricetin 3-O-rhamnoside, Quercetin 3-rhamnoside	Phenolic compounds	Chinese bayberry leaves flavonoids	A2780/CP70	In vitro	Induction of apoptosis with increased expression of cleaved caspase 3 and 7; Positive regulation of Bad and Bax and negative regulation of Bcl-xL and Bcl-2; Reduced expression of cyclin D1 and CDK4 and p-Erk leading to G1 cell cycle arrest.	IC_{50} 10.57 mg/ml	(Zhang, Chen, et al., 2018)
Flavonoids from *Scutellaria barbata D.* Don Quercetin-3-O-β-D-glycopyranoside, Luteolin-7-O-β-D-glycopyranoside, Rutin, Apigenin-7-O-β-D-glucopyranoside, Hispidulin-7-O-β-D-glycuronide, Baicalin, Scutelarein, Luteolin, Quercetin, Apigenin, Naringenin, Baicalein, Wogonin	Phenolic compounds	*Scutellaria barbata* D. Don	A2780 SKOV3	In vitro	Induction of apoptosis by inhibition of Bcl-2 and induction of Caspase 3 and 9; Cell migration inhibitory effect by negative regulation of MMP-2/9 expression.	IC_{50} 50 μg/ml and 100 μg/ml in both cell lines.	(L. Zhang et al., 2017)
Curcumin, Epigallocatechin-3-gallate, Genistein, Resveratrol	Phenolic compounds	Turmeric, tea, chocolate, grapes, soya, beans, chickpeas, alfalfa, blueberries, peanuts, raspberries, wine	A2780 $A2780^{cisR}$ $A2780^{ZD0473R}$	In vitro	Inhibition of NF-KB activation increasing apoptosis. Combined synergistic effect with platinum drugs.	Combination indices CI >1: synergistic.	(Huq et al., 2014)
Quercetin	Phenolic compounds	Onion, kale, leek, broccoli, buckwheat, red grapes, tea, apples	PA-1 cells from human metastatic ovarian cancer	In vitro	Regulates the intrinsic apoptotic pathway by inhibiting Bcl-2, Bcl-xL and increasing expression of caspase-3, caspase-9, cytoc-c, Bid, Bad and Bax.	IC_{50} 50 and 75 μM	(Teekaraman et al., 2019)
Baicalin Baicalein	Phenolic compounds	Isolated from *Scutellaria baicalensis* Georgi	OVCAR3/CP-70	In vitro	Decreased expression of VEGF, cMyc, NF-κB and HIF-1α.	Baicalin decreased expression of VEGF (20 μM), cMyc (80 μM), and NFkB (20 μM); baicalein decreased expression of VEGF (10 μM), HIF-1α (20 μM), cMyc (20 μM), and NFkB (40 μM).	(J. Chen et al., 2013)

(Continues)

TABLE 1 (Continued)

Chemical substance(s)	Class of compounds	Natural occurrence	Ovarian cancer cell lines	Assay In vitro/ In vivo	Main effects and mechanism of action	IC_{50}	References
Catechin, Ellagic acid, Epicatechin, Gallic acid, Nobiletin, Tangeretin, Baicalein, Baicalin	Phenolic compounds	Black tea, green tea, wine, chocolate, grapes, citrus fruits, and plants of the genus *Scutellaria*	OVCAR3 A2780/CP70	In vitro	VEGF inhibition exhibiting an anti-angiogenic effect in ovarian cancer cells.	20 and 40 μM	(Z. He et al., 2015)
Nobiletin	Phenolic compounds	Citrus fruits	A2780 OVCAR3	In vitro	Inhibition of cell proliferation and apoptosis by increasing the level of PARP cleavage. Decreased mitochondrial membrane potential and induction of reactive oxygen species generation and autophagy contributing to gasdermin D/ gasdermin E mediated pyroptosis.	IC_{50} of nobiletin against A2780 and OVCAR3 cells were 35.31 and 34.85 μM, respectively.	(R. Zhang et al., 2020)
Curcumin	Phenolic compounds	Tumeric	SKOV3	In vitro	Increased MIR-9 expression and subsequent modulation of the Akt/FOXO1 axis preventing cell proliferation and stimulating apoptosis	IC_{50} 60 μM	(Zhao et al., 2014)
			SKOV3 OVCAR3	In vitro	Increased sensitivity to cisplatin. Inhibition of Akt/mTOR/ERK and inhibition of NF-κB signalling activation inducing apoptosis.	IC_{50} values for SKOV3 and OVCAR3 were 60 and 105 μM, respectively.	(He, Wang, et al., 2016)
			A2780/ADM	In vitro	Combined synergistic effect with paclitaxel drugs, raising the concentration of paclitaxel in tumor cells.	IC_{50} values 50 μg/ml Nanoparticle 100 nm	(Liu et al., 2016)
Resveratrol	Phenolic compounds	Blueberries, grapes, peanuts, raspberries, wine	OVCAR3	In vitro In silico	Epigenetic modulation of miRNAs or lncRNAs.	100 mM	(Vallino et al., 2020)
Geraniin	Phenolic compounds	Isolated from *Phyllanthus amarus*Schum & Thonn.	OVCAR3 SKOV3	In vitro	Induction of apoptosis with increased cytochrome c release and caspase-3 activity; Downregulation of Mcl-1 and NF-κB p65 to the mcl-1 promoter.	IC_{50} values for OVCAR3 34.5 μM and SKOV3 were 23.6 μM.	(Wang, Chen, et al., 2017)

TABLE 1 (Continued)

Chemical substance(s)	Class of compounds	Natural occurrence	Ovarian cancer cell lines	Assay In vitro/ In vivo	Main effects and mechanism of action	IC_{50}	References
Prodelphinidins from *Morella rubra* Lour	Phenolic compounds	Isolated from *Morella rubra* Lour	OVCAR3	In vitro	Induction of apoptosis by activation of caspase, Bcl-2 and up-regulation of death receptor 5 (DR5) and Fas expression; Inhibition of the protein kinase B signaling pathway.	82.32 μg/ml	(Fu et al., 2017)
Corilagin	Phenolic compounds	Isolated from *Phyllanthus niruri* L	SKOv3ip Hey HO-8910 PM	In vitro In vivo	Cell cycle arrest at the G2/M; Negative regulation of Cyclin B1, Myt1, Phospho-cdc2 and Phospho-Weel; Blockade of the activation of the Smad and ERK/ AKT pathways;	30 μM	(L. Jia et al., 2013)
Hirsutenone	Phenolic compounds	Bark of *Alnus hirsuta*var. *sibirica*	CDDP-sensitive: OV2008 (wt-p53), A2780s (wt-p53), OVCAR-432 (p53-mutant). CDDP -resistant: OVCAR-433 (wt-p53), A2780cp, Occ-1 (*p53*-mutant), and SKOV3 (*p53*-null).	In vitro	Induction of apoptosis in CDDP-resistant strains through negative regulation of PI3K/ Akt function, leading to XIAP degradation via proteasome-ubiquitin, and AIF-dependent apoptosis.	10 μm	(Farrand et al., 2014)
Theaflavin-3, 3′-digallate	Phenolic compounds	Black tea	A2780/CP70 OVCAR3	In vitro	Induction of apoptosis by regulation of caspase-3 and -7 expression; Acting on the Wnt/β-catenin pathway.	IC50 values for A2780/ CP70 and OVCAR3 were 16.29 and 21.20 μM, respectively.	(Pan et al., 2018)
Mangiferin	Phenolic compounds	Plants of Anacardiaceae, Celastraceae and Gentianaceae	A2780 ES-2	In vitro In vivo	Negative regulation of the expression of metastasis-associated proteins MMP2 and MMP9.	IC50 values 49.85 μM for A2780 and 65.27 μM for ES-2.	(Zeng et al., 2020)
Osthole	Phenolic compounds	Isolated from *Cnidium monnieri* (L.) Cusson	A2780 OV2008	In vitro	Cell cycle arrest in the G2/M phase. Regulation of relative apoptotic protein Bcl-2, Bax and Caspase 3/9. Inhibition of the expression of metastasis-associated proteins MMP2 and MMP9.	20, 40, 80, 120, 160 and 200 μM	(G. Jiang et al., 2016)

(Continues)

TABLE 1 (Continued)

Chemical substance(s)	Class of compounds	Natural occurrence	Ovarian cancer cell lines	Assay In vitro/ In vivo	Main effects and mechanism of action	IC_{50}	References
Ethyl caffeate	Phenolic compounds	Isolated from *Ligularia fischeri*	SKOV3	In vitro	Cell cycle arrest of G1 phase. Inactivation of mitogenic signaling pathways, such as Akt, ERK, and p38 (MAPK), and negative regulation of cell surface signaling molecules, including receptor tyrosine kinases, integrin α3β1, and N-cadherin.	50 μM	(H. N. Lee et al., 2014)
Oridonin	Terpenes	Isolated from *Rabdosia rubescens*	SKOV3 A2780	In vitro	Cell cycle arrest in G1/S phase and induction of apoptosis; Suppression of the mTOR signaling pathway and increased FOXP3 expression. - Reduced expression of MMP-2 and MMP-9.	15 μM	(Y. Wang & Zhu, 2019)
			SKOV3 OVCAR3 A2780	In vitro In vivo	Inhibition of the mTOR signaling pathway; Inhibitory effects on solid ovarian tumor growth.	IC_{50} values for SKOV3, OVCAR-3 and A2780 cells were 17.21, 13.9 and 12.1 μM, respectively.	(Xia et al., 2016)
Cryptotanshinone	Terpenes	Isolated from *Salvia miltiorrhiza* Bge	A2780	In vitro	Induction of apoptosis by caspase pathway and inhibition of MMP-2 and MMP-9 expression.	14,31 μM	(G. Jiang et al., 2017)
Triptolide	Terpenes	Isolated from *Tripterygium wilfordii* Hook	carcinoma- derived COC1/ CDDP	In vitro In vivo	Induction of apoptosis via inhibition of PI3K/Akt-related proteins with reduced Akt and GSK3β phosphorylation.	10.78 ng/ml	(H. Hu et al., 2016)
Cyparissins A and B	Terpenes	Isolated from *Euphorbia cyparissias* L	A2780, A2780 ADR	In vitro	P-glycoprotein-mediated inhibition of multidrug resistance.	8.55 μM for compound A and 8.72 for compound B.	(Lanzotti et al., 2015)
Tanshinone IIA	Terpenes	Isolated from *Salvia miltiorrhiza* Bunge	A2780	In vitro In vivo	Apoptosis by PI3K/AKT/JNK signaling pathways and caspases 3, 8, 9.	150 μM.	(Zhang, Chen, et al., 2018)
			SKOV3	In vitro	Cell cycle arrest in the G2/M phase; Decrease of Bcl-2 and increase of Bax promoting apoptosis.	19.6 μM	(Huang et al., 2016)

TABLE 1 (Continued)

Chemical substance(s)	Class of compounds	Natural occurrence	Ovarian cancer cell lines	Assay In vitro/ In vivo	Main effects and mechanism of action	IC_{50}	References
Betulinic acid	Terpenes	Isolated from *Cornus walteri* Wagner	A2780	In vitro	Induction of caspase -8, -3, -9 and cleaved Bax and decrease of Bcl-2.	44.47 μM	(D. Lee et al., 2019)
Ursolic acid	Terpenes	Apple peels, cranberry juices, grape skins, holy basil, rosemary, thyme, oregano, sage, and other herbs.	SKOV3	In vitro	Cell cycle arrest in the G2/M phase; Apoptosis by increase in Bax and decrease in Bcl-2 levels; Downregulation of PI3K/AKT signaling pathways.	35 μM	(Lin & Ye, 2020)
Artemisinin, Oleanolic acid	Terpenes	Isolated from *Artemisia annua* L	A2780 $A2780^{ZD0473R}$ $A2780^{cisR}$	In vitro	Modulation of platinum resistance mechanisms.	Artemisinin: (16.78; 26.8 36.36) Oleanolic acid: (34.0; 26.15; 10.85) for A2780, $A2780^{cisR}$, and $A2780^{ZD0473R}$, respectively.	(Althurwi et al., 2020)
Betulinic acid, Ursolic acid	Terpenes	Apples, cranberries, peppermint, prunes, oregano, thyme	A2780 $A2780^{cisR}$ $A2780^{ZD0473R}$	In vitro	Combined synergistic effect with platinum drugs; Inhibition of NF-KB activation increasing apoptosis.	Combination indices CI >1: synergistic. Not find	(Huq et al., 2014)
Kudsuphilactone B	Terpenes	Isolated from *Schisandra chinensis* Baillon	A2780	In vitro	Activation of caspase -3, -8 and -9 and cleavages of PARP; Regulation of Bcl-2 and MAPK .	23.25 μM	(Jeong et al., 2017)
Cucurbitacin B	Terpenes	Plants of Cucurbitaceae	A2780 paclitaxel resistant	In vitro	Cell cycle arrest in G2/M phase; Activation of caspase-3; Increased expression of p53 and p21; Decreased expression of P-glycoprotein.	0.21 μM	(Qu et al., 2017)
Eclalbasaponin II	Saponins	Isolated from *Eclipta prostrata*	SKOV3 A2780	In vitro	Induction of apoptosis through JNK signaling, p38 and mTOR inhibition.	IC_{50} values for SKVOV3 and A2780 cells were 20.39 and 22.12 μM, respectively.	(Cho et al., 2016)
Saponins of *Allium affine* Ledeb (unidentified)	Saponins	*Allium affine* Ledeb	OVCAR3	In vitro	Dose-dependent decrease in succinate dehydrogenase activity.	7.13 μg/ml	(Kazemi et al., 2017)
Saponins de *Tupistra chinensis* Baker (unidentified)	Saponins	*Tupistra chinensis* Baker	SKOV3	In vitro	G0 - G1 phase arrest of ovarian cancer cells by inhibition of Wnt/β-catenin signaling pathway, inhibition of cell proliferation and induction of apoptosis.	40.22 mg/L	(Ji et al., 2020)

(Continues)

TABLE 1 (Continued)

Chemical substance(s)	Class of compounds	Natural occurrence	Ovarian cancer cell lines	Assay In vitro/ In vivo	Main effects and mechanism of action	IC_{50}	References
Saponins from *Camellia Sinensis* Foliathea saponin I Tea seed saponin D Chaka saponin V Chaka saponin II Chaka saponin V Florathea saponin A Florathea saponin B Florathea saponin C Florathea saponin D Florathea saponin E Florathea saponin G Florathea saponin J	Saponins	*Camellia Sinensis*	OVCAR3	In vitro	Induced autophagy in ovarian cancer cells was accompanied by ERK activation and ROS generation.	1.5 μg/ml	(Y. Wang et al., 2020)
			A2780/CP70	In vitro	Induction of apoptosis through the AKT-MDM2-p53 signaling pathway. Cell cycle arrest in S phase through regulation of ATM-Chk2 signaling pathway-related proteins.	2.6 μg/ml	(Tu et al., 2020)
			A2780/CP70 OVCAR3 cells	In vitro	Activation of Caspase-3, 7, 8 and 9 activities; Inhibition of Cdc25A, Cdk2, Cyclin D1, E and A; Cell cycle arrest in S phase.	IC_{50} values for A2780/CP70 and OVCAR3 cells, were 1.0 and 0.5 μg/ml respectively.	(Wang, Ren, et al., 2017)
Dioscin	Saponins	Present at high levels in leguminosae and Dioscoreaceae plants.	SKOV3	In vitro	Suppression of cell viability in ovarian cancer cells through regulation of VEGFR2 and PI3K/AKT/MAPK signaling pathways.	1.25, 2.5 or 5 μM dose dependent	(X. Guo & Ding, 2018)
Ginsenoside 20(S)-Rg3	Saponins	Red ginseng	SKOV3	In vitro In vivo (*xenograft*)	Induction of autophagy by positive regulation of LC3 II, ATG5 and ATG7 which are associated with the autophagic process.	146.8 mg/ml	(Zheng et al., 2017)
Withaferin A	Steroid	Isolated from *Withania somnifera*	CaOV3 SKOV3	In vitro	Negative regulation of Notch1, Notch3, cdc25C, total and phosphorylated Akt and bcl-2 proteins inducing apoptosis and cell cycle arrest.	IC_{50} values for CaOV3 and SKOV3, were 520 and 627 nM, respectively.	(X. Zhang et al., 2012)
Emetine	Alkaloids	*Ipecacuanha* species	A2780 $A2780^{CisR}$	In vitro	Synergistic effect of emetin with cisplatin leading to negative regulation of proteins (VIME, ENPL, GRP78, CARL, NACA and COF1) and positive regulation of PPIA and RSSA proteins.	IC_{50} values for A2780 and $A2780^{CisR}$ were 0.023 and 0.018 μM, respectively.	(Alam et al., 2020)

TABLE 1 (Continued)

Chemical substance(s)	Class of compounds	Natural occurrence	Ovarian cancer cell lines	Assay In vitro/ In vivo	Main effects and mechanism of action	IC_{50}	References
			SKOV3	In vitro	Synergistic effect of emetine with cisplatin activating caspases -3, -7 and -8; Negative regulation of bcl-xL increasing sensitivity to cisplatin.	2.5 μM	(Q. Sun
Palmatine	Alkaloids	Isolated from *Rutidea parviflora* DC	A2780 OVCAR4	In vitro	Increased activity of caspase 3,7, and PARP cleavage.	IC_{50} values for A2780 and OVCAR4 were 6.6 and 7.4, respectively.	(Johnson-Ajinwo et al., 2019)
Piperlongumine	Alkaloids	Isolated from *Piper longum* L	A2780 OVCAR3	In vitro In vivo	Induction of depletion of survivin protein levels through the proteasome-dependent pathway mediated by reactive oxygen species.	I4.59 μM	(Nan et al., 2019)
Piperine	Alkaloids	Black peppers	SKOV3	In vitro	Synergistic effect with paclitaxel; Cell cycle arrest in sub-G1 phase; Increased Bax/Bcl-2 ratio and positive regulation of cyt-c, Bax, caspase-3 genes leading to modulation of pro- and anti-apoptotic genes.	30 μM	(Pal et al., 2016)
			A2780	In vitro	Induction of apoptosis by intrinsic pathway mediated by JNK/p38 MAPK	20 μM	(Si et al., 2018)
Neferine	Alkaloids	Isolated from the green seed embryos of *Nelumbo nucifera* Gaertn (Lotus)	SKOV3 A2780	In vitro	Autophagy through activation of p38 MAPK/JNK.		(Xu, Zhang, et al., 2016)
Songorine	Alkaloids	*Aconitum soongaricum* Stap	SKOV3 A2780	In vitro In vivo	Antitumor effect through GSK3β/β-catenin and Bcl-2/Bax signaling pathways.	IC_{50} 55.63 μM for SKOV3 cells and 64.42 μM for A2780 cells.	(Zhang, Dong, et al., 2019)
Harmine	Alkaloids	Isolated from the seeds of *Peganum harmala* and *Banisterio psiscaapi*	SKOV3	In vitro	Inhibition of proliferation and migration mediated by the ERK/CREB pathway; Suppression of VEGF, MMP-2 and MMP-9 expression.	10 μM	(J. Gao et al., 2017)

(Continues)

TABLE 1 (Continued)

Chemical substance(s)	Class of compounds	Natural occurrence	Ovarian cancer cell lines	Assay In vitro/ In vivo	Main effects and mechanism of action	IC_{50}	References
Berbamine	Alkaloids	Isolated from *Berberis amurensis*	SKOV3 ES2	In vitro In vivo	Cell cycle arrest in the G0/G1 phase; Inhibition of the Wnt/β-catenin pathway; Increased cleaved caspase-3, cleaved caspase-9, Bax and decreased Bcl-2.	IC_{50} 4.7 μg/ml for SKOV3 cells and 5.3 μg/ml for ES2 cells.	(Zhang, Jiao, et al., 2018)
Thymoquinone	Quinones	Derived from the seeds of the plant *Nigella Sativa*	OVCA429, SKOV3, HeyA8, OVCAR3, OVCAR8 cells	In vitro	Inhibition of oncogenic pathways stimulated by LPA (lysophosphatidic acid). Abrogates Gαi2-induced invasive migration of ovarian cancer cells, whereby LPA stimulates cell migration.	10 μM	(Ha et al., 2020)
			A2780, $A2780^{cisR}$, $A2780^{ZD0473R}$	In vitro	Combined synergistic effect with platinum drugs; Inhibition of NF-KB activation increasing apoptosis.	Combination indices CI >1: synergistic.	(Huq et al., 2014)

Abbreviations: A2780, human ovarian cancer cell line; OVCAR3, human high-grade serous ovarian adenocarcinoma cell line; SKOV3, human ovarian cancer cell line derived from a serous cystadenocarcinoma; $A2780^{cisR}$, cisplatin-resistant human ovarian cancer cell line; $A2780^{ZD0473R}$, cisplatin-resistant human ovarian cancer cell line; A2780/ADM or A2780AD, human ovarian carcinoma cell line resistant to adriamycin and multiple drugs (multidrug resistant); A2780/CP70, cisplatin-resistant human ovarian cancer cell line; PA-1 cells, human metastatic ovarian cancer cell line; SKOv3ip, human ovarian cancer cell line derived from a serous cystadenocarcinoma with a higher degree of migration potential; HO-8910 PM, highly metastatic human ovarian cancer cell line; CDDP-sensitive, OV2008 (wt-p53), A2780s (wt-p53), OVCAR-432 (p53-mutant); CDDP-resistant, OVCAR-433 (wt-p53), A2780cp, Occ-1 (p53-mutant), and SKOV3 (p53-null); HEY, human ovarian cancer cell line; ES-2, high grade serous ovarian cancer cell line; OV2008, human epithelial ovarian cancer cell line; Ov7, human ovarian cancer cell line carcinoma-derived; COC1/CDDP, cisplatin resistant human ovarian adenocarcinoma cell subline; CaOV3, human ovarian cancer cell line with epithelial morphology; OVCAR4, human ovarian cancer cell line with epithelial morphology growing in adherent culture; OVCA429, human ovarian cancer cell line; HeyA8, human high-grade serous ovarian adenocarcinoma cell line.; CDDP, cisplatin.

TABLE 2 Phytochemicals currently in clinical trial on various cancers.

Phytochemical	Class of compound	Type of cancer	Phase	Treatment	Study title	Reference[a]	Locations
Epigallocatechin	Flavonoids	Colorectal cancer	I	• 900 mg daily for 1 year or 450 mg PO twice a day.	Chemopreventive effects of epigallocatechin gallate (EGCG) in colorectal cancer (CRC) patients	NCT02891538	United States
		Lung cancer	II	• 440 mol/L. The EGCG solution is given until two weeks after radiotherapy completed.	Study of epigallocatechin-3-gallate (EGCG) for esophagus protection in patients with lung cancer receiving radial radiotherapy	NCT02577393	China
		Prostate cancer	I	• Patients receive oral defined green tea catechin extract (EGCC) daily for 4–7 weeks.	Defined green tea catechins in treating patients with prostate cancer undergoing surgery to remove the prostate	NCT00459407	United States
Curcumin	Polyphenol	Colonic cancer metastasis	I and II	• Oral complex C3 curcumin + chemotherapy	Combining curcumin with FOLFOX chemotherapy in patients with inoperable colorectal cancer	NCT01490996	United Kingdom
		Prostate cancer	Not Applicable	• Patients take 3 grams of curcumin (as 6 capsules 500 mg)	Radiosensitizing and radioprotectve effects of curcumin in prostate cancer	NCT01917890	Iran
		Head and neck cancer	I	• 4 grams twice daily for 21–28 days	Curcumin biomarker trial in head and neck cancer	NCT01160302	United States
Genistein	Flavonoids	Colon cancer Rectal cancer Colorectal cancer	I and II	• Genistein combined with FOLFOX or FOLFOX-Avastin Genistein 60 mg/day orally for 7 days every 2 weeks. Genistein will be administered beginning 4 days prior to FOLFOX or FOLFOX-Avastin and continuing the 3 days of chemotherapy.	Genistein in treatment of metastatic colorectal cancer	NCT01985763	United States
		Prostate cancer	II	• Patients receive cholecalciferol orally (PO) on day 1 and genistein PO once daily (QD) on days 1–21 or 1–28.	Cholecalciferol and genistein before surgery in treating patients with early stage prostate cancer	NCT01325311	United States
		Breast cancer	II	• Gemcitabine IV-1000 mg: Days 1 and 8 every 21 days. Genistein orally-100 mg 2 times/day for 7 days; 2 times/day on Days 1–21 every 21 days.	Gemcitabine hydrochloride and genistein in treating women with stage IV breast cancer	NCT00244933	United States
Quercetin	Flavonoids	Prostate cancer	I	Patients receive green tea extract and quercetin orally twice daily for 3–6 weeks before undergoing prostatectomy.	Effect of quercetin on green tea polyphenol uptake in prostate tissue from patients with prostate cancer undergoing surgery	NCT01912820	United States
Resveratrol	Stilbenoid	Colorectal cancer and hepatic metastases	I	5.0 g orally once daily for 14 days.	A clinical study to assess the safety, pharmacokinetics, and pharmacodynamics of SRT501 in	NCT00920803	United Kingdom

(Continues)

TABLE 2 (Continued)

Phytochemical	Class of compound	Type of cancer	Phase	Treatment	Study title	Reference[a]	Locations
					subjects with colorectal cancer and hepatic metastases		
		Multiple myeloma	II	5.0 g orally once daily in 21 day cycles, with or without concurrent bortezomib administration.	A clinical study to assess the safety and activity of SRT501 alone or in combination with bortezomib in patients with multiple myeloma	NCT00920556	United Kingdom
Betulinic acid	Terpenes	Melanoma	I	Administered for4 weeks as a topical ointment, in escalating doses, to patients with cutaneous metastatic melanoma	Safety, tolerability, and preliminary efficacy study of ALS-357 in patients with cutaneous metastatic melanoma	NCT00701987	United States
Artemisinin	Terpenes	Ovarian cancer	I	1 cup of decaffeinated coffee (450 mg *Artemisia annua*) per day and with a maximum of 4 cups per day (1800 mg).	Phase 1 dose escalation of artemicoffee	NCT04805333	United States
Berberine	Alkaloid	Lung adenocarcinoma	II	Patients will be treated with Gefitinib (250 mg) and Berberine (50 mg) orally.	Gefitinib and berberine in the first-line treatment of lung adenocarcinoma with EGFR mutation	NCT03486496	China

[a]www.clinicaltrials.gov.

basis of the arrangement of the carbon chain attached to the aromatic ring (C6) and (C9), they are classified into the following classes: phenolic acids, flavonoids, coumarins, tannins, quinones, and stilbene compounds (Călinoiu & Vodnar, 2018). In this review, we found that the majority of studies examining the antitumor effects of phenolic compounds in ovarian cancer have focused on phenolic acids and flavonoids.

Phenolic acids

In multiple in vitro and in vivo studies, phenolic acids have been linked to antitumor activity by promoting apoptosis, reducing proliferation, and modulating diverse aspects of cancer, including angiogenesis, growth, differentiation, and metastasis (Majidinia et al., 2019). In addition, the therapeutic activities of phenolic acids are enhanced by their function as epigenetic regulators, as well as by minimizing adverse events and reducing resistance associated with conventional antitumor therapy (Sánchez-Carranza et al., 2018; Weng et al., 2018).

Their antitumor effect is primarily due to their antioxidant activity: being strong radical scavengers, metal chelators, and modifiers of endogenous defense mechanisms such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidases (GPx), potentiators of the redox status of glutathione (GSH), and regulators of various proteins and transcription factors, such as nuclear factor related to erythroid 2 (Abotaleb et al., 2020). Patients with ovarian cancer have increased expression of pro-oxidant enzymes and decreased expression of antioxidant enzymes in their epithelial tissues, indicating the importance of phenolic acids' antioxidant capacity (Z. Jiang et al., 2011; Xie et al., 2018).

In addition, their anticarcinogenic effects are associated with their ability to inhibit cell proliferation via the extracellular signal-regulated kinase (Erk) pathway, D-type cyclins, and cyclin-dependent kinases (CDKs); inhibit angiogenic factors including VEGF and micronemal protein (MIC-1); express oncogenic signaling cascades (phosphoinositide 3-kinase [PI3K] and protein kinase B [Akt]); induce apoptosis and prevent cell migration and metastasis, through regulation of caspase-3, antiapoptotic *B-cell lymphoma protein 2* (Bcl-2) and proapoptotic *BCL-2 associated protein X* (Bax) (Kleczka et al., 2020; Pan et al., 2018; Rajagopal et al., 2018; Rasmussen et al., 2019).

Among the phenolic acids, ellagic acid **(1)**, protocatechuic acid **(2)**,10-gingerol **(3)**, and gallic acid **(4)** stand out (Figure 2).

Ellagic acid (1) induced apoptosis via inhibition of Bcl-2 and activation of caspase 3, cell cycle arrest in the G1 phase via elevation of p53 and Cip1/p21 levels, and suppression of cyclin D1 and E levels in ES-2 and PA-1 ovarian carcinoma cells (Chung et al., 2013).

Protocatechuic acid (2) significantly reduced the viability of ovarian cell lines (SKOV3, OVCAR3, and A2780) by inducing apoptosis via activation of cleaved poly-ADP-ribose polymerase (PARP), caspase-3, and Bax, as well as a negative up-regulation of Bcl-2 and cell cycle arrest in the G2/M phase (Xie et al., 2018).

As evidenced by an arrest in the G2 phase of the cell cycle and a decrease in the expression of cyclins A, B1, and D3, the phenolic acid 10-gingerol (3) inhibited the proliferation of HEY, OVCAR3, and SKOV3 ovarian cancer cells (Rasmussen et al., 2019).

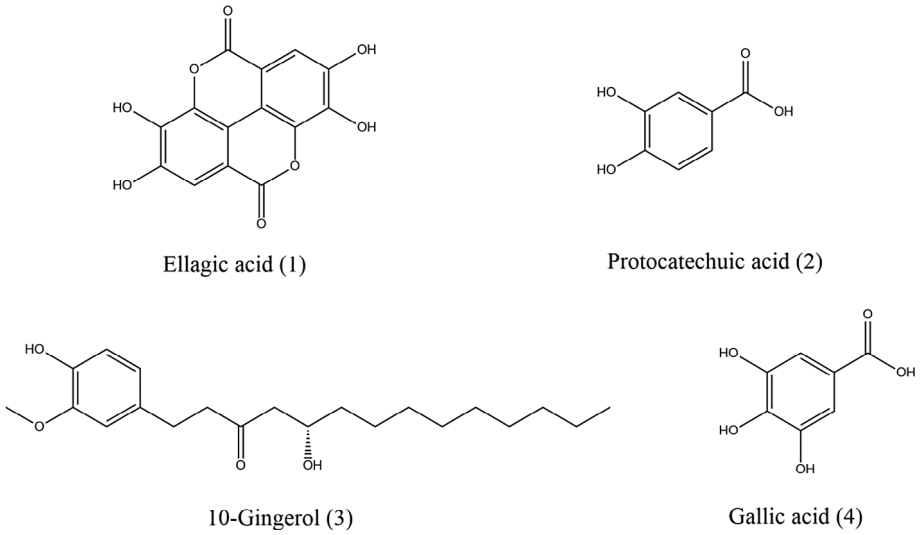


FIGURE 2 Chemical structures of phenolic acids with action on ovarian cancer.

Gallic acid **(4)** selectively inhibited growth and angiogenesis in vitro of two ovarian cancer cell lines, OVCAR3 and A2780/CP70, through inhibition of VEGF secretion by suppressing Protein kinase B (Akt) phosphorylation and hypoxia-inducible factor 1-alpha (HIF-1α) expression and promoting tensin homologous phosphatase (PTEN) expression, which acts as a tumor suppressor gene, suggesting that the PTEN/AKT/HIF-1α pathway is responsible for tumor suppression and angiogenesis in vitro (He, Chen, et al., 2016).

A pre-clinical in vivo study performed with SKOV3 cells subcutaneously xenotransplanted into female nude mice treated with 50 mg/kg gallic acid for 28 days revealed inhibitory effects on tumor lesions with decreased vascularization, necrotic/fibrotic areas, retraction of the neoplastic stroma, induction of apoptosis, and cell cycle regulation, through the phosphoinositide 3-kinases (PI3K) and carbonic anhydrase IX pathways, suggesting that gallic acid can be considered as a starting point for the development of new agents for the treatment of ovarian cancer (Varela-Rodríguez et al., 2020).

In addition, the combination of gallic acid and paclitaxel enhanced paclitaxel's ability to decrease cell proliferation, induced cell cycle arrest in the G2/M phase in paclitaxel-resistant A2780AD ovarian cancer cells, and inhibited the Erk pathway, indicating that gallic acid may be a useful adjuvant in the treatment of ovarian carcinoma due to the inhibition of the Erk pathway, which reduces signaling events that promote cell growth and proliferation (Sánchez-Carranza et al., 2018).

Concerning the low toxicity in normal cells, we highlight ellagic acid and gallic acid that selectively decreased the cell viability (in vitro) of cancer cells but had no effect on the cell viability of normal cell lines, indicating that they have the effect of selective inhibition of cell growth in ovarian carcinoma cells, thus suggesting that these phenolic acids may present greater safety for cancer treatment (Chung et al., 2013; Sánchez-Carranza et al., 2018).

Flavonoids

Numerous plant species contain flavonoids, which are essential anticancer compounds. In recent years, their therapeutic uses against the progression of cancer have been examined (Abotaleb et al., 2018).

Its effects in ovarian cancer are associated with multiple molecular mechanisms, including inhibition of DNA topoisomerase I and II, cell cycle arrest, and elevated expression of p53 (Abotaleb et al., 2018; Teekaraman et al., 2019; Wang, Chen, et al., 2017; Zhang, Jiao, et al., 2018), induction of apoptosis via Bcl-2, Bax, and Caspase 3 and 9 proteins, and inhibition of NF-B activation, and inhibition of cell migration via negative regulation of the expression of extracellular MMPs 2 and 9 (MMP-2 and MMP-9) (Tavsan & Kayali, 2019).

The flavonoids apigenin **(5)**, baicalein **(6)**, baicalin **(7)**, genistein **(8)**, luteolin **(9)**, quercetin **(10)**, wogonin **(11),** and epigallocatechin-3-gallate **(12)** (Figure 2) inhibit proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) as well as nuclear factor κB (NF-κB), a pro-inflammatory transcription factor (J. Chen et al., 2013; He, Wang, et al., 2016; Huq et al., 2014).

Nuclear factor κB is an essential regulator of both innate and adaptive immune responses, and it can promote cell proliferation, migration, and angiogenesis while inhibiting apoptosis (DiDonato et al., 2012). NF-κB is essential for normal immune responses against infection; however, dysregulated NF-κB activation is a major cause of chronic inflammatory diseases and can lead to the initiation of tumors (Fan et al., 2013). By increasing inflammatory cytokines and growth factors, NF-κB also promotes the proliferation of tumor-initiated cells. As NF-κB inhibition can also result in pro-apoptotic effects, it is the most effective method for treating ovarian cancer (Barboza et al., 2020; Yang et al., 2018).

The majority of flavonoids have also been shown to regulate the expression of the tumor suppressor gene p53, sensitize TRAIL-induced apoptosis (TNF receptor apoptosis-inducing ligand), and prevent or delay chemotherapy resistance (Abotaleb et al., 2018; George et al., 2017). Studies have shown that apigenin **(5)**, baicalein **(6)**, baicalin **(7)**, genistein **(8)**, luteolin **(9)**, quercetin **(10),** and kaempferol **(13)** inhibit VEGF production and the in vitro metastasis of ovarian cancer cells (Figure 3) (J. Chen et al., 2013; Z. He et al., 2015). Last but not least, wogonin **(11)** (Figure 3) can inhibit cancer cells by negatively regulating epithelial cell adhesion molecules (EpCAM), which are involved in carcinoma tumorigenesis and metastasis (S. S. Chen et al., 2012).

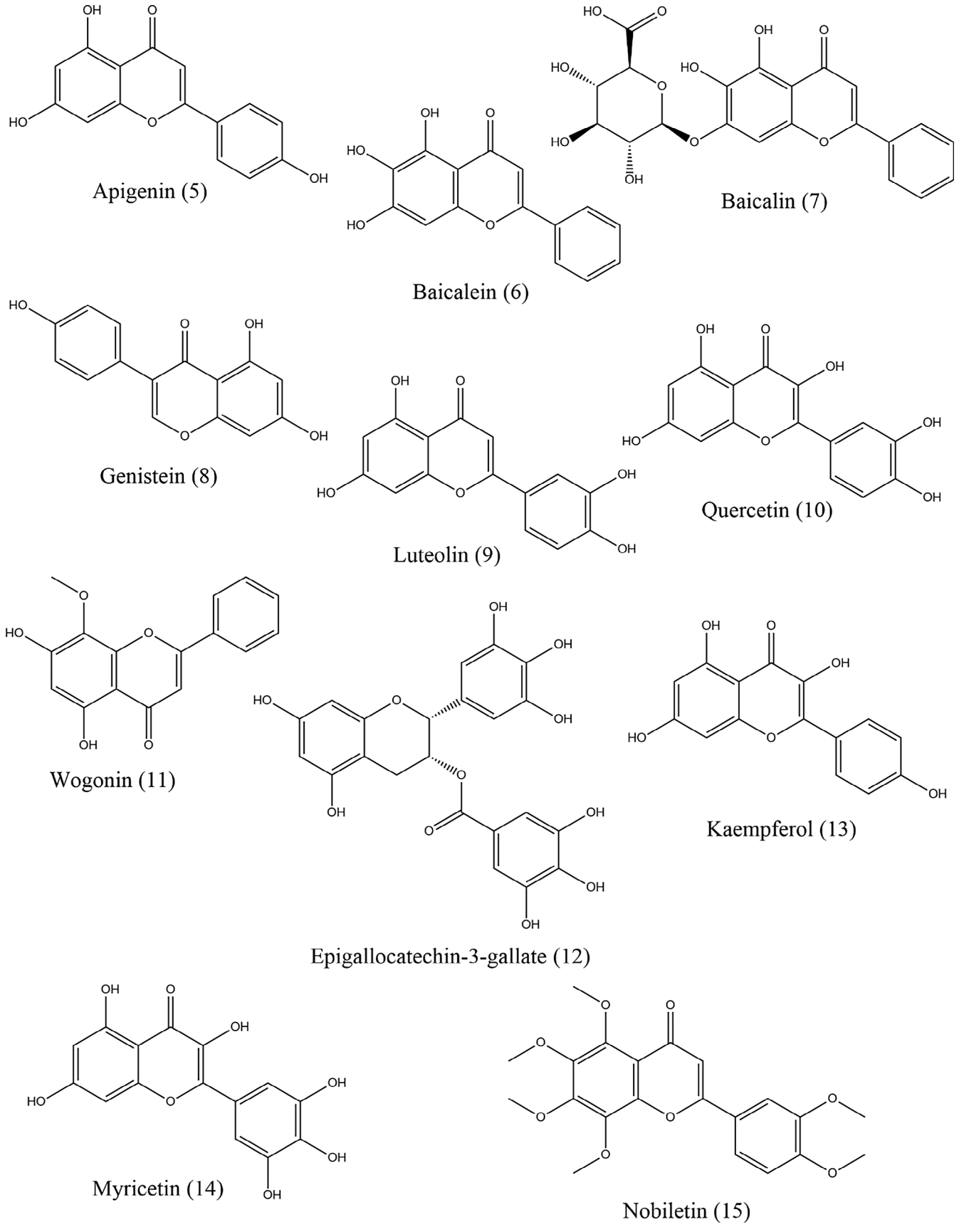


FIGURE 3 Molecular structures of flavonoids with anti-ovarian cancer properties.

As a mechanism of action, the studies also investigate the induction of apoptosis via the intrinsic or extrinsic pathway (Carneiro & El-Deiry, 2020). The intrinsic (mitochondrial) apoptotic pathway is regulated by the B-cell lymphoma protein family 2 (Bcl-2) that controls the release of cytochrome C from mitochondria to the cytosol, where it binds to the apoptotic protease-activating factor-1, thereby promoting the activation of caspase-9 and then caspase-3, resulting in apoptosis [90]. The Bcl-2 family includes pro-apoptotic proteins (including Bad and Bax) and anti-apoptotic proteins (including Bcl-2 and Bcl-xl) (Opferman & Kothari, 2018). In the extrinsic (cytoplasmic) pathway, apoptosis occurs through the interaction of death receptors that belong to the TNFR (tumor necrosis factor receptor) family, of which FAS, TNF-R1 and TRAIL are R1 and 2 (TNF-related apoptosis inducing ligand receptors 1 and 2), with their respective ligands FASL (FAs ligand), TNF-α, and TRAIL, which after interaction activate the cascade of caspases 8 and 3, executing death by apoptosis (Rajabi et al., 2021).

Consequently, the activation of an intrinsic or extrinsic pathway activates caspases, which initiate apoptosis (Carneiro & El-Deiry, 2020). In this context, quercetin **(10)** (Figure 3) regulates the intrinsic apoptotic pathway by decreasing the expression level of anti-apoptotic molecules such as Bcl-2 and Bcl-xL and increasing the expression level of apoptotic pro-molecules including caspase-3, caspase-9, cytoc-c, Bid, Bad, and Bax (Teekaraman et al., 2019). Myricetin **(14)** (Figure 3) also triggered the extrinsic apoptotic pathway by activating caspases 3 and 9 (Tavsan & Kayali, 2019; Varela-Rodríguez et al., 2020).

In addition, another mechanism of action investigated for the treatment of ovarian cancer is the inhibition of PARP (inhibitors), which prevents DNA repair and leads to DNA break accumulation and cell death (Smolle et al., 2013). PARP inhibitors have promising effects on ovarian carcinomas with mutations in the tumor suppressor genes BRCA1 and BRCA2 (breast cancer types 1 and 2). This is because these genes function as tumor suppressors in normal cells, but cells with defective BRCA1 and 2 do not interrupt the cell cycle, do not stimulate the repair cycle, and promote tumorigenesis (Slade, 2020). Nobiletin **(15)** (Figure 3) induced apoptosis by increasing the amount of poly (ADP-ribose) polymerase (PARP) cleaved in A2780 and OVCAR3 ovarian cancer cells, indicating its potential as a PARP inhibitor (R. Zhang et al., 2020).

Due to their ability to act on multiple cellular targets and multiple cellular and molecular processes, flavonoids have been demonstrated to be more effective than conventional anticancer drugs, with greater selectivity for cancer cells and low toxicity in normal cells (de Oliveira Júnior et al., 2018). In this review, we focus on myricetin, apigenin, luteolin, baicalin, and baicalein, which inhibited the growth of ovarian carcinoma cells selectively when tested in vitro (J. Chen et al., 2013; Tavsan & Kayali, 2019).

3.1.2 | Terpenes

Terpenes, another important class of phytochemicals, contain isoprene units and are known as isoprenoids. They can be categorized according to the number of C5 isoprene units in their structure. Terpenes thus form a large family of structurally diverse compounds, including the hemiterpenes (C5, 1 isoprene unit), monoterpenes (C10, 2 isoprene units), sesquiterpenes (C15, 3 isoprene units), diterpenes (C20, 4 isoprene units), triterpenes (C30, 6 isoprene units), tetraterpenes (C40, 8 isoprene units), and polyterpenes (C5)n, where *n* can be 9 to 30,000 isoprene units (Tholl, 2015).

Some structural carbon skeleton transformations of terpenes lead to the biosynthesis of natural product classes with unique physicochemical and pharmacological properties, such as steroids, lipophilic vitamins, saponins, and cardiotonic glycosides (Bergman et al., 2019). Among the terpenes that have antitumor effects in ovarian cancer, diterpenes, triterpenes, and saponins stand out.

Diterpenes

Diterpenes are naturally occurring, acyclic or polycyclic isoprenoid compounds of the pimarane, kaurane, abietane, beyerene, trachylobane, atisirane, or hibaene type (Barbosa & Vega, 2017).

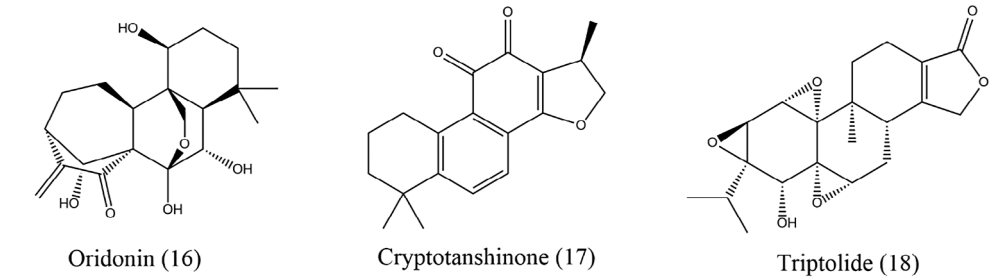
Some diterpenes have antitumor activity, such as taxanes (taxol/paclitaxel), triptolide, oridonin, andrographolide, and coffee diterpenes (cafestol and kahweol), which act by different molecular mechanisms in cancer cells to produce antioxidant effects, the induction of apoptosis by intrinsic and extrinsic pathways, cell cycle arrest, autophagy, angiogenesis inhibition, and metastasis (Islam, 2017). Oridonin **(16)**, cryptotanshinone **(17)**, triptolide **(18)**, cyparissins A **(19)**, B **(20)**, and tanshinone IIA **(21)** are among the diterpenes with antitumor effects in ovarian cancer (Figure 4).

In vitro, via the mTOR signaling pathway, oridonin **(16)** inhibited the proliferation, migration, and invasion of ovarian cancer cells, corroborating the in vivo findings of reduced tumor growth of ovarian cancer cells (SKOV3) (Xia et al., 2016). Oridonin (16) was tested on SKOV3 and A2780 ovarian cancer cells, confirming that this compound inhibited the cell cycle in the G1/S phase, induced apoptosis in cells, suppressed the mTOR signaling pathway, positively regulated the level of forkhead box protein 3 (FOXP3), and reduced the expression of MMP-2 and MMP-9, which are closely associated with metastasis. In both studies, oridonin was significantly less toxic to healthy cells and more selective toward ovarian cancer cells (Y. Wang & Zhu, 2019).

Cryptotansinone (17) inhibited the invasion of A2780 cells by decreasing the expression of the metalloproteinases MMP-2 and MMP-9 (G. Jiang et al., 2017). By remodeling the tumor's extracellular matrix, these proteolytic enzymes (MMP-2 and MMP-9) promote the metastasis of ovarian cancer by degrading various extracellular matrix molecules (Al-Alem & Curry, 2015). Therefore, compounds that inhibit the expression of MMP-2 and MMP-9 contribute to metastasis suppression (Y. Wang & Zhu, 2019; Weidle et al., 2016).

In platinum-resistant COC1/DDP cells derived from human ovarian carcinoma, triptolide **(18)** induced cell apoptosis and tumor suppression via the PI3K/Akt pathway, along with a significant decrease in Akt phosphorylation and GSK3 (H. Hu et al., 2016).

Cyparissins A **(19)** and B **(20)** inhibited P-glycoprotein-mediated multidrug resistance and displayed cytotoxic activity against ovarian



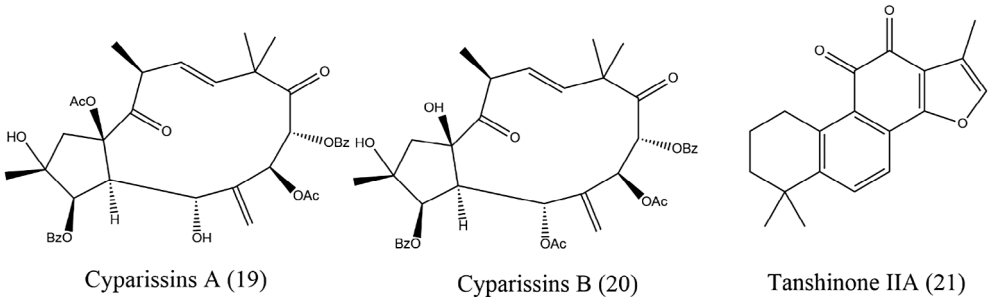


FIGURE 4 Diterpene chemical structures with anti-ovarian cancer properties.

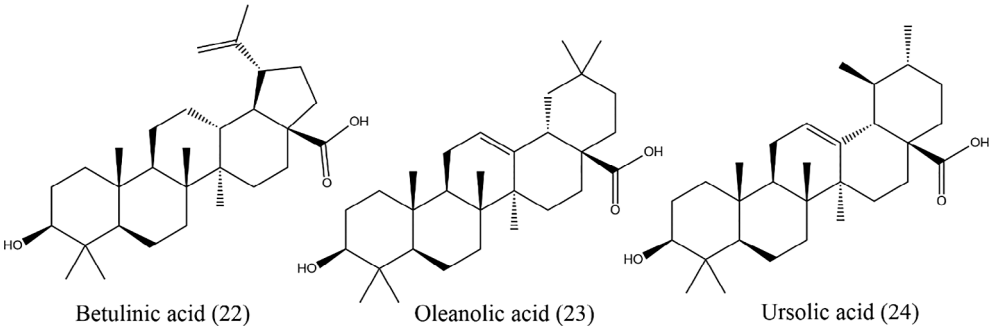


FIGURE 5 Triterpene structures with anti-ovarian cancer activity.

cancer patient-derived A2780 and A2780 ADR cells (Lanzotti et al., 2015).

Tanshinone IIA **(21)** induced apoptosis in A2780 ovarian cancer cells by inhibiting PI3K/AKT/JNK signaling pathways and via caspases 3, 8, and 9 (Zhang, Zhou, & Gu, 2018). SKOV3 cells exhibited a cell cycle arrest in the G2/M phase, a decrease in Bcl-2, and an increase in Bax, all of which promote apoptosis (Huang et al., 2016).

Triterpenes

Triterpenes are naturally occurring alkenes derived from plants, animals, and fungi with six isoprene units and 30 carbon atoms in their molecular structures (Lei et al., 2014). Triterpenes can be classified as tetracyclic or pentacyclic and divided into groups based on the carbon skeleton structures of their carbon atoms: cucurbitane, cycloartane, dammarane, euphane, friedelane, holostane, hopane, lanostane, lupane, oleanane, protostane, tirucalane, and ursane (Chudzik et al., 2015). The biological activities of these plant-isolated metabolites include antioxidant, anti-inflammatory, antinociceptive, hepatoprotective, sedative effect, antiallergic, antiangiogenic, antimicrobial, and antitumor properties (Salazar et al., 2020).

Numerous antitumor effects of triterpenes have been shown in in vitro and in vivo studies, including inhibition of cell proliferation, signal transduction effects, apoptosis, inhibition of MMP secretion, and inhibition of tumor invasion (G. Jiang et al., 2017; Lei et al., 2014). Multiple signaling pathways, including STAT3, PI3K, Akt, NF-B, PTEN, TRAIL, p53, and intrinsic and extrinsic apoptosis pathways, have been linked to the antitumor effect of triterpenes (Althurwi et al., 2020; H. Hu et al., 2016; Jeong et al., 2017; Qu et al., 2017).

Figure 5 highlights the pentacyclic triterpenes with antitumor activity in ovarian cancer: betulinic acid **(22)**, oleanolic acid **(23)**, and ursolic acid **(24)** (Hordyjewska et al., 2019; Lombrea et al., 2021).

Betulinic acid **(22)** is extremely promising due to its low toxicity to healthy cells and potent antiproliferative effects against ovarian cancer cells (Amiri et al., 2020). A2780 cells were induced to undergo apoptosis by betulinic acid via mitochondria-dependent and mitochondria-independent pathways, accompanied by increased expression of cleaved caspases 8, 3, and 9 and Bax and decreased expression of Bcl-2 (D. Lee et al., 2019).

Oleanolic acid (23) alone and in combination with cisplatin showed apoptotic effects including the increase of p38 mitogen-activated protein kinase (MAPK), apoptosis signal-regulating kinase 1 (ASK1) and reactive oxygen species (ROS), and its inhibition effect on signaling pathways including ribosomal protein S6 kinase (S6K), PI3K, mTOR, Akt, and NF-κB on human ovarian cancer cell lines

A2780, A2780ZD0473R, and A2780cisR. These functions make oleanolic acid more active against platinum-resistant cells, inhibiting the initiation, metastasis, invasion, and angiogenesis of platinum-resistant ovarian cancer (Althurwi et al., 2020).

Ursolic acid **(24)** decreased the viability of SKOV-3 ovarian carcinoma cells in a dose-dependent manner by inducing apoptotic cell death, accompanied by an increase in Bax and a decrease in Bcl-2 levels. In addition, an arrest in the G2/M cycle and an increase in ROS production were observed (Lin & Ye, 2020).

Importantly, chemotherapeutic drug resistance is the most significant barrier to the effective treatment of advanced ovarian cancer (C.-Y. Sun et al., 2019). Chemotherapy resistance in ovarian cancer is characterized by increased drug efflux pump activity mediated by multidrug resistance protein 1 (also known as P-gp), enhanced DNA damage repair capacity, decreased apoptosis, and cell cycle arrest (Cornelison et al., 2017). The oleanolic, betulinic, and ursolic acids can increase the sensitivity of ovarian cancer cells to chemotherapeutic agents (Althurwi et al., 2020). In the A2780, A2780cisR, and A2780ZD0473R strains, betulinic acid and ursolic acid inhibited NF-B activation by increasing apoptosis, and their effects were synergistic when combined with platinum drugs (Huq et al., 2014).

3.1.3 | Saponins

Saponins are glycosides of steroids or triterpenes (Figure 6), with high solubility in water and polar solvents, action on cell membranes, and complexation with steroids, which is responsible for their antifungal and hypocholesterolaemia effects (Vo et al., 2017). The most frequently cited saponin activities in the scientific literature are hemolytic, molluscicide, anti-inflammatory, antifungal, antibacterial/antimicrobial, antiparasitic, antiviral, and cytotoxic/antitumor (Juang & Liang, 2020). Saponins act via multiple targets and cell signaling pathways to disrupt the homeostasis of tumor cells, inhibiting their multiplication and angiogenesis or inducing their death via apoptosis and cell cycle arrest (Koczurkiewicz et al., 2019).

Ovarian cancer is examined in only 3.6% of studies examining the antitumor activity of saponins. However, these compounds are distinguished by their multiple molecular targets, as they are capable of modulating multiple oncogenic processes (cancer cell proliferation, migration, and apoptosis), inhibiting angiogenesis, and sensitizing chemotherapy-resistant ovarian cancer cells (Sobolewska et al., 2020).

Flowers of *Camellia sinensis* (L.) O. Kuntze contain saponins that have antitumor properties (L.-Y. Jia et al., 2017). *C. sinensis* flower saponins induce apoptosis in human ovarian cancer A2780/CP70 cells, demonstrating a strong antiproliferative effect, causing less cytotoxicity to normal cells, and S-phase arrest via the regulation of proteins associated with the ATM serine/threonine kinase-checkpoint kinase 2 (ATM-Chk2) signaling pathway. In addition, the induction of intrinsic and extrinsic apoptosis in A2780/CP70 cells via the Akt-MDM2-p53 signaling pathway was demonstrated by inhibiting the activation of Akt and MDM2 (Murine Doble Minute 2), a negative regulator of the tumor suppressor p53, and by increasing p53 levels in the cells (Tu et al., 2020).

Tupistra chinensis Baker saponins influence the proliferation and apoptosis of ovarian cancer (SKOV3) cells through the Wnt/β-catenin pathway (Ji et al., 2020). The intracellular Wnt/β-catenin signaling pathway controls cell survival, apoptosis, and self-renewal (Krishnamurthy & Kurzrock, 2018). This activated pathway promotes ovarian cancer cell proliferation, survival, migration, and invasion, as well as drug resistance (Nguyen et al., 2019). Zhang et al. (Zhang, Sun, et al., 2019) and Cao et al. (Cao et al., 2018) showed that inhibition of Wnt/β-catenin signaling pathway can inhibit ovarian cancer progression.

Increasing concentrations of dioscin induced apoptosis in ovarian cancer SKOV3 cells via the caspase-3, caspase-9, Bax, and poly (ADP-ribose) polymerase cleaved pathways, while suppressing the expression of VEGF receptor 2 (VEGFR2), phosphoinositide-3-kinase (PI3K), phosphorylated AKT, and phosphorylated p38 mitogen-activated protein kinase (MAPK) in SKOV3 cells (X. Guo & Ding, 2018).

In vitro and in vivo studies with 20(S)-ginsenoside Rg3 showed induction of autophagy in SKOV3 ovarian cancer cells via positive regulation of molecules involved in the autophagic process, such as light chain 3 protein (LC3 II) and autophagy related proteins 5 and 7 (ATG5 and ATG7); this mechanism is responsible for tumor suppression (Zheng et al., 2017).

In addition, the combination of saponins with antineoplastics (cisplatin, paclitaxel) increases the sensitivity of chemoresistant tumor cells to clinically administered chemotherapeutic agents (Koczurkiewicz et al., 2019).

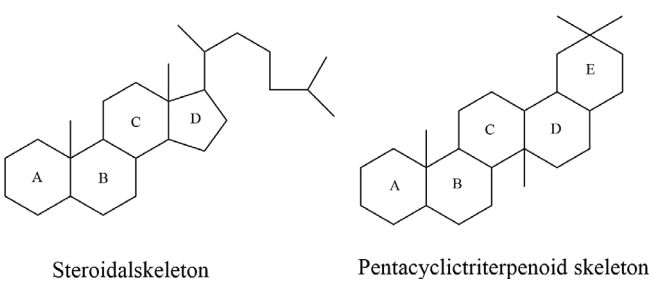


FIGURE 6 Steroidal and triterpenoid saponins skeleton.

3.1.4 | Alkaloids

Alkaloids are cyclic, nitrogen-containing, negatively oxidized compounds with a restricted distribution in living organisms. Their biosynthesis is complex and diverse, with true alkaloids and protoalkaloids originating from amino acids and pseudoalkaloids originating from other pathways that incorporate nitrogen via a transamination reaction (Ur-Rashid et al., 2019).

In addition to neurotransmitter properties and cytotoxic potential, they possess antiviral, antibacterial, anti-inflammatory, and antitumor

properties that act on a variety of molecular targets (Adamski et al., 2020).

Vimblastine and vincristine, which are derived from *Catharanthus roseus* (L.) G. Don, and camptothecin, which is derived from the Chinese plant *Camptotheca acuminata* Decne, contributed to the development of anticancer drugs such as topotecan and irinotecan (Efferth & Oesch, 2021).

In the context of ovarian cancer, we can highlight emetine **(25)**, palmatine **(26)**, piperlongumine **(27)**, piperine **(28)**, neferine **(29)**, songorin **(30)**, berberine **(31),** and harmine **(32)** (Figure 7).

Emetine **(25)** when combined with cisplatin against A2780 and A2780CisR cells (in vitro) demonstrated a synergistic effect and induced negative regulation of six proteins (vimentin [VIME], endoplasmin [ENPL], 78 kDa glucose-regulated protein [GRP78], Calreticulin [CARL], Nascent polypeptide associated complex [NACA], andCofilin-1[COF1]) and positive regulation of Peptidylprolyl Isomerase A (PPIA) and 40 S **ribosomal subunit** A (RSSA) proteins, resulting in cisplatin dose reductions in the A2780 ovarian cancer cell line (Alam et al., 2020). Coadministration of cisplatin and emetine increased apoptotic cell death in the ovarian cancer cell line SKOV3

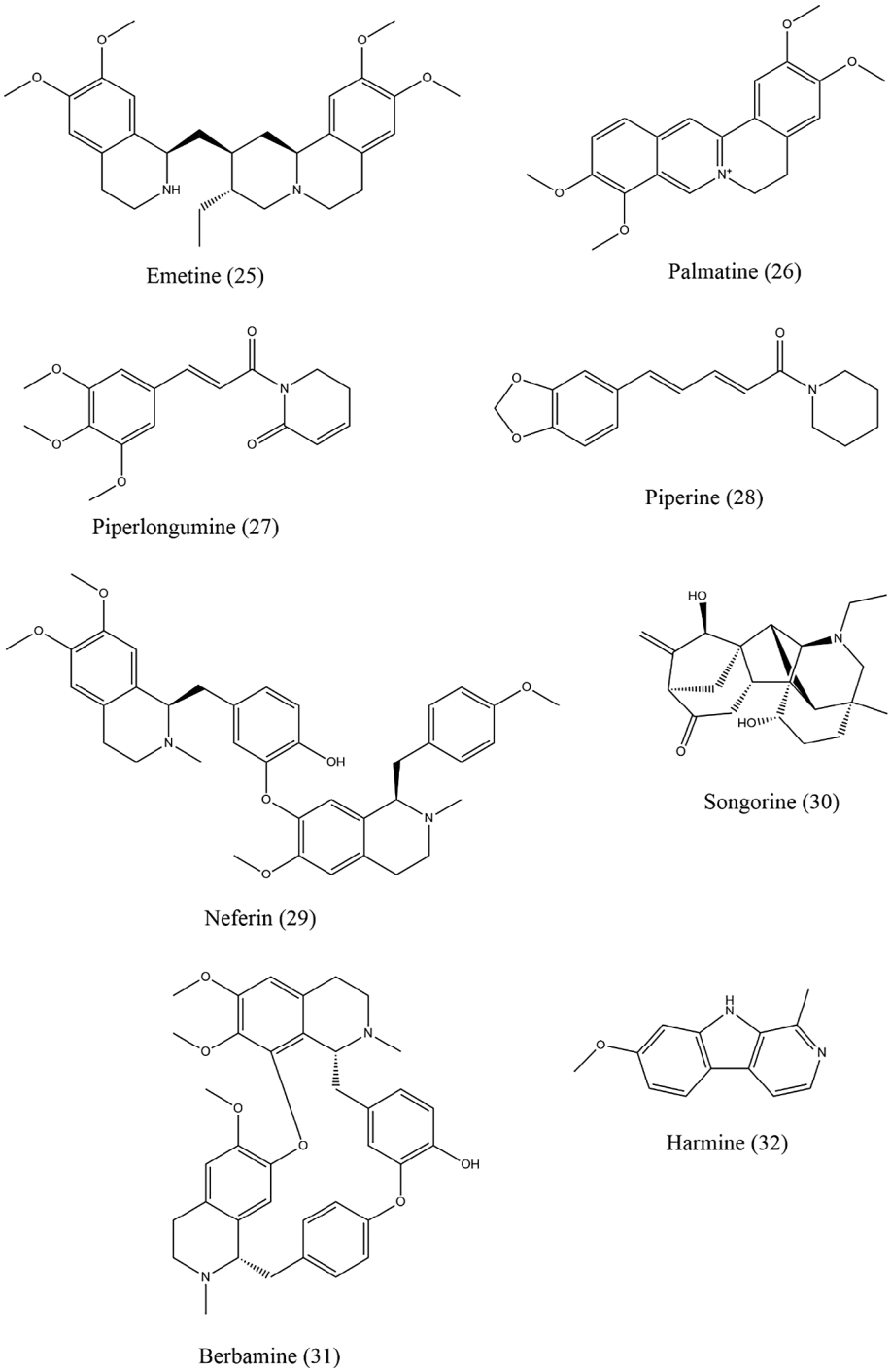


FIGURE 7 Chemical structures of alkaloids with action on ovarian cancer.

after 72 h, as demonstrated by the activation of caspases-3, −7, and − 8, with sensitization of cancer cells to the action of cisplatin correlated with negative regulation of Bcl-xL by emetine (Q. Sun et al., 2015).

In vitro, palmatine **(26)** induced apoptosis in A2780 and OVCAR4 cells via caspase 3, caspase 7, and PARP cleavage. Palmatine was found to be more selective for ovarian carcinoma cells than carboplatin and to be more cytotoxic than human ovarian epithelial cells (Johnson-Ajinwo et al., 2019).

In vitro, piperlongumine **(27)** decreased survivin protein through a proteasome-dependent pathway mediated by reactive oxygen species. Piperlongumine inhibited the growth of ovarian cancer cell xenograft tumors in vivo by downregulating survivin without causing systemic toxicity. (Nan et al., 2019). Survivin is an anti-apoptosis protein, and its overexpression increases apoptosis and chemotherapy resistance in ovarian cancer (J. Chen et al., 2013). Due to its low toxicity, piperlongumine may be a non-hazardous alternative for overcoming resistance to apoptosis induced by survivin overexpression.

Piperine **(28)** induced apoptosis via the activation pathway of caspases-3 and -9, as well as cleaved PARP and decreased phosphorylation of JNK and p38 MAPK in A2780 ovarian cancer cells, with a selective effect (Si et al., 2018). The synergistic effect of piperine and paclitaxel was also confirmed by observing a sub-G1 cell cycle arrest in SKOV3 cells, an increased Bax/Bcl-2 ratio, and positive regulation of cyt-c, Bax, and caspase-3 genes that modulate pro- and anti-apoptotic genes (Pal et al., 2016).

Neferine **(29)** induced G1 cell cycle arrest, apoptosis, and autophagy in human ovarian cancer cells by activating p38 MAPK/JNK (Xu, Zhang, et al., 2016). The signaling pathway involving c-Jun N-terminal kinase (JNK) and p38 MAPK (mitogen-activated protein kinase) plays essential roles in proliferation, differentiation, and apoptosis by activating the intrinsic apoptotic pathway (Peluso et al., 2019).

Songorine **(30)** exerted its antitumor activity via the glycogen synthase kinase-3 beta (GSK3/β-catenin) and Bcl-2/Bax signaling pathways. These findings highlight the potential use of songorine as a novel therapeutic agent for ovarian cancer, as the increased stability of GSK3 protein can hasten the degradation of β-catenin, resulting in negative regulation of MMP secretion and inhibiting tumor invasion and migration (Zhang, Dong, et al., 2019).

Berbamine **(31)** suppressed cell proliferation and tumor growth in vitro and in vivo by inducing cell cycle arrest in the G0/G1 phase and signaling of the Wnt/β-catenin pathway and by inducing apoptosis with increased expression of cleaved caspase-3, cleaved caspase-9, and Bax and a decreased protein level of Bcl-2 (Zhang, Jiao, et al., 2018).

Harmine **(32)** inhibited SKOV3 cell proliferation and migration via the ERK/cAMP Response Element-Binding Protein (CREB) pathway and suppressed the expression of the MMP family members MMP-2 and MMP-9 (J. Gao et al., 2017).

In this context, it is evident that alkaloids have antitumor effects via distinct and important mechanisms of action and that they can be used as a therapeutic alternative alone or in combination, as the synergistic effect enhances the antitumor response.

3.2 | Combining phytochemicals with anticancer drugs to overcome chemoresistance and/or improve the chemosensitivity of ovarian cancer treatments

Knowledge of the molecular mechanisms underlying the progression of cancer has led to the development of numerous anticancer drugs. Due to the tumor's chemoresistance, particularly to cisplatin and paclitaxel, which are the standard treatments for ovarian cancer, ovarian cancer remains difficult to treat, resulting in the progression of the disease (Kuroki & Guntupalli, 2020).

Multidrug resistance gene 1 (MDR1), nuclear factor-κB (NF-κB), and serine/threonine protein kinase Akt are the primary contributors to the development of drug resistance. In addition, ovarian cancer chemotherapy resistance is associated with molecular mechanisms involving increased P-glycoprotein-mediated drug efflux pump activity, increased DNA damage repair capacity, and decreased apoptosis (Yan et al., 2020).

Acquired resistance to cisplatin in ovarian cancer has been shown to be associated with NF-κB activation, whereas the chemosensitization of ovarian cancer cells due to the combination of cisplatin with phytochemicals such as genistein, curcumin, and resveratrol is associated with NF-κB inactivation and increased sensitivity to cisplatin with increasing concentration (Huq et al., 2014).

Curcumin was found to increase sensitivity to cisplatin with increasing concentration in SKOV3 and OVCAR3 cell lines through inhibition of NF-B and induction of apoptosis via the Akt/mTOR/ERK signaling pathway (M. He et al., 2016). In addition, it was possible to observe a synergistic effect between curcumin and paclitaxel (Liu et al., 2016).

The combination of gallic acid and paclitaxel inhibited the proliferation of A2780 and A2780AD cells, arrested the G2/M phase of the cell cycle, and sensitized paclitaxel-resistant ovarian carcinoma cells through ERK-mediated inhibition of reactive oxygen species (Sánchez-Carranza et al., 2018).

By inhibiting PI3K/Akt, hirsutenone induces apoptosis in cisplatin-resistant strains, resulting in XIAP degradation via proteasome-ubiquitin and AIF-dependent apoptosis (Farrand et al., 2014).

Resveratrol reversed cisplatin resistance in ovarian cancer cells by modulating molecular targets, such as EGFR or VEGFR from the receptor tyrosine kinase family (Engelke et al., 2016).

Associated with NF-κB inhibition, thymoquinone increases cisplatin-mediated cytotoxicity in ovarian cancer cells (Huq et al., 2014).

By inhibiting the miR-93/ PTEN/ Akt signaling pathway, berberine sensitizes human ovarian cancer cells to cisplatin (C.-Y. Sun et al., 2019).

Theaflavin-3,3′-digalate increased the growth-inhibiting effect of cisplatin on ovarian cancer cells via negative regulation of glutathione (GSH) and positive regulation of copper transporter 1 (CTR1) (Pan et al., 2018).

Betulinic acid and ursolic acid exhibited a synergistic effect when combined with platinum-based drugs, inhibiting NF-κB activation and promoting apoptosis (Huq et al., 2014).

Emetine and piperine exhibited synergistic effects when combined with cisplatin and paclitaxel, respectively. For the combined actions of cisplatin and emetine, eight proteins were considered: VIME, ENPL, GRP78, CARL, NACA, COF1, PPIA, and RSSA (Alam et al., 2020). The synergistic effect of piperine and paclitaxel disrupted the sub-G1 phase of the cell cycle, increased the Bax/Bcl-2 ratio, and induced the positive regulation of the cyt-c Bax and caspase-3 genes, modulating pro- and antiapoptotic genes (Pal et al., 2016). In addition, piperine has been shown to enhance anticancer drug activity in various drug-resistant cancer cell lines. (M. Wang et al., 2018).

Therefore, phytochemicals combined with platinum derivatives (cisplatin and oxaliplatin) or taxane derivatives (paclitaxel) can increase antitumor activity by inducing apoptosis via pro-apoptotic signaling, such as MAPKs, p53, and the anti-apoptotic Bcl-2 pathway, NF-κB, and Nrf2, since defects in apoptotic signaling are closely related to resistance to cisplatin and paclitaxel, and this synergism is responsible for decreasing chemoresistance and increasing sensitization.

3.3 | Clinical trials evaluating phytochemicals

Despite substantial preclinical evidence implicating phytochemicals in ovarian cancer, there have been few antitumor clinical trials for this disease. The majority of clinical trials for the phytochemicals identified in our study are for the treatment of other types of cancer (Table 2), demonstrating their efficacy, safety, and potential to be investigated in the treatment of ovarian cancer, as numerous preclinical trials have demonstrated their action and cellular mechanism (Althurwi et al., 2020; Huq et al., 2014; C.-Y. Sun et al., 2019; Vallino et al., 2020; Zhao et al., 2014).

Secondary metabolites derived from plants, including flavonoids, phenolic compounds, alkaloids, flavanols, steroids, and terpenes, have been shown to destroy tumor cells in a number of ways, including by inducing cancer cell cycle arrest and enhancing the apoptotic cell death process (Seca & Pinto, 2018). On the global pharmaceutical market, numerous anticancer drugs containing phytochemicals, such as tothecin, topotecan, irinotecan, etoposide, doxorubicin, taxel, docetaxel, vinblastine, and vincristine, are already available. Clinical trials can therefore establish optimal conditions for anticancer phytotherapy and personalized treatment utilizing advanced nanotechnology for cost-effective, target-specific, and less toxic chemopreventive agents (Dhupal & Chowdhury, 2020).

In ovarian cancer, preclinical studies have demonstrated the antitumor activity of epigallocatechin-3-gallate, curcumin, genistein, quercetin, resveratrol, and betulinic acid, with NF-kB inhibition effects, induction of apoptosis via intrinsic and extrinsic pathways, epigenetic modulation of miRNAs or lncRNAs, and synergistic effects with platinum-derived drugs (Amiri et al., 2020; He, Wang, et al., 2016; Huq et al., 2014; D. Lee et al., 2019; Liu et al., 2016; Vallino et al., 2020; Zhao et al., 2014).

Despite the absence of clinical trials with these phytochemicals for ovarian cancer, clinical trials of other cancer treatments, such as colorectal cancer, lung cancer, prostate cancer, breast cancer, and pancreatic cancer (Table 2), suggest that these phytochemicals may be therapeutic or adjuvant alternatives for the treatment of ovarian cancer.

Only artemisinin isolated from *Artemisia annua* L had preclinical and clinical trials for ovarian cancer among the phytochemicals listed in Table 2. Artemisinin modulated mechanisms of platinum resistance in preclinical studies (Althurwi et al., 2020). In the clinical trial, patients with advanced ovarian cancer who had completed carboplatin and paclitaxel chemotherapy were given daily doses of coffee in an effort to examine the use of coffee as maintenance therapy after primary treatment [NCT04805333].

New anticancer drugs derived from phytochemicals are a promising strategy for regulating carcinogenesis in ovarian cancer, given the difficult circumstances of current chemotherapy and the promising clinical evidence that these phytochemicals combat cancer with less systemic toxicity.

3.4 | Phytochemicals and nanomedicine: A therapeutic alternative for ovarian cancer

Numerous preclinical and clinical studies demonstrate that phytochemicals have promising anticancer activity for the treatment of ovarian cancer; however, their intrinsic properties, such as low aqueous solubility, low bioavailability, low stability, and solvent toxicity, limit their clinical application. By modulating the pharmacokinetics and pharmacodynamics of phytochemicals, as well as permitting passive or active targeting of the molecule to the tumor, phytonanomedicine can overcome these disadvantages and improve therapeutic efficacy (Dhupal & Chowdhury, 2020; Mohapatra et al., 2020).

The development of known targeted drug strategies for ovarian tumor cells has been made possible by nanotechnology, thereby preventing damage to healthy tissues. Biodegradable and biocompatible lipid- and polymer-based nanoparticles, such as liposomes, polymeric micelles, solid lipid nanoparticles, nanostructured lipid carriers, and protein nanoparticles, are the most utilized in cancer therapy (Rezaei-Tazangi et al., 2021).

Various nanocarriers, such as polymeric, lipidic, and inorganic nanoparticles, have been extensively used with phytochemicals, with some phytonanomedicines approved by the FDA or undergoing clinical trials for the treatment of various cancers (Mohapatra et al., 2022). Among these phytochemicals, we highlight curcumin, epigallocatechin-3-gallate, quercetin, apigenin, resveratrol, thymoquinone, ursolic acid, and betulinic acid, which, as previously demonstrated in our study (Tables 1 and 2), may offer an alternative therapy for ovarian cancer.

Curcumin exhibits in vitro and in vivo potential, but it has poor absorption, low bioavailability, low aqueous solubility, rapid systemic elimination, a high metabolism, and is degraded by alkaline conditions (Gera et al., 2017). To overcome these limitations, numerous nanoformulations of curcumin have been developed. Xu, Chen, et al. (2016) sought to effectively deliver curcumin to tumor sites using niosomes composed of nonionic surfactants Tween 80 and Pluronic 188 to

improve the solubility and therapeutic efficacy of curcumin, and they demonstrated this. Curcumin-niosomes exhibited enhanced cytotoxic activity and an increased apoptotic rate against ovarian cancer A2780 cells compared to free curcumin.

An in vivo and in vitro investigation demonstrated that the use of docetaxel and curcumin/methoxy poly (ethylene glycol)-poly (L-lactic acid) (MPEG-PLA) copolymers nanomicelles suppresses tumor proliferation and angiogenesis. In addition, the MTT assay and apoptotic study demonstrated that copolymer nanomicelles exhibited stronger inhibitory and pro-apoptotic effects on ovarian cancer A2780 cells compared with docetaxel or curcumin alone (Y. Hu et al., 2020). In addition, it was demonstrated that ovarian cancer OVCAR3 cells were treated with Gemini-Curcumin and free curcumin, and the results demonstrated that Gemini-Curcumin nanoparticles have a great deal of potential for the development of novel anti-ovarian cancer therapies (Ghaderi et al., 2021). An in vitro and in vivo study found that nanocurcumin in combination with cisplatin decreased PI3K, JAK, TGF-β, Ki67 expression, and Akt phosphorylation, which may result in a decrease in the weight and volume of ovarian tumors (Sandhiutami et al., 2020).

Epigallocatechin-3-gallate has anticancer activity in in vitro and in vivo models, and there are ongoing clinical studies; however, the compound's low bioavailability and instability are a drawback (Granja et al., 2016). To overcome these limitations, numerous nanoformulations for epigallocatechin-3-gallate, including gold, polymeric, metallic, carbohydrate-based, and liposomal delivery systems, have been developed (Chavva et al., 2019). To increase the effectiveness of epigallocatechin-3-gallate, it was attached to nanogold particles (EGCG-pNG), and the anti-cancer activity of EGCG-pNG-treated melanoma cells was enhanced. In a murine melanoma model, EGCG-pNG inhibited tumor growth 1.66 times more effectively than epigallocatechin-3-gallate (C.-C. Chen et al., 2014). Epigallocatechin-3-gallate encapsulated in solid lipid nanoparticles conjugated with gastrin-releasing peptide receptors, which are overexpressed in breast cancer, decreased tumor volume in melanoma in C57/BL6 mice when compared to non-conjugated formulations or epigallocatechin-3-gallate alone. (Radhakrishnan et al., 2019) .

Due to its low aqueous solubility, low oral bioavailability, and rapid gastrointestinal digestion, the therapeutic potential of quercetin is compromised (Vafadar et al., 2020). In order to enhance its pharmacokinetics, nanoparticles have been created. Quercetin was encapsulated in monomethoxy poly (ethylene glycol)-poly (3-caprolactone) micelles, and it was demonstrated that intravenous injection of these micelles significantly inhibits the growth of ovarian tumors in vivo by inducing cancer cell apoptosis and inhibiting angiogenesis (X. Gao et al., 2012). Another study evaluated the ability of PEGylated liposomal quercetin to inhibit the proliferation and growth of ovarian tumor cells in vivo and in vitro, as well as to induce cell cycle arrest and apoptosis (Long et al., 2013). Recently, wurtzite-type zinc oxide nanoparticles were synthesized with quercetin and demonstrated that these nanoparticles can be used to treat metastatic ovarian cancer in humans (Ramalingam et al., 2022).

Apigenin is poorly soluble in water and has low oral bioavailability (Alshehri et al., 2019). To increase its solubility and bioavailability, a dual drug-loaded liposomal formulation of 5-fluorouracil and apigenin was developed, and preclinical testing in a tumor xenograft model using tumor-free mice revealed greater antitumor activity for human colorectal cancer cell lines HCT-15 and HT-29 via passive targeting of liposomes. (Sen et al., 2019).

The bioavailability, metabolism, half-life, and elimination of resveratrol are all limited (Singh et al., 2015). Using resveratrol-bovine serum albumin nanoparticles on human primary ovarian carcinoma cells in nude mice suppresses tumor growth in nude mice with ovarian cancer by inducing ovarian cancer cell necrosis and cellular apoptosis. (L. Guo et al., 2010). An in vitro evaluation of resveratrol-zinc oxide nanohybrid against ovarian cancer cell lines revealed that this nanoformulation possesses anticancer properties (Khatun et al., 2016).

Thymoquinone has low solubility in water and bioavailability. Upon synthesis of thymoquinone nanoparticles conjugated with radioiodinated folic acid-chitosan, enhanced targeting of ovarian cancer cells was observed (İnce et al., 2020).

Ursolic acid has a low solubility in water, a brief half-life, and low bioavailability (L. Wang et al., 2021). Nanoformulations have been developed to overcome their pharmacological limitations and increase their therapeutic effects. Zhou et al. (2019) developed ursolic acid-loaded mPEG-PLA polymeric micelles (UA-PMs) and observed tumor growth inhibition and prolonged survival in H22 xenograft tumor-bearing mice. In the study of Wang et al. (2021), in vivo and in vitro, they reported the design of a dual prodrug amphiphile platinum IV/ursolic acid/polyethylene glycol self-assembled nanoparticle system (Pt(IV)/UA/NPs) for synergistic chemotherapy of platinum-resistant ovarian cancer. The system Pt(IV)/UA/NPs was efficiently taken up by cisplatin-resistant ovarian cancer cells and released the drug in intracellular reductive and acidic environments. Furthermore, the in vivo results indicated that Pt(IV)/UA nanoparticles have a prolonged blood circulation time, exhibit higher accumulation in tumor, and significantly improve antitumor efficacy in A2780/DDP tumor-bearing mice without causing side effects like changes in body weight or major organ lesions, demonstrating that Pt(IV)/UA nanoparticles may have potential application in the treatment of ovarian cancer.

The bioavailability and aqueous solubility of betulic acid are low. To overcome these drawbacks, micelles of betulic acid and the chemical drug lonidamine were combined with doxorubicin as chemosensitizers for the treatment of ovarian cancer. This micellar system permitted release at the tumor site and decreased cardiotoxicity in Skvo3 subcutaneous xenograft models, indicating that these micelles may be a promising strategy for the effective treatment of ovarian cancer (Jin et al., 2019).

Numerous studies are currently focusing on various phytochemicals and nanocarriers in ovarian cancer, as phytochemicals associated with nanoparticles exhibit more favorable pharmacokinetic and pharmacodynamic properties. For phytochemical nanoparticles to be used in clinical practice in the future, however, additional research is required to comprehend and improve their design, complexity, manufacturing, and biological interaction.

4 | CONCLUSION AND FUTURE PERSPECTIVES

In this review, we show that phytochemicals have antitumor effects on ovarian cancer (Figure 8) through multiple mechanisms of action and increase chemosensitivity to platinum and taxanes. The primary phytochemicals consist of phenolic acids, flavonoids, diterpenes, triterpenes, saponins, and alkaloids, which present as molecular targets for NF-κB, PARP, Akt, ERK, MAPKs, p53, VEGF, MMP, Wnt/β-catenin, autophagy, and apoptotic pathways. Moreover, several phytochemicals exhibited synergistic effects with cisplatin and paclitaxel, thereby reducing chemotherapeutic agent-induced chemoresistance and toxicity. However, some natural products can have unfavorable pharmacological properties, including instability, low bioavailability, and poor water solubility. Using nano-based formulations from these herbal therapeutic candidates, such as gemini, zinc oxide nanohybrids, PEGylated liposomes, nanoparticles, micelles, and niosomes, can not only overcome these obstacles but also improve the therapeutic potential of herbal medicine against ovarian cancer, according to the evidence.

Through pre-clinical and clinical trials, our literature review reveals the potential of phytochemicals in the treatment of ovarian cancer, contributing to the development of novel therapeutic alternatives for ovarian cancer.

AUTHOR CONTRIBUTIONS

Josianne Rocha Barboza: Conceptualization; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Francisco Assis Nascimento Pereira:** Formal analysis; investigation; methodology. **Cleydlenne Costa Vasconcelos:** Formal analysis; investigation; methodology; writing – original draft. **Maria Nilce de Sousa Ribeiro:** Conceptualization; formal analysis; investigation; supervision; visualization; writing – original draft. **Alberto Jorge Oliveira Lopes:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; validation; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the studies referred to.

ORCID

Alberto Jorge Oliveira Lopes https://orcid.org/0000-0001-5267-9500

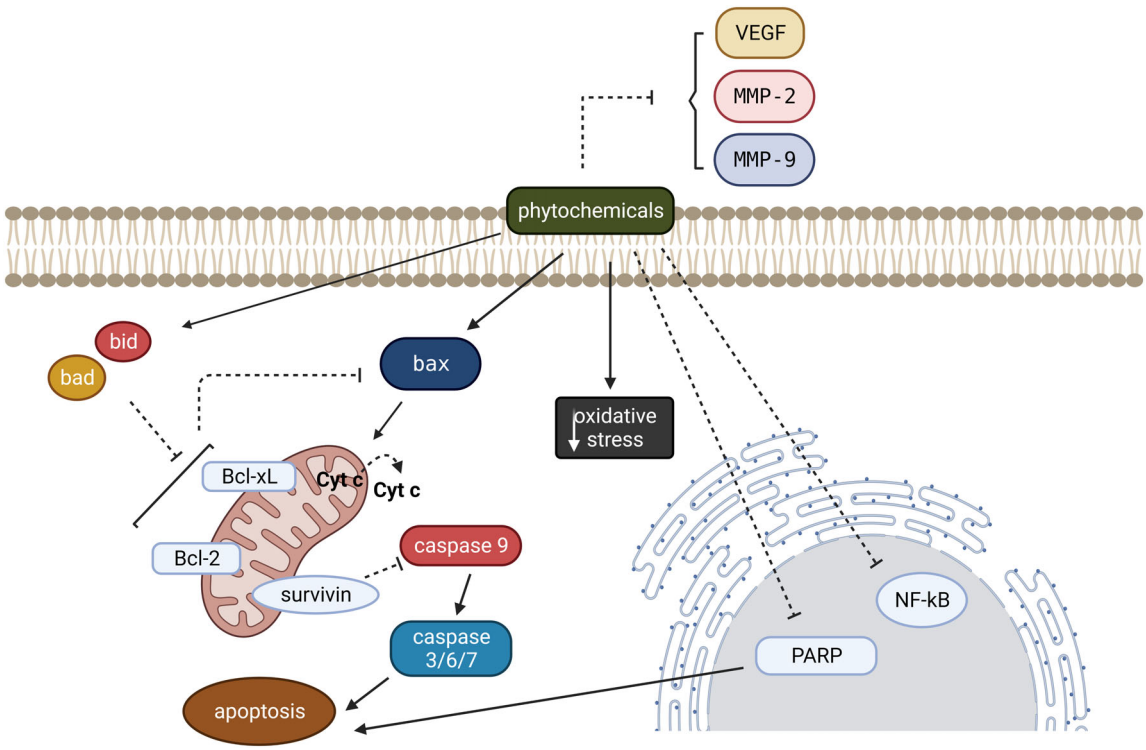

FIGURE 8 Schematic depiction of phytochemicals targeting distinct signaling pathways in ovarian cancer.

REFERENCES

Abotaleb, M., Liskova, A., Kubatka, P., & Büsselberg, D. (2020). Therapeutic potential of plant phenolic acids in the treatment of cancer. *Biomolecules*, *10*(2), 221. https://doi.org/10.3390/biom10020221

Abotaleb, M., Samuel, S., Varghese, E., Varghese, S., Kubatka, P., Liskova, A., & Büsselberg, D. (2018). Flavonoids in cancer and apoptosis. *Cancers*, *11*(1), 28. https://doi.org/10.3390/cancers11010028

Achkar, I. W., Abdulrahman, N., Al-Sulaiti, H., Joseph, J. M., Uddin, S., & Mraiche, F. (2018). Cisplatin based therapy: The role of the mitogen activated protein kinase signaling pathway. *Journal of Translational Medicine*, *16*(1), 96. https://doi.org/10.1186/s12967-018-1471-1

Adamski, Z., Blythe, L. L., Milella, L., & Bufo, S. A. (2020). Biological activities of alkaloids: From toxicology to pharmacology. *Toxins*, *12*(4), 210. https://doi.org/10.3390/toxins12040210

Al-Alem, L., & Curry, T. E. (2015). Ovarian cancer: Involvement of the matrix metalloproteinases. *Reproduction*, *150*(2), R55–R64. https://doi.org/10.1530/REP-14-0546

Alam, M. N., Yu, J. Q., Beale, P., & Huq, F. (2020). Cisplatin in combination with emetine and patulin showed dose and sequence dependent synergism against ovarian cancer. *Synergy*, *10*, 100060. https://doi.org/10.1016/j.synres.2019.100060

Alshehri, S. M., Shakeel, F., Ibrahim, M. A., Elzayat, E. M., Altamimi, M., Mohsin, K., Almeanazel, O. T., Alkholief, M., Alshetaili, A., Alsulays, B., Alanazi, F. K., & Alsarra, I. A. (2019). Dissolution and bioavailability improvement of bioactive apigenin using solid dispersions prepared by different techniques. *Saudi Pharmaceutical Journal*, *27*(2), 264–273. https://doi.org/10.1016/j.jsps.2018.11.008

Althurwi, S. I., Yu, J. Q., Beale, P., & Huq, F. (2020). Sequenced combinations of cisplatin and selected phytochemicals towards overcoming drug resistance in ovarian tumour models. *International Journal of Molecular Sciences*, *21*(20), 7500. https://doi.org/10.3390/ijms21207500

Amiri, S., Dastghaib, S., Ahmadi, M., Mehrbod, P., Khadem, F., Behrouj, H., Aghanoori, M.-R., Machaj, F., Ghamsari, M., Rosik, J., Hudecki, A., Afkhami, A., Hashemi, M., Los, M. J., Mokarram, P., Madrakian, T., & Ghavami, S. (2020). Betulin and its derivatives as novel compounds with different pharmacological effects. *Biotechnology Advances*, *38*, 107409. https://doi.org/10.1016/j.biotechadv.2019.06.008

Barbosa, L. T. C., & Vega, M. R. G. (2017). Diterpenes from the genus Xylopia. *Revista Virtual de Química*, *9*(4), 1712–1733. https://doi.org/10.21577/1984-6835.20170099

Barboza, J. R., Pereira, F. A. N., Fernandes, R. A., Vasconcelos, C. C., Cartágenes, M. d. S. d. S., Oliveira Lopes, A. J., de Melo, A. C., dos Guimarães, I. S., da Rocha, C. Q., & de Ribeiro, M. N. S. (2020). Cytotoxicity and pro-apoptotic, antioxidant and anti-inflammatory activities of Geopropolis produced by the stingless bee Melipona fasciculata smith. *Biology*, *9*(9), 292. https://doi.org/10.3390/biology9090292

Bergman, M. E., Davis, B., & Phillips, M. A. (2019). Medically useful plant Terpenoids: Biosynthesis, occurrence, and mechanism of action. *Molecules*, *24*(21), 3961. https://doi.org/10.3390/molecules24213961

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *68*(6), 394–424. https://doi.org/10.3322/caac.21492

Călinoiu, L. F., & Vodnar, D. C. (2018). Whole grains and phenolic acids: A review on bioactivity, functionality, health benefits and bioavailability. *Nutrients*, *10*(11), 1615. https://doi.org/10.3390/nu10111615

Cao, P., Zhao, S., Sun, Z., Jiang, N., Shang, Y., Wang, Y., Gu, J., & Li, S. (2018). BRMS1L suppresses ovarian cancer metastasis via inhibition of the β-catenin-wnt pathway. *Experimental Cell Research*, *371*(1), 214–221. https://doi.org/10.1016/j.yexcr.2018.08.013

Carneiro, B. A., & El-Deiry, W. S. (2020). Targeting apoptosis in cancer therapy. *Nature Reviews Clinical Oncology*, *17*(7), 395–417. https://doi.org/10.1038/s41571-020-0341-y

Chavva, S., Deshmukh, S., Kanchanapally, R., Tyagi, N., Coym, J., Singh, A., & Singh, S. (2019). Epigallocatechin Gallate-gold nanoparticles exhibit superior antitumor activity compared to conventional gold nanoparticles: Potential synergistic interactions. *Nanomaterials*, *9*(3), 396. https://doi.org/10.3390/nano9030396

Chen, C.-C., Hsieh, D.-S., Huang, K.-J., Chan, Y.-L., Hong, P.-D., Yeh, M.-K., & Wu, C.-J. (2014). Improving anticancer efficacy of (−)-epigallocatechin-3-gallate gold nanoparticles in murine B16F10 melanoma cells. *Drug Design, Development and Therapy*, *8*, 459–474. https://doi.org/10.2147/DDDT.S58414

Chen, J., Li, Z., Chen, A., Ye, X., Luo, H., Rankin, G., & Chen, Y. (2013). Inhibitory effect of Baicalin and Baicalein on ovarian cancer cells. *International Journal of Molecular Sciences*, *14*(3), 6012–6025. https://doi.org/10.3390/ijms14036012

Chen, S. S., Michael, A., & Butler-Manuel, S. A. (2012). Advances in the treatment of ovarian cancer: A potential role of antiinflammatory phytochemicals. *Discovery Medicine*, *13*(68), 7–17 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22284780

Cho, Y. J., Woo, J.-H., Lee, J.-S., Jang, D. S., Lee, K.-T., & Choi, J.-H. (2016). Eclalbasaponin II induces autophagic and apoptotic cell death in human ovarian cancer cells. *Journal of Pharmacological Sciences*, *132*(1), 6–14. https://doi.org/10.1016/j.jphs.2016.02.006

Chudzik, M., Korzonek-Szlacheta, I., & Król, W. (2015). Triterpenes as potentially cytotoxic compounds. *Molecules*, *20*(1), 1610–1625. https://doi.org/10.3390/molecules20011610

Chung, Y.-C., Lu, L.-C., Tsai, M.-H., Chen, Y.-J., Chen, Y.-Y., Yao, S.-P., & Hsu, C.-P. (2013). The inhibitory effect of Ellagic acid on cell growth of ovarian carcinoma cells. *Evidence-Based Complementary and Alternative Medicine*, *2013*, 1–12. https://doi.org/10.1155/2013/306705

Cornelison, R., Llaneza, D., & Landen, C. (2017). Emerging therapeutics to overcome chemoresistance in epithelial ovarian cancer: A mini-review. *International Journal of Molecular Sciences*, *18*(10), 2171. https://doi.org/10.3390/ijms18102171

de Oliveira Júnior, R. G., Christiane Adrielly, A. F., da Silva Almeida, J. R. G., Grougnet, R., Thiéry, V., & Picot, L. (2018). Sensitization of tumor cells to chemotherapy by natural products: A systematic review of preclinical data and molecular mechanisms. *Fitoterapia*, *129*, 383–400. https://doi.org/10.1016/j.fitote.2018.02.025

Dhupal, M., & Chowdhury, D. (2020). Phytochemical-based Nanomedicine for advanced cancer Theranostics: Perspectives on clinical trials to clinical use. *International Journal of Nanomedicine*, *15*, 9125–9157. https://doi.org/10.2147/IJN.S259628

DiDonato, J. A., Mercurio, F., & Karin, M. (2012). NF-κB and the link between inflammation and cancer. *Immunological Reviews*, *246*(1), 379–400. https://doi.org/10.1111/j.1600-065X.2012.01099.x

Efferth, T., & Oesch, F. (2021). Repurposing of plant alkaloids for cancer therapy: Pharmacology and toxicology. *Seminars in Cancer Biology*, *68*, 143–163. https://doi.org/10.1016/j.semcancer.2019.12.010

Engelke, L. H., Hamacher, A., Proksch, P., & Kassack, M. U. (2016). Ellagic acid and resveratrol prevent the development of cisplatin resistance in the epithelial ovarian cancer cell line A2780. *Journal of Cancer*, *7*(4), 353–363. https://doi.org/10.7150/jca.13754

Fan, Y., Mao, R., & Yang, J. (2013). NF-κB and STAT3 signaling pathways collaboratively link inflammation to cancer. *Protein & Cell*, *4*(3), 176–185. https://doi.org/10.1007/s13238-013-2084-3

Farrand, L., Kim, J. Y., Byun, S., Im-aram, A., Lee, J., Suh, J.-Y., Lee, K.-W., Lee, H. J., & Tsang, B. K. (2014). The diarylheptanoid hirsutenone sensitizes chemoresistant ovarian cancer cells to cisplatin via modulation of apoptosis-inducing factor and X-linked inhibitor of apoptosis. *Journal of Biological Chemistry*, *289*(3), 1723–1731. https://doi.org/10.1074/jbc.M113.513879

Fu, Y., Ye, X., Lee, M., Rankin, G., & Chen, Y. C. (2017). Prodelphinidins isolated from Chinese bayberry leaves induces apoptosis via the p53-dependent signaling pathways in OVCAR-3 human ovarian cancer

cells. *Oncology Letters*, *13*(5), 3210–3218. https://doi.org/10.3892/ol.2017.5813

Gao, X., Wang, B., Wei, X., Men, K., Zheng, F., Zhou, Y., Zheng, Y., Gou, M., Huang, M., Guo, G., Huang, N., Qian, Z., & Wei, Y. (2012). Anticancer effect and mechanism of polymer micelle-encapsulated quercetin on ovarian cancer. *Nanoscale*, *4*(22), 7021–7030. https://doi.org/10.1039/c2nr32181e

Gao, J., Zhu, H., Wan, H., Zou, X., Ma, X., & Gao, G. (2017). Harmine suppresses the proliferation and migration of human ovarian cancer cells through inhibiting ERK/CREB pathway. *Oncology Reports*, *38*(5), 2927–2934. https://doi.org/10.3892/or.2017.5952

Gasparyan, A. Y., Ayvazyan, L., Blackmore, H., & Kitas, G. D. (2011). Writing a narrative biomedical review: Considerations for authors, peer reviewers, and editors. *Rheumatology International*, *31*(11), 1409–1417. https://doi.org/10.1007/s00296-011-1999-3

George, V. C., Dellaire, G., & Rupasinghe, H. P. V. (2017). Plant flavonoids in cancer chemoprevention: Role in genome stability. *The Journal of Nutritional Biochemistry*, *45*, 1–14. https://doi.org/10.1016/j.jnutbio.2016.11.007

Gera, M., Sharma, N., Ghosh, M., Huynh, D. L., Lee, S. J., Min, T., Kwon, T., & Jeong, D. K. (2017). Nanoformulations of curcumin: An emerging paradigm for improved remedial application. *Oncotarget*, *8*(39), 66680–66698. https://doi.org/10.18632/oncotarget.19164

Ghaderi, S., Babaei, E., Hussen, B. M., Mahdavi, M., & Azeez, H. J. (2021). Gemini curcumin suppresses proliferation of ovarian cancer OVCAR-3 cells via induction of apoptosis. *Anti-Cancer Agents in Medicinal Chemistry*, *21*(6), 775–781. https://doi.org/10.2174/1871520620666200807223340

Granja, A., Pinheiro, M., & Reis, S. (2016). Epigallocatechin Gallate Nanodelivery Systems for Cancer Therapy. *Nutrients*, *8*(5), 1–23. https://doi.org/10.3390/nu8050307

Grunewald, T., & Ledermann, J. A. (2017). Targeted therapies for ovarian cancer. *Best Practice & Research Clinical Obstetrics & Gynaecology*, *41*, 139–152. https://doi.org/10.1016/j.bpobgyn.2016.12.001

Guo, X., & Ding, X. (2018). Dioscin suppresses the viability of ovarian cancer cells by regulating the VEGFR2 and PI3K/AKT/MAPK signaling pathways. *Oncology Letters*, *15*(6), 9537–9542. https://doi.org/10.3892/ol.2018.8454

Guo, L., Peng, Y., Yao, J., Sui, L., Gu, A., & Wang, J. (2010). Anticancer activity and molecular mechanism of resveratrol-bovine serum albumin nanoparticles on subcutaneously implanted human primary ovarian carcinoma cells in nude mice. *Cancer Biotherapy & Radiopharmaceuticals*, *25*(4), 471–477. https://doi.org/10.1089/cbr.2009.0724

Ha, J. H., Jayaraman, M., Radhakrishnan, R., Gomathinayagam, R., Yan, M., Song, Y. S., Isidoro, C., & Dhanasekaran, D. N. (2020). Differential effects of thymoquinone on lysophosphatidic acid-induced oncogenic pathways in ovarian cancer cells. *Journal of Traditional and Complementary Medicine*, *10*(3), 207–216. https://doi.org/10.1016/j.jtcme.2020.04.001

He, Z., Chen, A. Y., Rojanasakul, Y., Rankin, G. O., & Chen, Y. C. (2016). Gallic acid, a phenolic compound, exerts anti-angiogenic effects via the PTEN/AKT/HIF-1α/VEGF signaling pathway in ovarian cancer cells. *Oncology Reports*, *35*(1), 291–297. https://doi.org/10.3892/or.2015.4354

He, Z., Li, B., Rankin, G. O., Rojanasakul, Y., & Chen, Y. C. (2015). Selecting bioactive phenolic compounds as potential agents to inhibit proliferation and VEGF expression in human ovarian cancer cells. *Oncology Letters*, *9*(3), 1444–1450. https://doi.org/10.3892/ol.2014.2818

He, M., Wang, D., Zou, D., Wang, C., Lopes-Bastos, B., Jiang, W. G., Chester, J., Zhou, Q., & Cai, J. (2016). Re-purposing of curcumin as an anti-metastatic agent for the treatment of epithelial ovarian cancer: in vitro model using cancer stem cell enriched ovarian cancer spheroids. *Oncotarget*, *7*(52), 86374–86387. https://doi.org/10.18632/oncotarget.13413

Hordyjewska, A., Ostapiuk, A., Horecka, A., & Kurzepa, J. (2019). Betulin and betulinic acid: Triterpenoids derivatives with a powerful biological potential. *Phytochemistry Reviews*, *18*(3), 929–951. https://doi.org/10.1007/s11101-019-09623-1

Hu, H., Luo, L., Liu, F., Zou, D., Zhu, S., Tan, B., & Chen, T. (2016). Anticancer and Sensibilisation effect of Triptolide on human epithelial ovarian cancer. *Journal of Cancer*, *7*(14), 2093–2099. https://doi.org/10.7150/jca.16178

Hu, Y., Ran, M., Wang, B., Lin, Y., Cheng, Y., & Zheng, S. (2020). Co-delivery of docetaxel and curcumin via Nanomicelles for enhancing anti-ovarian cancer treatment. *International Journal of Nanomedicine*, *15*, 9703–9715. https://doi.org/10.2147/IJN.S274083

Huang, J., Lin, H., & Hong, Y. (2016). In vitro anti-tumor activity of the tanshinone IIA against SKOV3 cells. *Natural Product Research*, *30*(16), 1844–1846. https://doi.org/10.1080/14786419.2015.1068774

Huq, F., Yu, J. Q., Beale, P., Chan, C., Arzuman, L., Nessa, M. U., & Mazumder, M. E. H. (2014). Combinations of platinums and selected phytochemicals as a means of overcoming resistance in ovarian cancer. *Anticancer Research*, *34*(1), 541–545. http://www.ncbi.nlm.nih.gov/pubmed/24403514

Ibrahim, S. R. M., Khedr, A. I. M., Mohamed, G. A., Zayed, M. F., El-Kholy, A. A.-E. S., & Al Haidari, R. A. (2019). Cucumol B, a new triterpene benzoate from Cucumis melo seeds with cytotoxic effect toward ovarian and human breast adenocarcinoma. *Journal of Asian Natural Products Research*, *21*(11), 1112–1118. https://doi.org/10.1080/10286020.2018.1488832

İnce, İ., Yıldırım, Y., Güler, G., Medine, E. İ., Ballıca, G., Kuşdemir, B. C., & Göker, E. (2020). Synthesis and characterization of folic acid-chitosan nanoparticles loaded with thymoquinone to target ovarian cancer cells. *Journal of Radioanalytical and Nuclear Chemistry*, *324*(1), 71–85. https://doi.org/10.1007/s10967-020-07058-z

Islam, M. T. (2017). Diterpenes and their derivatives as potential anticancer agents. *Phytotherapy Research*, *31*(5), 691–712. https://doi.org/10.1002/ptr.5800

Jeong, M., Kim, H. M., Kim, H. J., Choi, J.-H., & Jang, D. S. (2017). Kudsuphilactone B, a nortriterpenoid isolated from Schisandra chinensis fruit, induces caspase-dependent apoptosis in human ovarian cancer A2780 cells. *Archives of Pharmacal Research*, *40*(4), 500–508. https://doi.org/10.1007/s12272-017-0902-5

Ji, X., Yang, C., Xie, J., Yin, X., & Hu, Q. (2020). Effect of Saponin from Tupistra chinensis baker on proliferation and apoptosis of ovarian cancer cells by Wnt/β <scp>-catenin</scp> pathway. *IUBMB Life*, *72*(8), 1780–1786. https://doi.org/10.1002/iub.2308

Jia, L., Jin, H., Zhou, J., Chen, L., Lu, Y., Ming, Y., & Yu, Y. (2013). A potential anti-tumor herbal medicine, Corilagin, inhibits ovarian cancer cell growth through blocking the TGF-β signaling pathways. *BMC Complementary and Alternative Medicine*, *13*(1), 33. https://doi.org/10.1186/1472-6882-13-33

Jia, L.-Y., Wu, X.-J., Gao, Y., Rankin, G. O., Pigliacampi, A., Bucur, H., Li, B., Tu, Y.-Y., & Chen, Y. C. (2017). Inhibitory effects of Total triterpenoid Saponins isolated from the seeds of the tea plant (Camellia sinensis) on human ovarian cancer cells. *Molecules*, *22*(10), 1649. https://doi.org/10.3390/molecules22101649

Jiang, Z., Fletcher, N. M., Ali-Fehmi, R., Diamond, M. P., Abu-Soud, H. M., Munkarah, A. R., & Saed, G. M. (2011). Modulation of redox signaling promotes apoptosis in epithelial ovarian cancer cells. *Gynecologic Oncology*, *122*(2), 418–423. https://doi.org/10.1016/j.ygyno.2011.04.051

Jiang, G., Liu, J., Ren, B., Tang, Y., Owusu, L., Li, M., Zhang, J., Liu, L., & Li, W. (2016). Anti-tumor effects of osthole on ovarian cancer cells in vitro. *Journal of Ethnopharmacology*, *193*, 368–376. https://doi.org/10.1016/j.jep.2016.08.045

Jiang, G., Liu, J., Ren, B., Zhang, L., Owusu, L., Liu, L., Zhang, J., Tang, Y., & Li, W. (2017). Anti-tumor and chemosensitization effects of Cryptotanshinone extracted from salvia miltiorrhiza Bge. On ovarian cancer cells in vitro. *Journal of Ethnopharmacology*, *205*, 33–40. https://doi.org/10.1016/j.jep.2017.04.026

Jin, X., Zhou, J., Zhang, Z., & Lv, H. (2019). Doxorubicin combined with betulinic acid or lonidamine in RGD ligand-targeted pH-sensitive micellar system for ovarian cancer treatment. *International Journal of Pharmaceutics*, *571*, 118751. https://doi.org/10.1016/j.ijpharm.2019.118751

Johnson-Ajinwo, O. R., Richardson, A., & Li, W.-W. (2019). Palmatine from unexplored Rutidea parviflora showed cytotoxicity and induction of apoptosis in human ovarian cancer cells. *Toxins*, *11*(4), 237. https://doi.org/10.3390/toxins11040237

Juang, Y.-P., & Liang, P.-H. (2020). Biological and pharmacological effects of synthetic Saponins. *Molecules*, *25*(21), 4974. https://doi.org/10.3390/molecules25214974

Kazemi, M., Zolfaghari, B., Shahrestanaki, M. K., & Dinani, M. S. (2017). Cytotoxic effects of Allium affine Ledeb Butanolic fraction on breast and ovary cancer cell lines. *Journal of Medicinal Plants*, *16*(64), 83–90 Retrieved from https://jmp.ir/article-1-1660-en.html

Khatun, M., Choudhury, S., Liu, B., Lemmens, P., Pal, S. K., & Mazumder, S. (2016). Resveratrol–ZnO nanohybrid enhanced anti-cancerous effect in ovarian cancer cells through ROS. *RSC Advances*, *6*(107), 105607–105617. https://doi.org/10.1039/C6RA16664D

Kleczka, A., Kubina, R., Dzik, R., Jasik, K., Stojko, J., Cholewa, K., & Kabała-Dzik, A. (2020). Caffeic acid Phenethyl Ester (CAPE) induced apoptosis in serous ovarian cancer OV7 cells by deregulation of BCL2/BAX genes. *Molecules*, *25*(15), 3514. https://doi.org/10.3390/molecules25153514

Koczurkiewicz, P., Klaś, K., Grabowska, K., Piska, K., Rogowska, K., Wójcik-Pszczoła, K., Podolak, I., Galanty, A., Michalik, M., Pękala, E., Wójcik-Pszczoła, K., Podolak, I., Galanty, A., Michalik, M., & Pękala, E. (2019). Saponins as chemosensitizing substances that improve effectiveness and selectivity of anticancer drug—Minireview of in vitro studies. *Phytotherapy Research*, *33*(9), 2141–2151. https://doi.org/10.1002/ptr.6371

Krishnamurthy, N., & Kurzrock, R. (2018). Targeting the Wnt/beta-catenin pathway in cancer: Update on effectors and inhibitors. *Cancer Treatment Reviews*, *62*, 50–60. https://doi.org/10.1016/j.ctrv.2017.11.002

Kuroki, L., & Guntupalli, S. R. (2020). Treatment of epithelial ovarian cancer. *BMJ (Clinical Research Ed.)*, *371*, m3773. https://doi.org/10.1136/bmj.m3773

Lanzotti, V., Barile, E., Scambia, G., & Ferlini, C. (2015). Cyparissins a and B, jatrophane diterpenes from Euphorbia cyparissias as Pgp inhibitors and cytotoxic agents against ovarian cancer cell lines. *Fitoterapia*, *104*, 75–79. https://doi.org/10.1016/j.fitote.2015.05.012

Lee, H. N., Kim, J.-K., Kim, J. H., Lee, S.-J., Ahn, E.-K., Oh, J. S., & Seo, D.-W. (2014). A mechanistic study on the anti-cancer activity of ethyl caffeate in human ovarian cancer SKOV-3 cells. *Chemico-Biological Interactions*, *219*, 151–158. https://doi.org/10.1016/j.cbi.2014.05.017

Lee, D., Lee, S. R., Kang, K. S., Ko, Y., Pang, C., Yamabe, N., & Kim, K. H. (2019). Betulinic acid suppresses ovarian cancer cell proliferation through induction of apoptosis. *Biomolecules*, *9*(7), 257. https://doi.org/10.3390/biom9070257

Lei, P., Zhang, W., & Men, X. (2014). Review on anti-tumor effect of triterpene acid compounds. *Journal of Cancer Research and Therapeutics*, *10*(5), 14–19. https://doi.org/10.4103/0973-1482.139746

Lin, W., & Ye, H. (2020). Anticancer activity of ursolic acid on human ovarian cancer cells via ROS and MMP mediated apoptosis, cell cycle arrest and downregulation of PI3K/AKT pathway. *Journal of B.U.ON.: Official Journal of the Balkan Union of Oncology*, *25*(2), 750–756 Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/32521863

Liu, Z., Zhu, Y.-Y., Li, Z.-Y., & Ning, S.-Q. (2016). Evaluation of the efficacy of paclitaxel with curcumin combination in ovarian cancer cells. *Oncology Letters*, *12*(5), 3944–3948. https://doi.org/10.3892/ol.2016.5192

Lombrea, A., Scurtu, A. D., Avram, S., Pavel, I. Z., Turks, M., Lugiņina, J., Peipiņš, U., Dehelean, C. A., Soica, C., & Danciu, C. (2021). Anticancer potential of Betulonic acid derivatives. *International Journal of Molecular Sciences*, *22*(7), 3676. https://doi.org/10.3390/ijms22073676

Long, Q., Xiel, Y., Huang, Y., Wu, Q., Zhang, H., Xiong, S., Liu, Y., Chen, L., Wei, Y., Zhao, X., & Gong, C. (2013). Induction of apoptosis and inhibition of angiogenesis by PEGylated liposomal quercetin in both cisplatin-sensitive and cisplatin-resistant ovarian cancers. *Journal of Biomedical Nanotechnology*, *9*(6), 965–975. https://doi.org/10.1166/jbn.2013.1596

Majidinia, M., Bishayee, A., & Yousefi, B. (2019). Polyphenols: Major regulators of key components of DNA damage response in cancer. *DNA Repair*, *82*, 102679. https://doi.org/10.1016/j.dnarep.2019.102679

Mohapatra, P., Singh, P., & Sahoo, S. K. (2020). Phytonanomedicine: A novel avenue to treat recurrent cancer by targeting cancer stem cells. *Drug Discovery Today*, *25*(8), 1307–1321. https://doi.org/10.1016/j.drudis.2020.06.003

Mohapatra, P., Singh, P., Singh, D., Sahoo, S., & Sahoo, S. K. (2022). Phytochemical based nanomedicine: A panacea for cancer treatment, present status and future prospective. *OpenNano*, *7*, 100055. https://doi.org/10.1016/j.onano.2022.100055

Nan, X.-W., Gong, L.-H., Chen, X., Zhou, H.-H., Ye, P.-P., Yang, Y., Xing, Z.-H., Wei, M.-N., Li, Y., Wang, S.-T., Liu, K., Shi, Z., & Yan, X.-J. (2019). Survivin promotes Piperlongumine resistance in ovarian cancer. *Frontiers in Oncology*, *9*, 1345. https://doi.org/10.3389/fonc.2019.01345

Nguyen, V. H. L., Hough, R., Bernaudo, S., & Peng, C. (2019). Wnt/β-catenin signalling in ovarian cancer: Insights into its hyperactivation and function in tumorigenesis. *Journal of Ovarian Research*, *12*(1), 122. https://doi.org/10.1186/s13048-019-0596-z

Opferman, J. T., & Kothari, A. (2018). Anti-apoptotic BCL-2 family members in development. *Cell Death & Differentiation*, *25*(1), 37–45. https://doi.org/10.1038/cdd.2017.170

Pal, M. K., Jaiswar, S. P., Srivastav, A. K., Goyal, S., Dwivedi, A., Verma, A., Singh, J., Pathak, A. K., Sankhwar, P. L., & Ray, R. S. (2016). Synergistic effect of piperine and paclitaxel on cell fate via cyt-c, Bax/Bcl-2-caspase-3 pathway in ovarian adenocarcinomas SKOV-3 cells. *European Journal of Pharmacology*, *791*, 751–762. https://doi.org/10.1016/j.ejphar.2016.10.019

Pan, H., Kim, E., Rankin, G. O., Rojanasakul, Y., Tu, Y., & Chen, Y. C. (2018). Theaflavin-3,3′-digallate inhibits ovarian cancer stem cells via suppressing Wnt/β-catenin signaling pathway. *Journal of Functional Foods*, *50*, 1–7. https://doi.org/10.1016/j.jff.2018.09.021

Peluso, I., Yarla, N. S., Ambra, R., Pastore, G., & Perry, G. (2019). MAPK signalling pathway in cancers: Olive products as cancer preventive and therapeutic agents. *Seminars in Cancer Biology*, *56*, 185–195. https://doi.org/10.1016/j.semcancer.2017.09.002

Pistollato, F., Calderón Iglesias, R., Ruiz, R., Aparicio, S., Crespo, J., Dzul Lopez, L., Giampieri, F., & Battino, M. (2017). The use of natural compounds for the targeting and chemoprevention of ovarian cancer. *Cancer Letters*, *411*, 191–200. https://doi.org/10.1016/j.canlet.2017.09.050

Qu, Y., Cong, P., Lin, C., Deng, Y., Li-Ling, J., & Zhang, M. (2017). Inhibition of paclitaxel resistance and apoptosis induction by cucurbitacin B in ovarian carcinoma cells. *Oncology Letters*, *14*(1), 145–152. https://doi.org/10.3892/ol.2017.6148

Radhakrishnan, R., Pooja, D., Kulhari, H., Gudem, S., Ravuri, H. G., Bhargava, S., & Ramakrishna, S. (2019). Bombesin conjugated solid lipid nanoparticles for improved delivery of epigallocatechin gallate for breast cancer treatment. *Chemistry and Physics of Lipids*, *224*, 104770. https://doi.org/10.1016/j.chemphyslip.2019.04.005

Radu, M. R., Prădatu, A., Duică, F., Micu, R., Creţoiu, S. M., Suciu, N., Creţoiu, D., Varlas, V. N., & Rădoi, V. E. (2021). Ovarian cancer: Biomarkers and targeted therapy. *Biomedicine*, *9*(6), 693. https://doi.org/10.3390/biomedicines9060693

Rajabi, S., Maresca, M., Yumashev, A. V., Choopani, R., & Hajimehdipoor, H. (2021). The Most competent plant-derived natural products for targeting apoptosis in cancer therapy. *Biomolecules*, *11*(4), 534. https://doi.org/10.3390/biom11040534

Rajagopal, C., Lankadasari, M. B., Aranjani, J. M., & Harikumar, K. B. (2018). Targeting oncogenic transcription factors by polyphenols: A novel approach for cancer therapy. *Pharmacological Research*, *130*, 273–291. https://doi.org/10.1016/j.phrs.2017.12.034

Ramalingam, V., Muthukumar Sathya, P., Srivalli, T., & Mohan, H. (2022). Synthesis of quercetin functionalized wurtzite type zinc oxide nanoparticles and their potential to regulate intrinsic apoptosis signaling pathway in human metastatic ovarian cancer. *Life Sciences*, *309*, 121022. https://doi.org/10.1016/j.lfs.2022.121022

Rasmussen, A., Murphy, K., & Hoskin, D. W. (2019). 10-Gingerol inhibits ovarian cancer cell growth by inducing G2Arrest. *Advanced Pharmaceutical Bulletin*, *9*(4), 685–689. https://doi.org/10.15171/apb.2019.080

Rezaei-Tazangi, F., Roghani-Shahraki, H., Khorsand Ghaffari, M., Abolhasani Zadeh, F., Boostan, A., ArefNezhad, R., & Motedayyen, H. (2021). The therapeutic potential of common herbal and Nano-based herbal formulations against ovarian cancer: New insight into the current evidence. *Pharmaceuticals*, *14*(12), 1315. https://doi.org/10.3390/ph14121315

Salazar, J. R., Loza-Mejía, M. A., & Soto-Cabrera, D. (2020). Chemistry, biological activities and in silico bioprospection of sterols and triterpenes from Mexican columnar Cactaceae. *Molecules*, *25*(7), 1649. https://doi.org/10.3390/molecules25071649

Sánchez-Carranza, J. N., Díaz, J. F., Redondo-Horcajo, M., Barasoain, I., Alvarez, L., Lastres, P., Romero-Estrada, A., Aller, P., & González-Maya, L. (2018). Gallic acid sensitizes paclitaxel-resistant human ovarian carcinoma cells through an increase in reactive oxygen species and subsequent downregulation of ERK activation. *Oncology Reports*, *39*(6), 3007–3014. https://doi.org/10.3892/or.2018.6382

Sandhiutami, N. M. D., Arozal, W., Louisa, M., Rahmat, D., & Wuyung, P. E. (2020). Curcumin nanoparticle enhances the anticancer effect of cisplatin by inhibiting PI3K/AKT and JAK/STAT3 pathway in rat ovarian carcinoma induced by DMBA. *Frontiers in Pharmacology*, *11*, 603235. https://doi.org/10.3389/fphar.2020.603235

Seca, A., & Pinto, D. (2018). Plant secondary metabolites as anticancer agents: Successes in clinical trials and therapeutic application. *International Journal of Molecular Sciences*, *19*(1), 263. https://doi.org/10.3390/ijms19010263

Sen, K., Banerjee, S., & Mandal, M. (2019). Dual drug loaded liposome bearing apigenin and 5-fluorouracil for synergistic therapeutic efficacy in colorectal cancer. *Colloids and Surfaces B: Biointerfaces*, *180*, 9–22. https://doi.org/10.1016/j.colsurfb.2019.04.035

Shafabakhsh, R., & Asemi, Z. (2019). Quercetin: A natural compound for ovarian cancer treatment. *Journal of Ovarian Research*, *12*(1), 55. https://doi.org/10.1186/s13048-019-0530-4

Si, L., Yang, R., Lin, R., & Yang, S. (2018). Piperine functions as a tumor suppressor for human ovarian tumor growth via activation of JNK/p38 MAPK-mediated intrinsic apoptotic pathway. *Bioscience Reports*, *38*(3), 1–11. https://doi.org/10.1042/BSR20180503

Singh, C. K., Ndiaye, M. A., & Ahmad, N. (2015). Resveratrol and cancer: Challenges for clinical translation. *Biochimica et Biophysica Acta*, *1852*(6), 1178–1185. https://doi.org/10.1016/j.bbadis.2014.11.004

Slade, D. (2020). PARP and PARG inhibitors in cancer treatment. *Genes & Development*, *34*(5–6), 360–394. https://doi.org/10.1101/gad.334516.119

Smolle, E., Taucher, V., Pichler, M., Petru, E., Lax, S., & Haybaeck, J. (2013). Targeting signaling pathways in epithelial ovarian cancer. *International Journal of Molecular Sciences*, *14*(5), 9536–9555. https://doi.org/10.3390/ijms14059536

Sobolewska, D., Galanty, A., Grabowska, K., Makowska-Wąs, J., Wróbel-Biedrawa, D., & Podolak, I. (2020). Saponins as cytotoxic agents: an update (2010–2018). Part I—steroidal saponins. *Phytochemistry Reviews*, *19*(1), 139–189. https://doi.org/10.1007/s11101-020-09661-0

Stewart, C. J. R., Stewart, L. M., Holman, C. D. J., Jordan, S., Semmens, J., Spilsbury, K., & Threlfall, T. (2017). Value of pathology review in a population-based series of ovarian tumors. *International Journal of Gynecological Pathology*, *36*(4), 377–385. https://doi.org/10.1097/PGP.0000000000000342

Sun, Q., Yogosawa, S., Iizumi, Y., Sakai, T., & Sowa, Y. (2015). The alkaloid emetine sensitizes ovarian carcinoma cells to cisplatin through down-regulation of bcl-xL. *International Journal of Oncology*, *46*(1), 389–394. https://doi.org/10.3892/ijo.2014.2703

Sun, C.-Y., Zhang, Q.-Y., Zheng, G.-J., & Feng, B. (2019). Phytochemicals: Current strategy to sensitize cancer cells to cisplatin. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*, *110*, 518–527. https://doi.org/10.1016/j.biopha.2018.12.010

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249. https://doi.org/10.3322/caac.21660

Tavsan, Z., & Kayali, H. A. (2019). Flavonoids showed anticancer effects on the ovarian cancer cells: Involvement of reactive oxygen species, apoptosis, cell cycle and invasion. *Biomedicine & Pharmacotherapy*, *116*, 109004. https://doi.org/10.1016/j.biopha.2019.109004

Teekaraman, D., Elayapillai, S. P., Viswanathan, M. P., & Jagadeesan, A. (2019). Quercetin inhibits human metastatic ovarian cancer cell growth and modulates components of the intrinsic apoptotic pathway in PA-1 cell line. *Chemico-Biological Interactions*, *300*, 91–100. https://doi.org/10.1016/j.cbi.2019.01.008

Tholl, D. (2015). Biosynthesis and biological functions of terpenoids in plants. *Advances in Biochemical Engineering/Biotechnology*, *148*, 63–106. https://doi.org/10.1007/10_2014_295

Torre, L. A., Trabert, B., DeSantis, C. E., Miller, K. D., Samimi, G., Runowicz, C. D., Gaudet, M. M., Jemal, A., & Siegel, R. L. (2018). Ovarian cancer statistics, 2018. *CA: A Cancer Journal for Clinicians*, *68*(4), 284–296. https://doi.org/10.3322/caac.21456

Tu, Y., Chen, L., Ren, N., Li, B., Wu, Y., Rankin, G. O., Rojanasakul, Y., Wang, Y., & Chen, Y. C. (2020). Standardized Saponin extract from Baiye No.1 tea (Camellia sinensis) flowers induced S phase cell cycle arrest and apoptosis via AKT-MDM2-p53 signaling pathway in ovarian cancer cells. *Molecules*, *25*(15), 3515. https://doi.org/10.3390/molecules25153515

Ur-Rashid, M., Alamzeb, M., Ali, S., Ullah, Z., Shah, Z. A., Naz, I., & Khan, M. R. (2019). The chemistry and pharmacology of alkaloids and allied nitrogen compounds from Artemisia species: A review. *Phytotherapy Research*, *33*(10), 2661–2684. https://doi.org/10.1002/ptr.6466

Vafadar, A., Shabaninejad, Z., Movahedpour, A., Fallahi, F., Taghavipour, M., Ghasemi, Y., Akbari, M., Shafiee, A., Hajighadimi, S., Moradizarmehri, S., Razi, E., Savardashtaki, A., & Mirzaei, H. (2020). Quercetin and cancer: New insights into its therapeutic effects on ovarian cancer cells. *Cell & Bioscience*, *10*(1), 32. https://doi.org/10.1186/s13578-020-00397-0

Vallino, L., Ferraresi, A., Vidoni, C., Secomandi, E., Esposito, A., Dhanasekaran, D. N., & Isidoro, C. (2020). Modulation of non-coding RNAs by resveratrol in ovarian cancer cells: In silico analysis and literature review of the anti-cancer pathways involved. *Journal of Traditional and Complementary Medicine*, *10*(3), 217–229. https://doi.org/10.1016/j.jtcme.2020.02.006

Varela-Rodríguez, L., Sánchez-Ramírez, B., Hernández-Ramírez, V. I., Varela-Rodríguez, H., Castellanos-Mijangos, R. D., González-Horta, C., Chávez-Munguía, B., & Talamás-Rohana, P. (2020). Effect of Gallic acid and Myricetin on ovarian cancer models: A possible alternative antitumoral treatment. *BMC Complementary Medicine and Therapies*, *20*(1), 110. https://doi.org/10.1186/s12906-020-02900-z

Vo, N. N. Q., Fukushima, E. O., & Muranaka, T. (2017). Structure and hemolytic activity relationships of triterpenoid saponins and sapogenins. *Journal of Natural Medicines*, *71*(1), 50–58. https://doi.org/10.1007/s11418-016-1026-9

Wang, X., Chen, Z., Li, X., Jiang, Z., Zhao, Y., & Ping, F. (2017). Geraniin suppresses ovarian cancer growth through inhibition of NF-κB activation and downregulation of Mcl-1 expression. *Journal of Biochemical and Molecular Toxicology*, *31*(9), e21929. https://doi.org/10.1002/jbt.21929

Wang, M., Liu, Z.-F., Tang, H., & Chen, B.-A. (2018). Application of alkaloids in reversing multidrug resistance in human cancers. *Chinese Journal of Natural Medicines*, *16*(8), 561–571. https://doi.org/10.1016/S1875-5364(18)30093-1

Wang, Y., Ren, N., Rankin, G. O., Li, B., Rojanasakul, Y., Tu, Y., & Chen, Y. C. (2017). Anti-proliferative effect and cell cycle arrest induced by saponins extracted from tea (Camellia sinensis) flower in human ovarian cancer cells. *Journal of Functional Foods*, *37*, 310–321. https://doi.org/10.1016/j.jff.2017.08.001

Wang, Y., Xia, C., Chen, L., Chen, Y. C., & Tu, Y. (2020). Saponins extracted from tea (camellia Sinensis) flowers induces autophagy in ovarian cancer cells. *Molecules*, *25*(22), 5254. https://doi.org/10.3390/molecules25225254

Wang, L., Yin, Q., Liu, C., Tang, Y., Sun, C., & Zhuang, J. (2021). Nanoformulations of Ursolic acid: A modern natural anticancer molecule. *Frontiers in Pharmacology*, *12*, 706121. https://doi.org/10.3389/fphar.2021.706121

Wang, Y., & Zhu, Z. (2019). Oridonin inhibits metastasis of human ovarian cancer cells by suppressing the mTOR pathway. *Archives of Medical Science*, *15*(4), 1017–1027. https://doi.org/10.5114/aoms.2018.77068

Weidle, U. H., Birzele, F., Kollmorgen, G., & Rueger, R. (2016). Mechanisms and targets involved in dissemination of ovarian cancer. *Cancer Genomics & Proteomics*, *13*(6), 407–424. https://doi.org/10.21873/cgp.20004

Weng, Y.-P., Hung, P.-F., Ku, W.-Y., Chang, C.-Y., Wu, B.-H., Wu, M.-H., Yao, J.-Y., Yang, J.-R., & Lee, C.-H. (2018). The inhibitory activity of gallic acid against DNA methylation: Application of gallic acid on epigenetic therapy of human cancers. *Oncotarget*, *9*(1), 361–374. https://doi.org/10.18632/oncotarget.23015

Woźniak, M., Krajewski, R., Makuch, S., & Agrawal, S. (2021). Phytochemicals in gynecological cancer prevention. *International Journal of Molecular Sciences*, *22*(3), 1219. https://doi.org/10.3390/ijms22031219

Xia, R., Chen, S.-X., Qin, Q., Chen, Y., Zhang, W.-W., Zhu, R.-R., & Deng, A.-M. (2016). Oridonin suppresses proliferation of human ovarian cancer cells via blockage of mTOR signaling. *Asian Pacific Journal of Cancer Prevention*, *17*(2), 667–671. https://doi.org/10.7314/APJCP.2016.17.2.667

Xie, Z., Guo, Z., Wang, Y., Lei, J., & Yu, J. (2018). Protocatechuic acid inhibits the growth of ovarian cancer cells by inducing apoptosis and autophagy. *Phytotherapy Research*, *32*(11), 2256–2263. https://doi.org/10.1002/ptr.6163

Xu, Y.-Q., Chen, W.-R., Tsosie, J. K., Xie, X., Li, P., Wan, J.-B., He, C.-W., & Chen, M.-W. (2016). Niosome encapsulation of curcumin: Characterization and cytotoxic effect on ovarian cancer cells. *Journal of Nanomaterials*, *2016*, 1–9. https://doi.org/10.1155/2016/6365295

Xu, L., Zhang, X., Li, Y., Lu, S., Lu, S., Li, J., Wang, Y., Tian, X., Wei, J., Shao, C., & Liu, Z. (2016). Neferine induces autophagy of human ovarian cancer cells via p38 MAPK/ JNK activation. *Tumor Biology*, *37*(7), 8721–8729. https://doi.org/10.1007/s13277-015-4737-8

Yan, Y.-B., Tian, Q., Zhang, J.-F., & Xiang, Y. (2020). Antitumor effects and molecular mechanisms of action of natural products in ovarian cancer (review). *Oncology Letters*, *20*(5), 1. https://doi.org/10.3892/ol.2020.12001

Yang, W., Liu, L., Li, C., Luo, N., Chen, R., Li, L., Yu, F., & Cheng, Z. (2018). TRIM52 plays an oncogenic role in ovarian cancer associated with NF-kB pathway. *Cell Death & Disease*, *9*(9), 908. https://doi.org/10.1038/s41419-018-0881-6

Zeng, Z., Lin, C., Wang, S., Wang, P., Xu, W., Ma, W., Wang, J., Xiang, Q., Liu, Y., Yang, J., Ye, F., Xie, K., Xu, J., Luo, Y., Liu, S.-L., & Liu, H. (2020). Suppressive activities of mangiferin on human epithelial ovarian cancer. *Phytomedicine*, *76*, 153267. https://doi.org/10.1016/j.phymed.2020.153267

Zhang, R., Chen, J., Mao, L., Guo, Y., Hao, Y., Deng, Y., Han, X., Li, Q., Liao, W., & Yuan, M. (2020). Nobiletin triggers reactive oxygen species-mediated Pyroptosis through regulating autophagy in ovarian cancer cells. *Journal of Agricultural and Food Chemistry*, *68*(5), 1326–1336. https://doi.org/10.1021/acs.jafc.9b07908

Zhang, Y., Chen, S., Wei, C., Rankin, G. O., Ye, X., & Chen, Y. C. (2018). Flavonoids from Chinese bayberry leaves induced apoptosis and G1 cell cycle arrest via Erk pathway in ovarian cancer cells. *European Journal of Medicinal Chemistry*, *147*, 218–226. https://doi.org/10.1016/j.ejmech.2018.01.084

Zhang, H., Dong, R., Zhang, P., & Wang, Y. (2019). Songorine suppresses cell growth and metastasis in epithelial ovarian cancer via the Bcl-2/Bax and GSK3β/β-catenin signaling pathways. *Oncology Reports*, *41*(5), 3069–3079. https://doi.org/10.3892/or.2019.7070

Zhang, H., Jiao, Y., Shi, C., Song, X., Chang, Y., Ren, Y., & Shi, X. (2018). Berbamine suppresses cell proliferation and promotes apoptosis in ovarian cancer partially via the inhibition of Wnt/β-catenin signaling. *Acta Biochimica et Biophysica Sinica*, *50*(6), 532–539. https://doi.org/10.1093/abbs/gmy036

Zhang, L., Ren, B., Zhang, J., Liu, L., Liu, J., Jiang, G., Li, M., Ding, Y., & Li, W. (2017). Anti-tumor effect of Scutellaria barbata D. Don extracts on ovarian cancer and its phytochemicals characterisation. *Journal of Ethnopharmacology*, *206*, 184–192. https://doi.org/10.1016/j.jep.2017.05.032

Zhang, X., Samadi, A. K., Roby, K. F., Timmermann, B., & Cohen, M. S. (2012). Inhibition of cell growth and induction of apoptosis in ovarian carcinoma cell lines CaOV3 and SKOV3 by natural withanolide Withaferin a. *Gynecologic Oncology*, *124*(3), 606–612. https://doi.org/10.1016/j.ygyno.2011.11.044

Zhang, H., Sun, D., Qiu, J., & Yao, L. (2019). SFRP1 inhibited the epithelial ovarian cancer through inhibiting Wnt/β-catenin signaling. *Acta Biochimica Polonica*, *66*(4), 393–400. https://doi.org/10.18388/abp.2019_2757

Zhang, X., Zhou, Y., & Gu, Y. (2018). Tanshinone IIA induces apoptosis of ovarian cancer cells in vitro and in vivo through attenuation of PI3K/AKT/JNK signaling pathways. *Oncology Letters.*, *17*, 1896–1902. https://doi.org/10.3892/ol.2018.9744

Zhao, S.-F., Zhang, X.-J., Zhang, X.-J., Shi, X.-Q., Yu, Z.-J., & Kan, Q.-C. (2014). Induction of MicroRNA-9 mediates cytotoxicity of curcumin against SKOV3 ovarian cancer cells. *Asian Pacific Journal of Cancer Prevention*, *15*(8), 3363–3368. https://doi.org/10.7314/APJCP.2014.15.8.3363

Zheng, X., Chen, W., Hou, H., Li, J., Li, H., Sun, X., Zhao, L., & Li, X. (2017). Ginsenoside 20(S)-Rg3 induced autophagy to inhibit migration and invasion of ovarian cancer. *Biomedicine & Pharmacotherapy*, *85*, 620–626. https://doi.org/10.1016/j.biopha.2016.11.072

Zhou, M., Yi, Y., Liu, L., Lin, Y., Li, J., Ruan, J., & Zhong, Z. (2019). Polymeric micelles loading with ursolic acid enhancing anti-tumor effect on hepatocellular carcinoma. *Journal of Cancer*, *10*(23), 5820–5831. https://doi.org/10.7150/jca.30865

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