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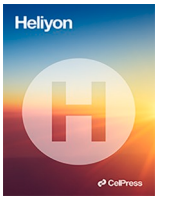

Review article

Medicinal plants as a potential resource for the discovery of novel structures towards cancer drug resistance treatment

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A R T I C L E I N F O

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A B S T R A C T

Despite extensive research in chemotherapy, global cancer concerns persist, exacerbated by the challenge of drug resistance, which imposes economic and medical burdens. Natural compounds, particularly secondary metabolites from medicinal plants, present promising avenues for overcoming cancer drug resistance due to their diverse structures and essential pharmacological effects. This review provides a comprehensive exploration of cancer cell resistance mechanisms and target actions for reversing resistance and highlights the *in vitro* and *in vivo* efficacy of noteworthy alkaloids, flavonoids, and other compounds, emphasizing their potential as therapeutic agents. The molecular properties supporting ligand interactions are thoroughly examined, providing a robust theoretical foundation. The review concludes by discussing methods including quantitative structure-activity relationships and molecular docking, offering insights into screening potential candidates. Current trends in clinical treatment, contributing to a holistic understanding of the multifaceted approaches to address cancer drug resistance are also outlined.

1. Introduction

Cancer is rising as a global health problem, and in 2020, nearly million new cases and 10.0 million deaths [1,2]. According to the World Health Organization, cancer ranks second among the most common causes of death in the world [3]. Although many novel and promising combinations of therapies for cancer treatment have been developed in the past decades, chemotherapy is still a frontline choice in case surgery and radiation therapy cannot be applied. The cost of chemotherapy is estimated to be about $100,000 annually

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on average for each patient [4]. Several chemotherapeutic drugs such as 5-fluorouracil [5], methotrexate [6], cisplatin [7], and doxorubicin [8] are widely used in clinical practice. Also, many studies have continuously searched for new potential chemical compounds in cancer treatment based on previously popular chemical structures such as platinum-based [9] and pyrazole heterocycle [10]. Noteworthy, a new chemotherapy drugs research and development process requires a lot of time and money, averaging 7.3 years and costing 648.0 million dollars [11].

Parallel to these outstanding achievements and restless efforts, the emergence of cancer drug resistance has become a challenge for contemporary medicine. Since cancer is a heterogeneous disease with the abnormal division of cells and cell growth with very accelerated speed, it makes diagnosis and treatment increasingly difficult. Under the influence of pharmacokinetic factors, some drugs are inhibited by the metabolism of the body's cytochrome P450 enzyme system [12], thereby reducing drug concentrations and creating conditions for developing resistance. In addition, the body itself has a signaling mechanism that activates the creation of detoxifying enzymes [13]. Under normal conditions, these enzymes are responsible for resisting environmental oxidative stress. However, this benefits cancer cells by helping them cope with stress [14]. Therefore, it is necessary to understand the mechanism deeply and seek chemo-sensitizing agents to overcome chemotherapy drug resistance.

Natural compounds are extracted from many sources, the most abundant of which are medicinal herbs [15]. Because of biological diversity, crude extracts from medicinal herbs often contain novel compounds that are chemically and structurally diverse [16]. This diversity includes primary metabolites substances with simple and common structures such as amino acids, carbohydrates, fatty acids, and secondary metabolites substances with complex structures and restricted species distribution [17]. In recent years, medicinal plants have gained attention as the sources of secondary metabolites for screening towards chemotherapy drug resistance treatment *in vitro*, *in vivo,* and *in silico*. Currently, more than 30 % of small molecule drugs approved were natural products and their derivatives [18]. In which, natural compounds account for half of the anti-tumor drugs in chemotherapy including paclitaxel and docetaxel (from the Taxus genus), teniposide and etoposide (from *Podophyllum peltatum*) or vincristine and vinblastine (from *Madagascar periwinkle*)

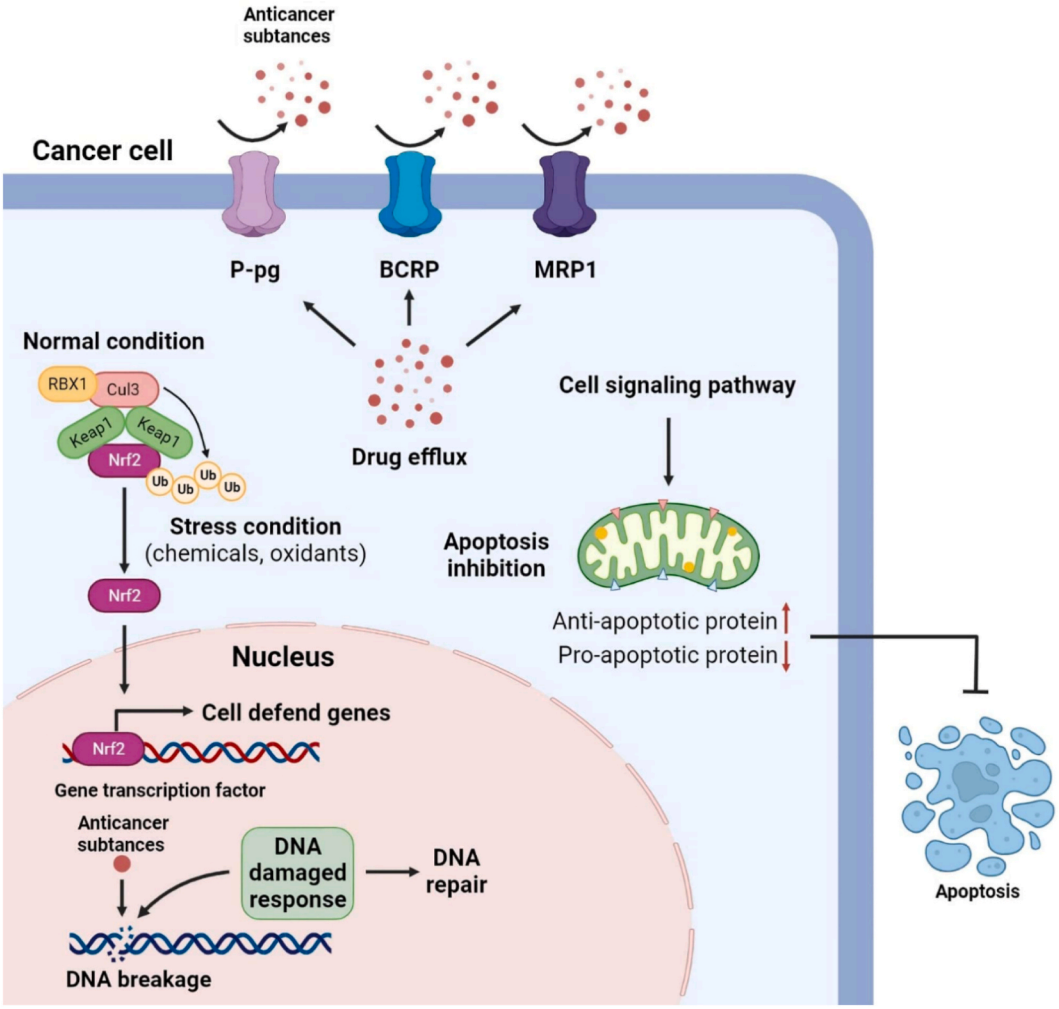


Fig. 1. An overview of cancer drug resistance mechanisms.

[19]. It is apparent that isolated compounds from plants can serve as valuable lead compounds for further modification *in silico*, leading to semi-synthesis of more potent derivatives, expediting the research and development of novel drug processes.

2. An overview of cancer drug resistance mechanism

Cancer drug resistance might be inquired or acquired by different mechanisms, for instance, increasing efflux through ATP binding cassette transporters (ABC transporters), activation of DNA repair pathways, reduced cell susceptibility to apoptosis, or inactivation of cancer drugs by intrinsic and acquired mechanisms [20,21]. Fig. 1 illustrates a brief view of drug resistance mechanisms in cancer cells.

2.1. Drug efflux

The ABC transporter superfamily, including several transmembrane proteins carrying substrates outside the cells, protects cells by eliminating toxins, anticancer drugs, and other endogenous metabolites [22]. The best-known proteins in this family include MDR1 (encoded by the ABCB1 gene), also called P-glycoprotein (P-gp), multidrug resistance-related protein (MRP1, ABCC1), and breast cancer-related protein (BCRP, ABCG2) [23]. The anticancer agents such as daunorubicin, doxorubicin, camptothecin, tamoxifen, teniposide, etoposide, cisplatin, cytarabine, mitoxantrone act as substrates for ABC transporters [24–26] resulted in increasing the drug efflux and a significant decrease in concentrations of active ingredients in cancer cells [27]. ABC transporter's inherent or acquired overexpression is the crucial reason for the drug resistance phenomenon in cancer treatment by barring sufficient drug accumulation, thereby avoiding the cytotoxicity or apoptotic effects [28].

2.2. Cell signaling pathway

Two critical signal transduction pathways in cellular processes are the PI3K (*phosphoinositide 3-kinase*)/AKT(*protein kinase B*) signal transduction pathway and the Ras/Raf/MEK (*mitogen-activated protein kinase*)/ERK (*extracellular-signal-regulated kinase*) pathway or also known as the Ras/Raf/MAPK (*mitogen-activated protein kinase*) pathway [29,30].

These pathways transmit signals from the extracellular environment to the cell nucleus to regulate gene expression for cell growth, division, and differentiation. Fig. 2 demonstrates the cascade of these two signaling pathways. The interactions of cellular signaling pathways can result in regulation of cell cycle progression and apoptosis. It has been established that these signaling pathways play vital roles in tumor formation metastasis, are frequently dysregulated in cancer, and contribute to drug resistance [31,32]. In the PI3/AKT pathway, activation of these cascades promotes cellular survival and proliferation, leading to apoptosis down-regulation

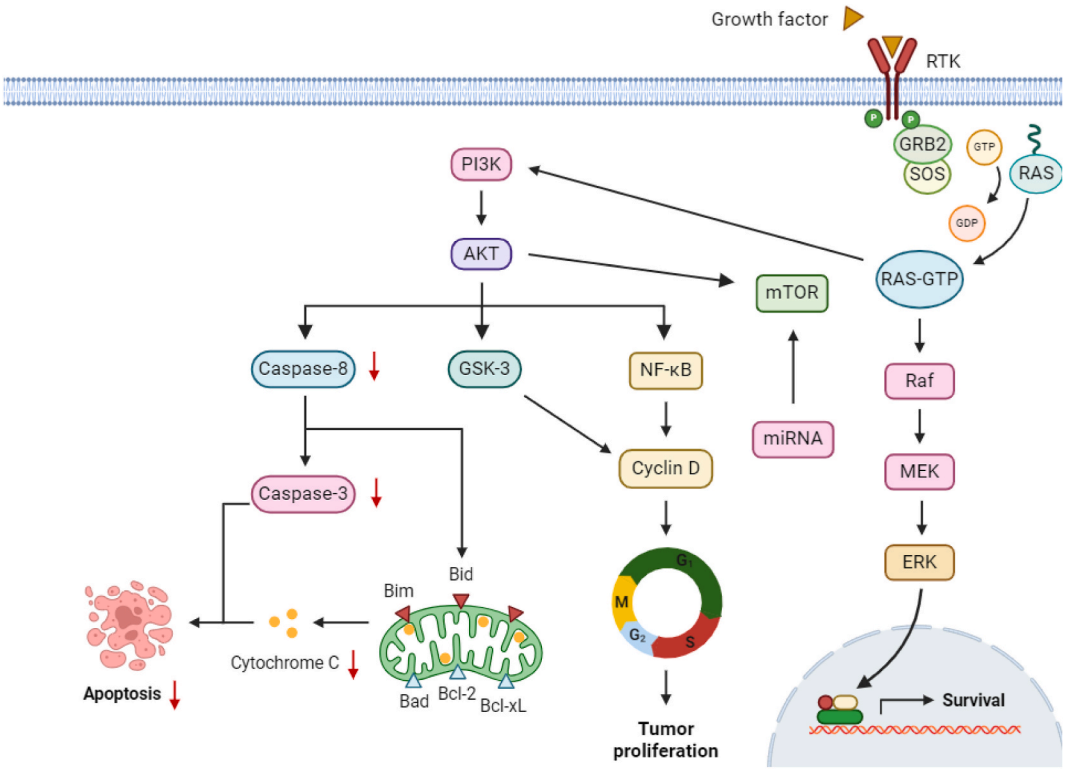


Fig. 2. The signaling cascades in Raf/MEK/ERK and PI3K/AKT Pathways.

[33]. It can also modulate drug resistance by regulating the expression of ABC transporters, inhibiting pro-apoptotic proteins, and activating pro-survival pathways [34]. On the other hand, dysregulation of the MAPK/ERK pathway can lead to overexpression of anti-apoptotic proteins, promoting DNA repair mechanisms, and decreased drug-induced apoptosis [35]. In particular, approximately 40 % of human cancers exhibit alterations in the Ras/Raf/MAPK pathway, around 10 % are caused by mutations in BRAF, and about 30 % by its upstream activator RAS [36].

Nuclear factor erythroid-2 p45-related factor 2 (Nrf2) is a crucial transcription factor that activates promoter sequence genes for cellular stress adaptation or antioxidant response elements [37]. Nrf2 serves as a cellular safeguard, protecting cells from DNA damage caused by reactive oxygen species. Unfortunately, Nrf2 also defends cancer cells against the effects of chemotherapy or radiotherapy under a similar mechanism [38]. Increased levels of Nrf2 expression have also been demonstrated to stimulate the proliferation of cancer cells [39,40]. In hepatocellular carcinoma cells, upregulation of the Nrf2 pathway is associated with increased levels of MMP9 and Bcl-xL, which facilitate cancer invasion and inhibit apoptosis [41]. Additionally, Nrf2 reduces apoptosis by overstimulating the anti-apoptotic protein such as Bcl-2, which contains an ARE sequence in its promoter [42].

2.3. Inhibition of apoptosis

While most of cancer therapies rely on apoptosis activation to damage cancer cells, abnormalities in apoptosis-related proteins contribute to drug resistance [43]. Fig. 3 demonstrated the signaling pathway of apoptotic cell death. Cancer cells evade apoptosis through various means, such as upregulating anti-apoptotic proteins such as Bcl-2, AKT, Mcl-1 and downregulating pro-apoptotic proteins including Bax, Bak, Bad [44]. This phenomenon disrupts mitochondrial apoptosis-induced channel formation, inhibits cytochrome *c* release, and promotes cancer cell survival [45]. Bcl-2 suppresses the activation of apoptotic signals toward their target molecules. Increased levels of Bcl-2 prevent cell death induced by various cytotoxins, thereby enhancing the ability to resist DNA

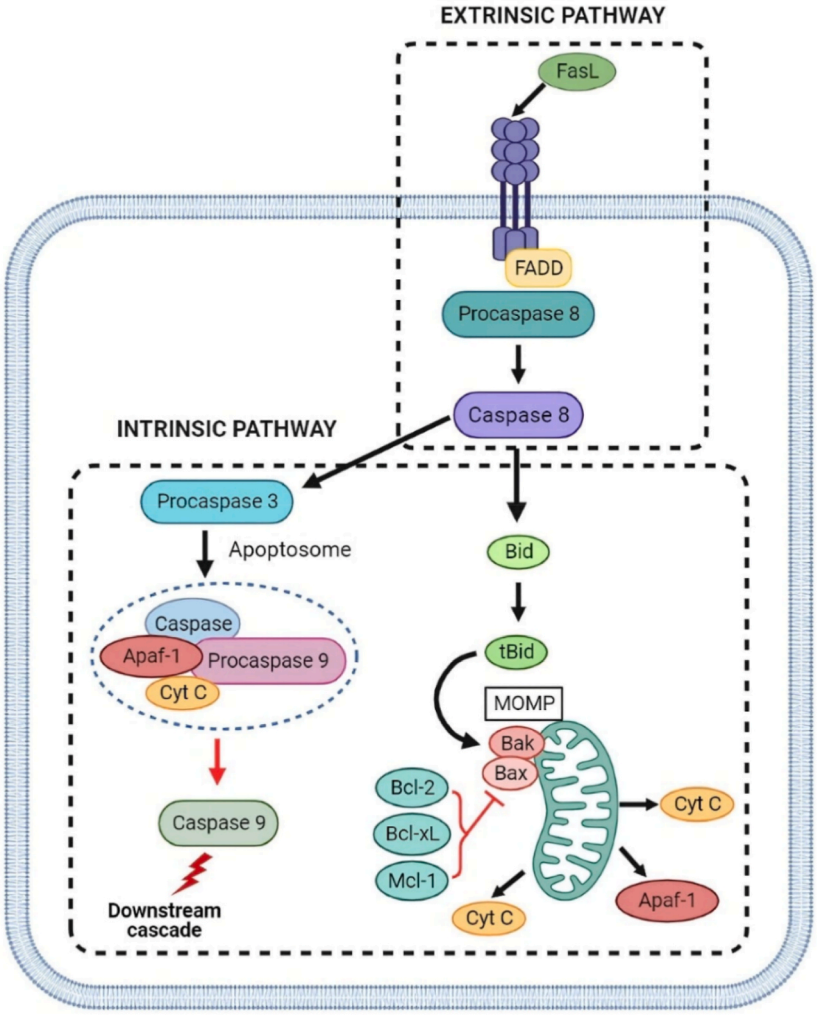


Fig. 3. The signaling pathway of apoptotic cell death.

damage and cancer drug efficiency [46]. Moreover, abnormal expression of inhibitors of apoptosis proteins is associated with increased malignancy. For instance, expression apoptosis proteins including BIRC3, BIRC5, BIRC6, and BIRC7 inhibit the caspase pathway and suppress apoptosis by reducing the catalytic activity of caspases 3, 7, and 9, which play crucial roles in regulating tumor cell death cycles and chemo-sensitivity [47]. Therapeutic strategies targeting apoptosis mechanisms aim to reduce anti-apoptosis protein expression and increase pro-apoptosis protein activity, improving cancer cell sensitivity to apoptosis and combating drug resistance.

2.4. DNA damage repair

Genotoxic stresses during metabolic, physical, or chemical processes contribute to DNA damage and are responsible for genomic instability [48]. Without proper DNA repair, cell survival and integrity are compromised. In cancer cells, the induction of DNA damage response protects against genetic instability and promotes tumor growth [49]. DNA damage response involves signal transduction, cell-cycle checkpoints, DNA repair response, transcriptional regulation, and apoptosis pathway. Current anticancer drugs often have the mechanism of action as DNA breakage or inhibition of DNA synthesis [50]. This triggers DNA damage repairing during the cell cycle in response to chemo-drugs to fix DNA damage, significantly reducing drug efficacy.

2.5. Cancer stem cells in chemo-resistance

Cancer stem cells (CSCs), similar characteristics to normal stem cells, were defined as cancer cells with the ability to self-renewal, which differentiate into various cell types, causing the heterogeneous population of cells in the tumor [51,52]. Different hypotheses have been proposed to explain the origin of CSCs, but so far, has yet to be specifically explained. CSCs are identified by studying various surface biomarkers specific to the tumor type, such as $CD44^{+}$, $CD24^{+}$, CD133+, Aldehyde Dehydrogenase 1 (ALDH1), Epithelial Cell Adhesion Molecule, Musashi-1, Sox2, Oct4, Nanog [53]. However, due to the heterogeneous nature of CSCs, their identification requires specifying multiple biomarkers rather than relying on a single specific biomarker [54]. The population of CSCs is rare, with an incidence of 0.1–2% in tumors of different cancer types [55,56]; however, they are considered a significant cause of progression, metastasis, and drug resistance [57]. Like non-CSCs, CSCs also develop resistance to cancer drugs through efflux pumps, DNA repair, dormancy, increased anti-apoptotic proteins, ROS defense, and interactions with the tumor microenvironment [58–60]. Many studies show that CSCs possess endogenous resistance mechanisms against radiation and chemotherapy much higher than non-CSCs differentiated tumors [55,61,62]. CSCs were also reported to have a superior ability to repair DNA damage compared to non-CSCs [63,64]. Additionally, CSCs are usually quiescent or dormant, thus evading CSCs from therapies targeting rapidly dividing cells [65,66]. The capacity to differentiate into various cell types enables CSCs to generate progeny that can adapt to and resist treatment therapies, significantly enhancing the ability to drug resistance of recurrent cancer cells and metastatic relapse [67,68]. Therefore, tumor progression from CSC exhibits complexity, diversity, and heterogeneity, making it highly challenging to develop effective therapies to target them.

3. Application of active compounds in medicinal plants in overcoming drug resistance

Active compounds from plants such as alkaloids and flavonoids can interact with single or multiple targets which can help enhance the sensitivity of cancer cells to therapies, thereby helping to overcome drug resistance. In addition, the combination of two or more compounds based on different chemical structures can mediate and influence several resistant mechanisms, synergistically reducing dose required, expanding the therapeutic window, and avoiding the adverse effects of high drug concentrations [69].

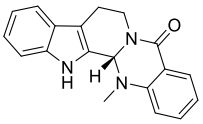
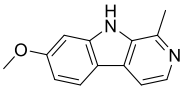
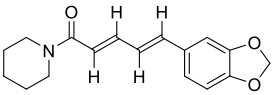
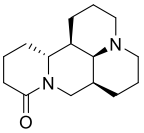
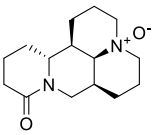
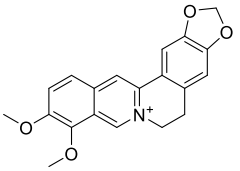
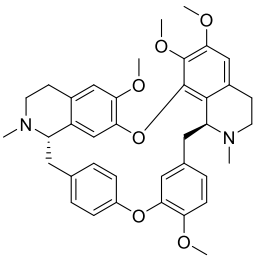
3.1. Alkaloids

Alkaloids have been promising metabolites to prevent chemotherapeutic drug resistance in recent years because nitrogen atoms in alkaloid compounds have been considered necessary in P-gp inhibitors [24,70]. All alkaloids discussed in this section for antidrug resistance reversal activities have been summarized in Table 1.

Evodiamine is an alkaloid extracted from *Evodia rutaecarpa* (Juss.) Benth. (family Rutaceae) has an indole structure [71,72]. According to Guo et al., evodiamine could suppress NF-κB activity in the CAL-27 tongue squamous carcinoma cell line *in vitro* and *in vivo*. Additionally, combining evodiamine with gemcitabine enhanced the chemosensitivity of tongue squamous cancer cells, resulting in an improved treatment response [73]. In studies conducted on oxaliplatin-resistant human colorectal cancer HCT-116 cell line, evodiamine demonstrated its ability to suppress MDR by inhibiting ABCG2 expression at concentrations ranging from 0.4 to 1.6 mM, leading to a remarkable downregulation of NF-κB phosphorylation (p65 and p50) [74]. Moreover, in research on doxorubicin-resistant human breast cancer MCF-7/DOX cells, Wang et al. revealed that evodiamine could reverse the phenomenon of apoptosis resistance by inhibiting both the expression of apoptosis inhibitors and the Ras/MEK/ERK pathway cascade without inhibiting P-gp [75]. These findings highlight the potential of evodiamine in overcoming drug resistance and its significance in cancer treatment.

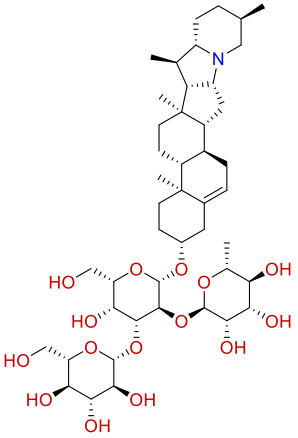
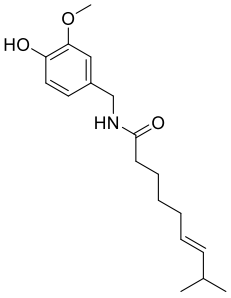
Harmine, an alkaloid isolated from *Banisteriopsis caapi* and *Peganum harmala* L., was discovered as a potential compound to reverse the gene expression profile induced by TRIB2, a protein known to promote resistance to various anti-cancer drugs. By sensitizing cancer cells to chemotherapy agents, harmine offers a potential strategy to enhance the efficacy of chemotherapy and overcome resistance [76]. The synergic activity of harmine and gemcitabine remarkably inhibited the proliferation of pancreatic cancer cells. This effect was achieved through the induction of apoptosis, with harmine enhancing the apoptotic response triggered by gemcitabine

Table 1
Alkaloids compounds from medicinal plants with reversing drug resistance.

No.	Compounds	Medicinal resources	Experimental model	Mechanisms of overcoming MDR	Reference
1	Evodiamine 	*Evodia rutaecarpa* (Rutaceae)	CAL-27 HCT-116/L-OHP cells MCF-7/DOX cells	×NF-κB pt.; ↓Bcl-2, Bcl-xl ↓NF-κB pt. ×Ras/MEK/ERK pt.	[73] [78] [75]
2	Harmine 	*Banisteria caapi* (Malpighiaceae) *Passiflora foetida* L. (Passifloraceae)	U2OS-TRIB2 cells PaCa cells	×PI3K/mTOR pt. ×AKT/mTOR pt.	[79] [80]
3	Piperine 	*Piper nigrum* (Piperaceae)	Caco-2 cells, CEM/DOX 5000 cells, MCF-7/DOX cells, MDCK-MDR1 cells	↓P-gp, MRP1, BCRP	[81–85]
4	Matrine 	*Sophora flavescens* (Leguminosae)	MCF-7/DOX cells UBC cells NCI-H520/PTX25 cells MCF-7/DOX cells	↓PI3K/AKT pt. ↑ apoptosis; ↓fibronectin, vimentin, Bcl-2, caspase-3, p-AKT, p-PI3K; ↓ VEGF/PI3K/Akt pt. ↑sensitivity ↓ P-gp, MRP1, p-AKT, Bcl-2	[86] [87] [88] [89]
5	Oxymatrine 	*Sophora flavescens* (Leguminosae)	K562/A02 cells HCT-8/5-FU cells	↓ P-gp × NF-κB pt.	[90] [91]
6	Berberine 	*Coscinium fenestratum* (Menispermaceae)	A549 cells K562/DOX cells HEK293 cells MCF-7/MDR cells CD44+/CD24- breast CSCs	↓P-gp, MRP ↓BCRP ↓AMPK-HIF-1α-P-gp pt. ↓ABCC1 and ABCG2, ↑apoptosis	[92,93] [94] [95] [96]
7	Tetrandrine 	*Stephania tetrandra* (Menispermaceae)	K562/A02 cells Hep-2 cells SKOV3/PTX cells A2780/PTX cells U2OS cells	↓MRP7 ↓MDR1, RGS10, ↑HTRA1 ×β-catenin/c-Myc/Cyclin D1 pt. ×P-gp, ↑endocytosis × NF-κB pt.	[97] [98] [99] [100] [101]

(*continued on next page*)

Table 1 (*continued*)

No.	Compounds	Medicinal resources	Experimental model	Mechanisms of overcoming MDR	Reference
8	Solanine 	*Solanum dulcamara* (Solanaceae)	K562/DOX cells	↓MRP1	[102]
			Jurkat cells	↓Bcl-2, ↑BaX, ↑apoptosis	[103]
9	Capsaicin 	*Capsicum annuum* (Solanaceae)	Caco-2 cells	↓P-gp	[81]
			CEM/DOX 5000 cells		
			T24-GCB cells	↓ABCC2, DCK, and TKs	[104]
			CCA cells	×5-FU-induced autophagy	[105]

Note: ↓: downregulate, ×: inhibit, ↑: increase, pt.: pathway, ADR: Adriamycin, Bcl-2: B-cell lymphoma-2, BaX: Bcl-2-associated X, CAL-27: tongue squamous carcinoma cell, L-OHP: oxaliplatin, HCT: human ileocecal adenocarcinoma, MCF: human breast cancer, UBC: Urothelial bladder cancer, DOX: Doxorubicin, U2OS: Osteosarcoma, mTOR: mammalian target of rapamycin, TRIB2: Tribbles homologue 2, PaCa: pancreatic cancer, AKT: , Caco-2: Human colorectal adenocarcinoma cells, MDCK: Madin-Darby canine kidney, MDR1: Multi-Drug Resistance 1, P-gp: P-glycoprotein, BCRP: Breast Cancer Resistance Protein, PI3K: Phosphoinositide 3-kinases, NCI- H520: Lung cancer cells, PTX: paclitaxel, HCT: Human colon cancer cell, 5-FU: 5-Fluorouracil, HEK: Human embryonic kidney, A549: human non-small cell lung cancer cells, K562: leukemia cell lines, AMPK: 5′ AMP-activated protein kinase, RGS10: G-protein signaling 10, HTRA1: high-temperature requirement protein A1, SKOV3: Human ovarian cancer cell line, T24-GCB: The gemcitabine resistant UCC cell line, CCA: Cholangiocarcinoma.

in these cells. Specifically, harmine significantly suppressed the AKT/mTOR signaling pathway involved in gemcitabine resistance mechanisms of pancreatic cancer cells [77].

Piperine is a piperidine alkaloid in *Piper nigrum* L. (family Piperaceae) [106]. In a study on Caco-2 and CEM/DOX 5000 cell lines, piperine strongly inhibits their efflux from the MDR cell lines and simultaneously increases the intracellular accumulation of the fluorescent P-gp substrates [81]. In previous research, the expression levels of ABCB1, ABCC1, and ABCG2 genes in tumor cells were lowered when exposed to piperine [82]. Remarkably, the reverse resistance to doxorubicin by 32.16 and 14.14-folds on doxorubicin-resistant MCF-7/DOX have seen at a concentration 50 μM of piperine [82]. Zhou et al. also confirmed that piperine could reverse MDR in MCF-7/DOX cells with a reversal fold of about 25 when treated with 50 μM combined with DOX [85]. Li et al. suggested that piperine powerfully enhanced docetaxel accumulation in MDCK-MDR1 *via* inhibited P-gp and CYP1B1 gene expression [85]. The prevention development of breast cancer cell tamoxifen resistance through probably inhibited P-gp expression was reported [107].

Matrine is an active component of piperidine alkaloid extracted from *Solanum dulcamara* L. (family Solanaceae). Liao et al. confirmed that matrine could downregulate expressions of fibronectin, vimentin, Bcl-2, caspase-3, p-AKT, p-PI3K, vascular endothelial growth factor (VEGF), and VEGF receptor 2 [87]. Luo et al. discovered a reversal of paclitaxel resistance of matrine in the NCI-H520/PTX25 cell line with a reversal rate of about 1.74 [88]. Matrine reduced the expression of P-gp, MRP1, p-AKT, and Bcl-2 proteins *via* modulating the PI3K/AKT signaling pathway by decreasing cell phosphorylation of AKT level [86]. At the 0.2 mg/mL concentration, matrine may increase 3.56 times of the intracellular accumulation concentration of doxorubicin in MCF-7/DOX [86]. Another piperidine alkaloid, oxymatrine is found in *Sophora flavescens* aiton (family Leguminosae), was observed to partly reverse the MDR in the K562/A02 leukemia cell lines by 2.62 times, could decrease the expression of P170 from 90.22 % to 44.24 %, and inhibit

the efflux pumping of anti-cancer drugs out of the cell [90]. Moreover, with the treatment of 50 μg/mL concentration of oxymatrine, the IC_{50} value of doxorubicin in the K562/A02 cell line significantly decreased (from 34.9 ± 0.21 μg/mL to 13.3 ± 0.21 μg/mL) [90]. In the 5-FU-resistant colon HCT-8/5-FU subline cancer cell model of Liang et al. oxymatrine (≥2 mg/mL) exhibited tumor cell inhibition [91]. This observation indicates that oxymatrine effectively reversed the resistance of HCT-8 cells to 5-FU, attributing to the inhibition of the NF-κB signaling pathway and regulating tumor cell epithelial-mesenchymal transition.

Berberine is a well-known isoquinoline alkaloid isolated from numerous families of medicinal plants, particularly Menispermaceae, Rutaceae, Ranunculaceae, and Berberidaceae, with species such as *Coscinium fenestratum*, *Coptis chinensis*, *Mahonia nepalensis*, and *Berberis wallichiana*, and *Phellodendron amurense* [72,108]. Much research has reported berberine as a promising bioactive herbal ingredient to overcome cancer chemo-resistance. For instance, berberine, both 0.5 μg/mL and 4 μg/mL concentrations, significantly increased the retention of Rhodamine 123 dye, an assay to evaluate the MDR, suggesting inhibition of P-gp and/or MRP efflux property in the A549 human non-small cell lung cancer cells due to the prolonged intracellular retention of the chemotherapeutic drugs, particularly 5-FU, camptothecin, and paclitaxel [92]. On doxorubicin-resistant human leukemia cell lines (K562/DOX) research, berberine showed a 1.5-fold reduction in IC_{50} at the nontoxic dose, <1 μM, which exposed the improvement effect on doxorubicin-induced apoptosis. Berberine inhibits the efflux activity of P-gp and increases the intracellular accumulation of DOX in K562/DOX [93]. Moreover, berberine demonstrated significant inhibition of BCRP transport. Remarkably, at 50 μM concentration berberine, the mitoxantrone accumulation on wild-type and ABCG2-overexpressing human embryonic kidney HEK293 cell lines were 164.3 ± 13.0 % and 108.9 ± 0.8 %, respectively; the methotrexate membrane vesicular transport was 28.4 ± 0.6 % compared with control using rapid filtration technique [94]. In addition, Pan et al. investigated the chemosensitivity effect of dosage-based berberine on MCF-7 multi-drug resistance cell line; the results illustrated that low-dose berberine can render drug-resistance breast cancer cells more susceptible to doxorubicin in *via* the AMPK-HIF-1α-P-gp pathway. On the other hand, high-dose berberine directly induces apoptosis through the AMPK-p53 pathway with the independence of hypoxia-inducible factor 1-alpha (HIF-1α) expression *in vitro* and *in vivo* [95]. Additionally, Qian et al. demonstrated that berberine enhanced the intracellular concentration and retention of doxorubicin in tumor cells *via* inhibiting the efflux ABC transporters function and reducing the drug efflux rate in MCF-7/DOX cells *in vitro* [109]. Berberine encapsulated in liposome was studied to directly deliver the compound to mitochondria of CD44+/CD24-breast CSCs, causing the produced dose-dependent apoptosis ranging from 1 to 50 μM [96]. In conclusion, berberine is a promising compound used to prevent cancer drug resistant.

Another isoquinoline alkaloid having the property of reverse MDR *in vitro* and modulated P-gp mediated drug efflux is tetrandrine. Tetrandrine could inhibit MRP7 overexpression in leukemic cell line K562/A02 multidrug resistance cells and increase anticancer drug concentration in the cells [97]. To clarify, the results of Cheng et al. showed that after administration of 1 μmol/L tetrandrine, the mRNA level of MRP7 in K562/A02 cells decreased to 2 %. The protein level of MRP7 decreased by 53.2, the protein level of P-gp decreased by 58.47 %, and the accumulation of daunorubicin significantly increased by 94.32 % [97]. Additionally, Li et al. confirmed that tetrandrine could reverse 2.22 times the MDR of human laryngeal cancer (Hep-2) cells by significantly lowering the IC_{50} value of vincristine in Hep-2 variant cells, downregulating the mRNA and protein expression of MDR1 and RGS10, and upregulating expression of HTRA1 in Hep-2 variant cells [98]. Jiang et al. found that tetrandrine could reduce paclitaxel-resistant SKOV3 cells (SKOV3/PTX) by inhibiting the β-catenin/c-Myc/Cyclin D1 signaling pathway [99]. Thus, the synergistic effects targeting P-gp inhibition, enhanced endocytosis, and intracellular sequential drug release have been proved as a potential treatment for chemo-resistant cancer [110]. The combination of paclitaxel and tetrandrine exhibits the highest cytotoxicity against A2780/PTX cells [100]. Therefore, the synergistic effects targeting P-gp inhibition, enhanced endocytosis, and intracellular sequential drug release have been proved as a potential treatment for chemo-resistant cancer [100]. Tetrandrine was suggested to prevent multidrug resistance by inhibiting P-gp overexpression *via* NF-κB signaling in osteosarcoma cell lines [101]. Among Vietnamese traditional medical plants, tetrandrine could be found on *Stephania tetrandra* S. Moore (family Menispermaceae).

Solanine is a steroidal alkaloid, a primary chemical constituent of *Solanum dulcamara* L. (family Solanaceae). Yi et al. reported that solanine inhibited doxorubicin-resistant human myelogenous leukemia cell line K562, sensitized K562 cells with doxorubicin, and increased intracellular doxorubicin accumulation [102]. This could result from the downregulation of MRP1 expression *via* the JNK signaling pathway [102]. Furthermore, solanine significantly increased the chemosensitivity to doxorubicin on the Jurkat cells by modulating the mRNA levels of Bcl-2 and Bcl-2-associated X protein (Bax) revealed by Western blot analysis [103].

Capsaicin is a primary alkaloid from *Capsicum annuum* L. (family Solanaceae), a common spice pepper. Capsaicin significantly blocked the efflux of fluorescent P-gp substrates from MDR cell lines and enhanced their intracellular accumulation [81]. Capsaicin decreased ABCC2, DCK, and TKs expression in gemcitabine resistance bladder cancer cells by increasing intracellular retention of gemcitabine [104]. Moreover, Hong et al. demonstrated that capsaicin inhibits 5-FU-induced autophagy by enhancing 5-FU-induced sensitivity to cholangiocarcinoma cells [105].

Several distinctive structural features of alkaloids have a decisive role in anticancer drug resistance, including regulating P-gp inhibitory activity [24]. The heterocycle containing the basic nitrogen atom, preferred along with the carbonyl group, can form conventional hydrogen bonds with an amino group derived from the protein backbone of a potential target for cancer treatment. These protein-ligand interactions can be observed in evodiamine and harmine, as the indole nitrogen is particularly adept at interacting with multiple cancer targets, including ERK-1 pocket intermediate [111], DNA topoisomerase I [112], and mammalian DNA methyltransferases 3B [113]. Despite their low specificity and high toxicity, unique chemical scaffolds of certain alkaloids have the potential for further modification to inhibit cell signaling and apoptosis pathways. These included matrine derivatives with modifications in L-shaped conformation for Hsp90 inhibition [114], D-ring substitution for PI3K/AKT pathway inhibition [115], or solanine with modifications in cholestane structure for the K562 cell line or sugar moiety alteration for cytotoxicity [116]. The benzodioxol-like structure – which consists of two neighboring oxygen atoms forming hydrogen bond acceptor pharmacophores for P-gp inhibition

[117] – can be found in piperine, berberine, tetrandrine, and capsaicin, which all have been previously demonstrated to be effective in P-gp inhibitory action for chemotherapeutic accumulation [118–120]. Table 1 depicts the structures of certain alkaloids known for their capability to inhibit cancer drugs resistance. The structure can also be recognized within some natural flavonoids in the following section.

3.2. Flavonoids

Flavonoids are a diverse class of natural polyphenolic compounds found abundantly in plants, with over 8000 identified and reported compounds. Flavonoids possess a flavan nucleus structure and can be classified into seven subclasses: flavonols, flavones, isoflavones, anthocyanidins, flavanones, flavanols, and chalcones (Fig. 4) [121]. Flavonoid metabolites exhibited several bioactive properties, such as antioxidant [122], antibacterial [123], antimicrobial [124], anti-inflammation [125], anti-diabetic [126], anti-aging [127], cardiovascular protective effects [128], and anti-cancer [129]. The most prominent among these benefits is their ability to re-sensitize conventional chemotherapeutics to resistant cancer cells and reverse drug resistance *via* different pathways [130–132]. Table 2 summarizes all the flavonoids discussed in this review for anti-chemotherapy drug resistance ability.

Quercetin exhibits promising potential in overcoming cancer drug resistance by targeting resistance factors, enhancing drug accumulation within cancer cells [133], and significantly reducing drug efflux [134]. Particularly, quercetin has been found to inhibit the nuclear translocation of YB-1, resulting in reduced P-gp expression in doxorubicin-resistant MCF-7 cancer cells [135]. In the research of Borska et al., quercetin synergistically increased the cytotoxicity and inhibited the growth of the parental and P-gp expressing cells along with downregulation of the ABCB1 gene [136]. Furthermore, quercetin has been shown to downregulate the expression of pro-caspase-3, Mcl-1, Bcl-2, and Bcl-XL, thereby inhibiting the growth, migration, and invasion of human prostate cancer cells through the VEGF/AKT/PI3K pathway [137]. Quercetin with a concentration of 75 μM inhibited the proliferation of CD133+ colon CSCs and significantly enhanced the CSCs' sensitivity to doxorubicin, as reported by Atashpour et al. [138]. The ability to enhance apoptosis of quercetin were also reported in CD44+/CD24-breast CSCs [139] and CD44+/CD133+ prostate CSCs [140]. Another dietary flavonol, fisetin, was reported that the combination therapy of fisetin and sorafenib against HeLa cells effectively interfered with the apoptosis signaling pathways *in vitro* and *in vivo* [141]. Research by Pal et al. also reported that sorafenib enhanced the apoptosis activity mediated by fisetin in BRAF-mutated melanoma cells by activating mitochondrial-dependent caspase-3 apoptotic signaling by suppressing MAPK, PI3K, and VEGF expression [142].

Within the flavone subclass, apigenin, known for its natural sedative properties, has demonstrated the ability to inhibit several oncogenic factors, including epidermal growth factor receptor (EGFR), hypoxia-inducible factor 1 (HIF-1), and glucose transporter protein type 1 (Glut1). Together with gefitinib, apigenin effectively decreases Bcl-2 expression, increases Bax expression, and inactivates AMPK signaling in EGFR L858R-T790M-mutated H1975 lung cancer cells [143]. Erdogan et al. reported that the combination therapy of 15 μM apigenin and 7.5 μM cisplatin for 48 h led to the up-regulation and down-regulation of mRNA expressions of caspase-8, apoptotic protease activating factor-1 (Apaf-1), and p53 in the anti-apoptotic Bcl-2 in $CD44^{+}$ prostate cancer stem cells [144]. Furthermore, co-treatment with cisplatin and apigenin resulted in the dephosphorylation of PI3K and AKT and the inhibition of NF-κB expression. Li et al. demonstrated that after the addition of apigenin, the tumor suppressor p53 was activated, which repressed the CDDP-induced growth in CSCs. Therefore, apigenin can enhance anti-tumor effect of cisplatin in non-small cell lung cancer [145]. According to a study by Tang et al., luteolin flavone was discovered that luteolin acts as a potent small-molecule inhibitor of Nrf2. It effectively reduced Nrf2 mRNA levels by 34 % when co-treated with actinomycin D for 30 min and 43 % at 1.5 h in human lung carcinoma A549 cells [146]. Luteolin also increased apoptosis, activated ATR/Chk2/p53 signaling pathways, and inhibited the NF-κB signaling pathway in breast cancer mitoxantrone-resistant cells, reported by Rao et al. [147]. A study by Hong et al. showed that luteolin increased apoptosis and downregulated EGFR, the PI3K/AKT/mTOR signaling pathway; hence, erlotinib-resistant tumor cells were more sensitized to erlotinib [148]. Additionally, mice treated with luteolin and cisplatin exhibited a reduction in tumor mass. In combination with molecular docking, Mediratta et al. have identified that luteolin is highly complementarity with CD73, one of the novel immunotherapeutic targets that is excessively expressed on tumors. In addition, luteolin, quercetin, and paclitaxel in a

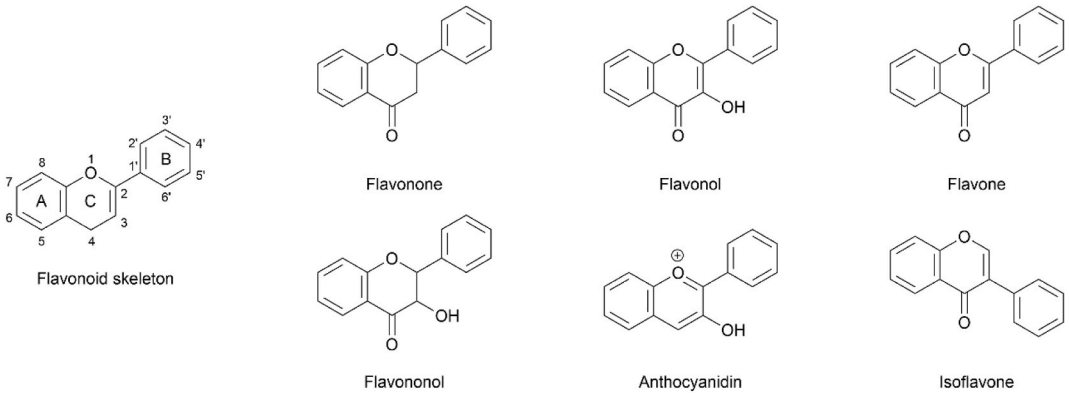
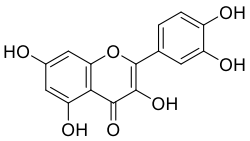
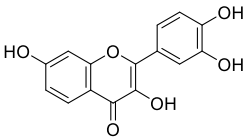
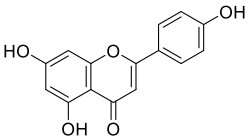
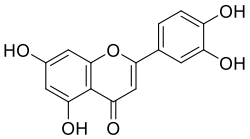
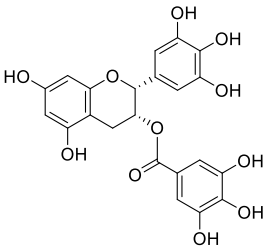
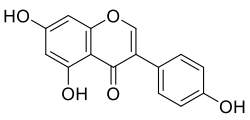


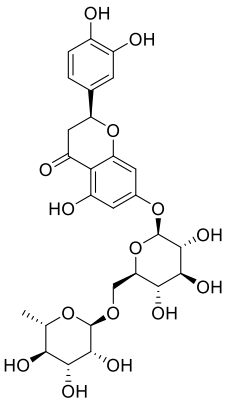
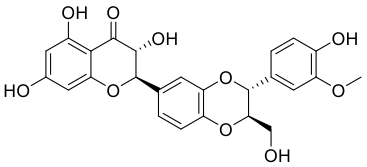
Fig. 4. The structures of seven subclasses of flavonoids.

Table 2
Flavonoids compounds from medicinal plants with reversing drug resistance.

No.	Compounds	Medicinal resources	Experimental model	Mechanisms of overcoming MDR	Reference
1	Quercetin 	*Allium cepa* L. (Alliaceae)	MCF-7/DOX	↑sensitivity, ↓P-gp	[135]
			EPG85-257P; EPG85-257RDB	↓P-gp, ×growth factors, ↓ABCB1	[136]
			PC-3 and LNCaP;	×growth; ×VEGF/AKT/PI3K pt.	[137]
			BALB/c nude male mice injected with PC-3 cells	↓pro-caspase-3, Mcl-1, Bcl-2, Bcl-xl expression.	[137]
			CD133+ colon CSCs	×proliferation, ↑apoptosis	[138]
			CD44+/CD24- breast CSCs	×proliferation, ↑apoptosis	[139]
			PC3 and CD44+/CD133+ prostate stem cell	×proliferation, ×migration, G1 cell cycle arrest ↓PI3K/PTEN, MAPK and NF-κB	[140]
2	Fisetin 	*Panax notoginseng* (Araliaceae)	HeLa cells	↑apoptosis	[141]
			In vivo athymic nude mice subcutaneously implanted with A375 and SK-MEL-28 cells	↑mitochondrial-dependent caspase-3 apoptotic signaling; ↓MAPK, PI3K, VEGF expression	[142]
3	Apigenin 	*Chrysanthemum indicum* (Asteraceae)	H1975	↓metabolism, ↑apoptosis, ↓EGFR, ↓HIF-1, ↓Glut1, ↓ Bcl-2, ↓Bax expression, ×5′ AMPK pt.	[143]
		Lonicera japonica (Caprifoliaceae)	PC-3; $CD44^{+}$ prostate CSCs	↑caspase 8, ↑Apaf-1, ↑p53 expression; ↓Bcl-2, ↓NF-κB	[144]
			A549 and H1299	↑ p53	[145]
4	Luteolin 	Asteraceae, Lamiaceae, Poaceae, Leguminosae, and Scrophulariaceae species	A549	↓Nrf2	[146]
			MCF-7/MitoR cell	↑apoptosis, ↑ATR/Chk2/p53, ↓NF-κB	[147]
			NSCLC	↓ EGFR, ↓PI3K/AKT/mTOR pt.,↑apoptosis	[148]
			MDA-MB-231 breast CSCs	↓Nrf2, HO-1, Sirt3, and Cripto-1	[149]
			MDA-MB-231 breast CSCs	↓ YAP and Wnt target genes	[150]
5	EGCG 	*Camellia sinensis*	HCT-116; DLD1	GRP78/NF-κB/miR-155-5p/MDR1 pt., ×5-FU efflux	[151]
			A549/H460/cisplatin cells	↓AXL receptor tyrosine kinase, ↓ ALDH1A1; ↓SLUG	[152]
			Rat model of breast carcinogenesis	↑sensitivity PTX, ↑ phosphorylated JNK, ↑apoptosis, ↑GRP78 expression	[153]
			Rat model of breast carcinogenesis	↑apoptosis, ↓VEGF expression, ↓MMP-2	[154]
			CD44+/CD133+ prostate CSCs	↑capase-3/7, ×Bcl-2, survivin and XIAP	[155]
6	Genistein 	Glycine max	HeLa and CaSki cells	↓p-ERK1/2; ↑p53 expression; ↑caspase-3	[156]
			Mice treated with diethylnitrosamine to induce HCC at 2 weeks of age	↓phospho-AMPK; ↑phospho-AMPK promoted apoptosis	[157]
			Hepa1-6	↑apoptosis	[158]
			HT-29	↓perilipin-1, ADRP and Tip-47 family proteins expression; ↑apoptosis	[159]
			HepG2	↑apoptosis	[160]
			HT-29	↑caspase-3; ↑p38 MAPK; ↑apoptosis	[161]

(*continued on next page*)

Table 2 (*continued*)

No.	Compounds	Medicinal resources	Experimental model	Mechanisms of overcoming MDR	Reference
7	Hesperidin 	Citrus sp. (Rutaceae)	Gall bladder carcinoma cells	↓proliferation, ↑ROS, ↑caspase-3	[162]
			A549 cells	↓SDF-1/CXCR-4 pt.	[163]
			A549 and NCI-H358	↑caspase-3; ↑apoptosis; FGF and NF-κB	[164]
			A2780	↑apoptosis; ↑caspase-3 expression; anti-growth arrest-and DNA damage-inducible gene 153, anti-CCAAT' enhancer-binding protein homologous protein, glucose-regulated protein 78, cytochrome *c*	[165]
			Eca109	×proliferation, ↓PI3K/AKT pt.	[166]
			SGC-7901, MGC-803, and HGC-27	↑ROS; ↑mitochondrial pathway	[167]
8	Silibinin 	*Silybum marianum* (Asteraceae)	A2780/DOX	↓ABC transporters expression	[168]
			A2780/cisplatin-resistant	↓proliferation; ↑apoptosis	[169]
			T47D cells	↓proliferation	[170]
			MDA-MB-435/DOX	↑growth effects, ↑apoptosis	[171]

Note: ↓: downregulate; ×: inhibit; ↑: increase; pt.: pathway; MCF-7: human breast cancer; DOX: Doxorubicin; P-gp: P-glycoprotein; PC-3: Human prostate cancer cells 3; LNCaP: Lymph Node Carcinoma of the Prostate cell line; VEGF: vascular endothelial growth factor; PI3K: Phosphoinositide 3-kinases; EPG85-257P: Gastric adenocarcinoma cell line; EPG85-257RDB: Gastric adenocarcinoma cell line; HeLa: Human papillomavirus-related cervical adenocarcinoma cell line; A375: Amelanotic melanoma cell line; SK-MEL-28: Cutaneous melanoma cell line; MAPK: mitogen-activated protein kinase; H1975: lung adenocarcinoma cell line; EGFR: epidermal growth factor receptor; HIF-1: hypoxia-inducible factor 1; Glut1: glucose transporter protein type 1; AMPK: 5′ AMP-activated protein kinase; Apaf-1: apoptotic protease activating factor-1; NSCLC: non-small cell lung cancer cell line; AKT: protein kinase B; mTOR: mammalian target of rapamycin; A549: human alveolar epithelial cell line; HCT-116: human colon carcinoma cell line; DLD1: human colon carcinoma cell line; HCC: hepatocellular carcinoma; HT-29: human colorectal adenocarcinoma cell line; HepG2: hepatoblastoma cell line; A2780: human ovarian adenocarcinoma cell line; Eca109: human esophageal carcinoma cell line; NCI-H358: human non-small cell lung cancer cell line; SGC-7901, MGC-803, HGC-27: human gastric cancer cells lines; ROS: reactive oxygen species; DOX: doxorubicin; T47D: human breast cancer cell line; MDA-MB-435.

triplet-drug regimen efficiently reduced the proliferation of human breast cancer cell lines and inhibited paclitaxel-enriched CSCs by reducing the transcriptional activity of YAP and Wnt. Thus, medications that target CD73, as well as CSCs, have the potential to overcome treatment resistance and increase the efficacy of chemotherapy [150].

Green tea epigallocatechin-3-gallate (EGCG) is a polyphenol known for its potent antioxidant and chemo-preventive activities, exhibiting protective effects against experimentally induced cancer [172]. According to Zhang et al., EGCG enhanced the chemotherapeutic activity of doxorubicin, cisplatin, and tamoxifen *via* inhibiting the multiple drug transporters, down-regulating AKT and mTOR signaling pathways and acting as a receptor tyrosine kinases inhibitor [173]. The co-treated therapy of 50 μM of EGCG and 5-FU significantly decreased the IC_{50} values in human colon carcinoma cell line HCT-116 and human colon carcinoma cell line-DLD1, from 40 ± 4.2 μM to 5 ± 0.36 μM and 150 ± 6.4 μM to 11 ± 0.96 μM, respectively [151]. The interaction of EGCG with the GRP78/NF-κB/miR-155-5p/MDR1 pathway blocked the efflux of 5-FU, enhancing its intracellular accumulation. Kim et al. investigated the effect of EGCG on A549/H460 cisplatin-resistant cells with the treatment of 80 μM EGCG and cisplatin over 24 h [152]. The results demonstrated that EGCG inhibited AXL receptor tyrosine kinase and reduced ALDH1A1 and SLUG in tumors. In the *in vivo* model, the co-administration of EGCG and paclitaxel resulted in higher levels of phosphorylated JNK, increased apoptosis, and induced GRP78 expression [153]. In a rat model of breast carcinogenesis, the application of EGCG and paclitaxel at the same time showed increased apoptosis and decreased VEGF expression and MMP-2 activity [154]. EGCG was reported to induce apoptosis in CD44+/CD133+ prostate CSCs by activating caspase-3/7 and inhibiting the expression of Bcl-2, survivin, and XIAP while also suppressing the self-renewal capacity of CD44+α2β1+CD133+ CSCs isolated from human primary prostate tumors [155].

Genistein, an isoflavone, has been the subject of numerous studies investigating its effects on various types of human cancer. Research by Liu et al. suggested that combining genistein and cisplatin increased chemotherapeutic effects and dramatically decreased p-ERK1/2, p52, and Bcl2 expression in HeLa and CaSki cells, compared with cisplatin control group [156]. Furthermore, genistein has been reported to induce apoptosis in hepatocellular carcinoma (HCC) cancer cells through energy-dependent caspase pathways [157].

Sanaei et al. found that genistein induced apoptosis in the Hepal-6 HCC cell line during a 24-h treatment, with an IC_{50} = 20 μM and a maximum inhibition of cell growth of 52 % [158]. Genistein also affected activated apoptosis in HepG2 HCC cells with a dose of 20 μM [160]. Combining genistein and daidzein was found to downregulate the expression of Perilipin-1, ADRP, and Tip-47 family proteins, and vimentin levels cause final apoptosis of human colorectal adenocarcinoma cell line HT-29 [159]. After treatment with genistein, the apoptosis in HT-29 cells was also reported with a different mechanism by regulating caspase-3 and p38 MAPK signaling pathways [161].

Hesperidin is a flavanone isolated in various citrus fruits, has been reported for several health properties, including antioxidant activity, anti-inflammatory, cardiovascular properties, and anticancer [174]. A study on the human gall bladder carcinoma (GBC) cells showed that hesperidin exposure for 24h with a dose of 200 μM significantly decreased the cell proliferation [162]. Furthermore, hesperidin induced reactive oxygen species (ROS) generation, nuclear condensation, activated caspase-3, and caused cell cycle arrest at the G2/M phase in the treated GBC cells [162]. Hesperidin demonstrated the ability to inhibit migration and invasion of non-small cell lung cancer A549 cells by suppressing the SDF-1/CXCR-4 pathway and modulating MMP-9, CK-19, and vimentin expression [163]. The FGF and NF-κB signal transduction pathways could be affected by hesperidin, with the upregulation of caspase-3 resulting in apoptosis in A549 and NCI-H358 cells [164]. Hesperidin was reported to increase the expression of anti-growth arrest- and DNA damage-inducible gene 153 (GADD153) and anti-CCAAT' enhancer-binding protein homologous protein in A2780, together with the cytotoxicity of hesperidin lead it to reduce cells' viability [165]. Moreover, hesperidin has shown the ability to inhibit proliferation and induce apoptosis by increasing ROS production in the mitochondrial pathway in gastric and esophageal cancer cells [166,167,175].

Silibinin, a major flavonolignan isolated from *Silybum marianum* (L.) cypselae, has long been recognized as a natural medicinal plant for liver disorder treatment [176]. Recent studies have shed light on its potential role as a modulator of drug resistance in cancer. Dobiasová et al., 2020 reported that silibinin inhibited P-gp ATPase activity and regulated the expression of ABC protein in the multidrug-resistant ovarian sub-line resistant to doxorubicin (A2780/DOX) cells [168]. The *in vitro* experiments revealed that silibinin could restore the sensitivity of A2780-resistant cells to cisplatin and taxol, resulting in suppressed cell proliferation and induction of apoptosis [169]. Another study by Maasomi et al., 2017 showed that silibinin could impede the proliferation of breast cancer T47D cells [170]. Compared with the drug alone, the combination of chrysin and silibinin resulted in the down-regulated mRNA levels of hTERT and cyclin D1 after 48h treatment. Molavi et al. reported that silibinin exerted significant growth inhibitory effects on chemo-resistant human breast cell lines to doxorubicin and paclitaxel with IC_{50} ranged from 200 to 570 μM [171]. While dietary flavones such as apigenin and luteolin show apoptosis-inducing effects in human colon carcinoma cells [177], green tea catechin, including EGCG, is proven to be highly potent in prostate cancer cells [178]. SAR studies reveal that isoflavones like genistein and glycosylated derivatives are less active than flavones [179].

Different structural requisites, along with specific substitution patterns, can modify the action mechanism and significantly impact the activity. Table 2 demonstrates the structural composition of remarkable flavonoids with the capacity to prevent or reverse resistance to the chemotherapy drug. The carbonylation at C4 and the hydroxyl group at C5 are vital for the capacity to imitate the adenine moiety of ATP, resulting in P-gp inhibition except for fisetin [180]. Substitution in these 5,7-OH flavone derivatives by increasing the hydrophobicity also correlated to the decrease of daunomycin efflux activity from leukemia cell line K562/R7, with the maximum effect of the isoprenylated derivatives even higher than that of cyclosporin A – a potent modulator offered [180]. Research has observed hydroxylation at C3 in flavone decreases activity for the NorA MDR pump in *Staphylococcus aureus* [181]. Thus, methylation of that hydroxyl group shows a higher inhibitory effect in BCRP [182]. The lack of a double bond between positions 2 and 3 in hesperidin and silibinin might not directly affect multidrug resistance and apoptosis induction; however, it serves an essential role in other therapeutic-related mechanisms, including differentiation induction [183], topoisomerase inhibition [184], and protein kinase inhibition [185].

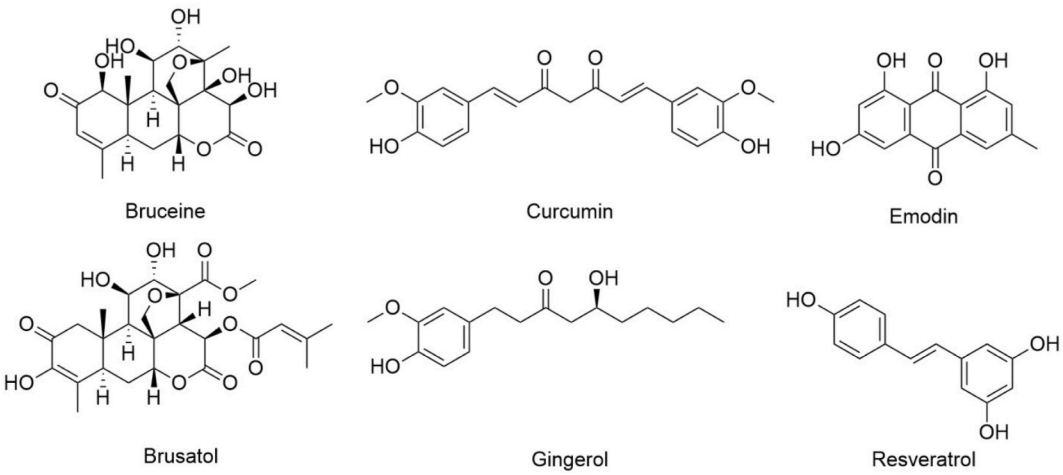


Fig. 5. The structures of other compounds are reported to have the potential to prevent/reverse cancer drug resistance.

3.3. Other compounds

Other natural compounds with different structures have been reported with remarkable therapeutic potential outcomes. The significance of natural compounds in anticancer treatment extends beyond molecular structure diversity (Fig. 5).

3.3.1. Brucein

Brucein is a phytochemical derived from the seeds of *Brucea javanica* (family Simaroubaceae) [186]. Studies have indicated that brucein can regulate signaling pathways linked to drug resistance through the MAPK signaling cascade [187,188]. In particular, brucein can enhance the phosphorylation of the p38 protein in the MAPK pathway, inducing apoptotic signals in pancreatic cancer cells [189]. Additionally, brucein has been reported that the induction of apoptosis and autophagy is achieved through the upregulation of Bax expression, downregulation of cytochrome C and Bcl-2 expression, and inhibition of MAPK signaling via the activation of the ROS-dependent pathway [190]. In a dose-dependent manner from 1 μM to 4 μM of brucein, it was also found that brucein significantly took part in the regulation of protein expression in the PI3K/AKT pathway, reduced cell viability, and inhibited cancer cell invasion and migration [191].

3.3.2. Brusatol

Another compound derived from the *Brucea javanica* is brusatol. This compound showed anticancer activity by inducing cell death via modulating various cell signaling pathways, promoting ROS production, and elevating DNA damage [192–194]. However, the markable potential of brusatol in overcoming drug resistance is the inhibitory of Nrf2 activation in cancer cells [195]. The study published by Ren et al. indicated that brusatol suppresses the Nrf2-mediated defense mechanism in lung cancer cells [196]. Later, much research also reported its ability to regress Nrf2 activity in cells, which induced other signaling pathways and exerted the growth-inhibitory effects or apoptosis [197,198]. The synergistic effect of brusatol with anticancer drugs showed desirable results. Compared to treatment alone with either brusatol or gemcitabine, brusatol has been discovered to enhance the effectiveness of gemcitabine by inhibiting cell growth and inducing apoptosis in human pancreatic cancer cells than others through the suppression of the Nrf2 pathway when combining 1 μM brusatol and 20 μM gemcitabine for 48 h in treatment [197]. Another study by Yang et al. provided a new insight into brusatol synergistically enhancing the anticancer efficacy of trastuzumab against HER2 cells by inhibiting the Nrf2/HO-1 and HER2-AKT/ERK1/2 signaling pathways [199]. Besides the potential of brusatol as a promising sensitizing agent for cancer treatment, the toxicity of brusatol is a big challenge for clinical research. Brusatol has been indicated with high toxicity at a lethal dose of 16.2 mg/kg in an acute toxicity assay [200]. It was also found that brusatol nonspecifically inhibits Nrf2 in human hepatocytes and decreases cell viability in healthy human colonic cells [201,202]. Thus, there is considerable importance in exploring new derivatives of brusatol with enhanced efficacy and reduced toxicity through structural modifications for potential clinical applications [203].

3.3.3. Curcumin

Curcumin from *Curcuma longa* (family Zingiberaceae) is a polyphenolic compound with various pharmacological properties notably antioxidant, anti-inflammatory, antimicrobial, antitumor, and hepatoprotective activities [204–207]. Soni et al. demonstrated that curcumin could inhibit the survival of HepG2 and HuT78 cells and modulate the susceptibility of HCC to chemotherapy. Curcumin inhibited a wide range of genes (monocarboxylate transporter 1, signal transducer and activator of transcription 3 and MDR1) and protein (hypoxia-inducible factor 1-alpha and hydroxycarboxylic acid receptor 1) that involved chemotherapy resistance [208]. In addition, curcumin exerts chemo-preventive properties by targeting the cisplatin chemoresistance factors such as Nrf-2, NF-κB, and the phosphorylation of STAT-3 [209]. Curcumin also showed a remarkable potential for enhanced effects of gefitinib on gefitinib-resistant NSCLC cell lines H157 and H1299. The combination of curcumin and gefitinib markedly decreased EGFR activity by inhibiting Sp1, tyrosine kinase receptors, ERK/MEK pathway, and AKT/S6K pathway [210]. In clinical trials, the intention-to-treat analysis showed that the objective response rate of a combination of curcumin with paclitaxel was superior to that of a paclitaxel-placebo combination (51 % *vs.* 33 %, $p < 0.01$) [211].

3.3.4. Emodin

Emodin (1, 3, 8-trihydroxy-6-methylanthraquinone) is a derived anthraquinone compound extracted from roots and barks of herbal including *Polygonum cuspidatum* (family Polygonaceae), *Aloe vera* (family Acanthaceae) [212,213]. According to Guo et al., combining gemcitabine and emodin reduced xenograft volume and tumor growth in mice compared to treatment with gemcitabine or emodin monotherapy. Emodin decreased expression of P-gp, MRP1, and MRP5 led to reduced resistance to gemcitabine in the combination therapy group [214]. Additionally, emodin can be used as an inhibitor of the PI3K/AKT signaling pathway because of the increasing inhibitory effect of 5-FU at 12 μg/mL 5-FU plus 9 μM emodin therapy [215]. The proliferation of A549 cells could be promoted by emodin 1 μM and could be significantly inhibited by emodin >5 μM, so increase the sensitivity of cancer cells to cisplatin by inhibiting P-gp expression [216].

3.3.5. Gingerol

Gingerols are prominent phenolic compounds found in ginger *Zingiber officinale* (family Zingiberaceae) and other plants in the Zingiber genus, including 6-gingerol, 8-gingerol, 10-gingerol, 12-gingerol, 6-shogaol, 8-shogaol [217]. Gingerol has been found to regulate various signaling pathways in cancer cells, including Signal Transducer and Activator of Transcription 3, β-catenin, EGFR, VEGFR, MAPK, and pro-inflammatory mediators (TNF-α and COX-2). The efficacy of gingerol in *in vitro*, *in vivo* studies, and clinical

trials has also been reported. According to Lou et al., the combination of 6-gingerol with cisplatin decreased cyclin D1, cyclin A2, matrix metalloproteinase-9, p-PI3K, AKT, and p-AKT protein expressions and increased P21 and P27 mRNA levels. 6-gingerol enhances the cisplatin sensitivity of gastric cancer cells, and mechanisms involve G1 phase arrest, migration, and invasion suppression *via* PI3K/AKT signaling pathway [218]. Liu et al. reported that the bioactive isolated compounds, including 6-gingerol, 10-gingerol, 6-shogaol, and 10-shogaol at the concentration of 100 μM, significantly inhibited docetaxel-resistant human prostate cancer cells growth and reverse drug resistance protein expression including MRP1 and GSTπ expression [219].

3.3.6. Resveratrol

Resveratrol (3,4′,5-trihydroxystilbene) is a stilbene compound having various pharmacological potentials such as antioxidant, antimicrobial, antifungal, anti-inflammatory, and anticancer [220–223]. Li Wang et al. demonstrated that resveratrol enhanced the antiproliferative activity of bestatin by downregulating P-gp expression via suppressing the PI3K/AKT/mTOR signaling pathway. The IC_{50} value of bestatin in K562/doxorubicin cells was significantly reduced, and the activation of caspase3 and caspase8 increased, indicating that resveratrol enhanced bestatin-induced apoptosis [40]. Resveratrol decreased the expression of phosphorylated Akt-mediated and NF-κB, which is also substantiated by the downregulation of anti-apoptotic factors Bcl-2 and Bcl-XL in non-small cell lung adenocarcinoma [224]. The study by Shankar et al. reported that resveratrol with a concentration of 10–30 μM caused apoptosis in CD44+/CD24+/ESA + pancreatic CSCs [225]. The stem cell maintaining factors such as Nanog and Oct-4, along with anti-apoptosis proteins of the Bcl-2 family, were also inhibited with the dose of 10–20 μM [225]. The ability to induce apoptosis of resveratrol was also reported in a CD24-/CD44+/ESA + model of breast CSCs through a FAS-mediated pathway after being treated with 50 or 100 μM resveratrol [226].

4. Discussion

In recent years, several novel chemical compounds have emerged to support the treatment of multidrug-resistant cancer; however, they remain behind natural substances in many aspects. These specifically include metalloid and micro-structure compounds, with the most well-known example being cis-platinum, which has been proven to be effective in the treatment of breast cancer, NSCLC, and chronic myelocytic leukemia efficient through the mechanism of DNA repair [227], or organosilicon compound namely ALIS 409 showing great potential as a multidrug-resistance reverting agents through inducing apoptosis, delaying tumor growth, and cell desensitization [228]. These compounds emerge due to their advantages over natural compounds, which are diverse substances with multi-target effects and synergistic mechanisms of action [229]. While the specific structures of alternative compounds meet difficulties in developing and finding suitable experimental models [230], the structures of particular natural compounds are already available, and resources need to be centered on optimization through semi-synthesis. Although new compounds with microstructure have significant advantages in increasing bioavailability and tissue accumulation [231], this advantage can be directly integrated with natural compounds, including derivatization metals with structurally specific natural-derived ligands [232], or using micro-particles as a drug delivery system for encapsulating natural molecules [233]. Also, prevalent groups of natural compounds have synergistic effects in regulating multidrug resistance in combination with chemotherapy found in well-known medication [234,235].

Flavonoids and alkaloids are two typical groups of secondary metabolites that have not only standard merits of natural compounds, such as low levels of toxicity and a variety of implications, but also possess unique chemical structural features - as previously discussed - allowing them to become a tremendous prospective direction in the utilization of multidrug resistance treatment. It is estimated that of the approximately 27,000 identified alkaloids and 6000 flavonoids, many of which have been shown to modulate multidrug resistance by synergistic mechanisms, with extensive studies in the most common cancers, including breast cancer, lung cancer, colon and rectum cancer, prostate cancer and stomach cancer [236–238]. Nearly all structural subgroups of alkaloids and flavonoids have molecular families of therapeutic targets; typical examples include isoquinoline alkaloid for two gastric cancer cell lines (SC-M1, NUGC-3), and two colon cancer cell lines (CT26, COLO 205) [239] or flavanone glycoside for several oncogenes (MDR-1, MRP1, BCRP) and the PI3K/Akt signaling pathway whose goal purpose is to suppress medication resistance in osteosarcoma cells [240]. Additionally, models evaluating the activity of natural compounds on Nrf2 in cancer cells are potential testable alternatives against chemotherapeutic drug resistance. The commonly used model is a luciferase reporter gene transfecting into cancer cell genome as high-throughput screening model for Nrf2 activity [241]. Besides, the dual function of Nrf2 protecting normal cells and preventing drug resistance in cancer cell could enhance the therapeutic effects of anticancer drugs without exacerbating side effects.

Natural products have mainly been used for a long time in traditional medicines. Thus, natural compounds tend to have lower toxicity compared to synthetic drugs, reducing the risk of adverse side effects for long-term use. The diversity of chemical structures of natural compounds is an accessible source for research. However, purified natural compounds have several limitations besides the specific advantages. From the beginning, new compound discovery is time-consuming, requiring systematic operation in multiple steps, including cultivation, harvesting, isolation, and targeted activity assessment [242]; to the constraints of reliance on *in vitro* and *in vivo* results leading to limited clinical translatability [243].

Recently, *in silico* drug discovery has accelerated due to rapid advancements in computational methods and the accumulation of publicly available biological data. Crude extracts often contain multiple compounds with complex structures that interact with various biological targets, potentially leading to broader therapeutic effects. However, isolating pure natural compounds is challenging and might reduce their pharmacological properties. Despite this, about three-quarters of cancer drugs are derived from natural compounds, primarily of plant origin. The current essential direction to overcome these challenges is to utilize computational learning approaches to screen natural compounds and identify leading candidates with high application potential [244]. *In silico* techniques play a crucial role in this process by leveraging structural information of either the drug target—structure-based approach or ligands with known

bioactivity—ligand-based approach to facilitate the identification of promising drug candidates. These approaches fast-track drug discovery by utilizing existing knowledge on ligand-receptor interactions, structural optimization, and synthesis. Each *in silico* approach has unique strengths. Machine learning based screening can efficiently process vast publicly available datasets to identify potential drug candidates, significantly reducing the time and resources required [245]. Molecular docking provides insights into the specific molecular targets and pathways affected by these compounds by simulating the interaction between a drug and its target, offering a detailed understanding of binding affinities and interaction sites [245]. Molecular dynamics goes a step further by simulating the physical movements of atoms and molecules over time, providing a dynamic view of drug-target interactions and helping to predict the stability and conformational changes of the complexes formed [246]. These approaches collectively enhance our understanding of structural sites and modes of action, enabling systematic classification with valuable predictive properties for emerging targets, such as P-gp in the regulation of multidrug resistance. Subsequently, isolation, semi-synthesis, and synthesis research can enhance performance and pharmacological effects while reducing toxicity. With advancements in artificial intelligence algorithms, network pharmacology offers a systems-level understanding of the mechanisms of action of natural products. This novel approach identifies the bioactivity of natural compounds and their putative molecular targets, predicting molecules' direct and indirect targets and confirming the synergistic action of natural compounds. Additionally, these approaches screen for toxicity due to adverse interactions and assess the bioavailability of the compounds. Overall, combining multiple *in silico* approaches significantly increases the efficiency of lead compound development, from which appropriate optimization methods can be established [247].

The lead compound taken from the development step is further improved and optimized for clinical properties. The most notable method is partial or combinatorial chemical fabrication, which has an extensive number of branches that revolve around the characteristic of the lead compound and the clinical improvement of interest. For example, numerous flavonoids can be integrated using the emerging lipid-based drug delivery system niosome to increase bioavailability and cell accumulation [248,249], whereas chemical intervention such as alpha-substitution or metal complexation for an acknowledged alkaloid like matrine can enhance clinical effectiveness compared to employing pure substances [250,251]. Additionally, the use of metabolomics and integration of biosynthetic pathway alteration may hold the promise of significantly improving efficiency and purity in the identification and isolation of lead compounds [252,253].

5. Conclusions

In general, secondary metabolites from medicinal plants present promising resources for cancer drug-resistance treatment due to their diverse structures and noteworthy pharmacological effects. This study has reviewed the research on natural compounds that can overcome anticancer drug resistance by multiple mechanisms. Despite the advantages of natural compounds, they also have several drawbacks, including limitations in supply, low concentrations, complex structures, and difficulty in extraction and isolation. *In silico* combination strategies are employed to discover new structural framework compounds based on natural compounds, leveraging advanced computational methods to simulate and predict molecular interactions. Integrating various approaches based on the structure-activity relationship and reconfirming by *in vitro* and *in vivo* assay will boost the drug discovery process from natural sources in general and medicinal plants in particular.

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CRediT authorship contribution statement

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Declaration of competing interest

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

List of abbreviation

5-FU	5-fluorouracil
ABC transporters	ATP binding cassette transporters
AKT	Protein kinase B
BCRP	Breast cancer resistance protein
CDK	Cyclin-dependent kinases
CSC	Cancer stem cells

DDR	DNA damage response
DOX	Doxorubicin
EGCG	Epigallocatechin-3-gallate
EGFR	Growth factor receptor
EOC	Epithelial ovarian carcinoma
ERK	Extracellular-signal-regulated kinase
GBC	Human gall bladder carcinoma
GSK-3	Glycogen synthase kinase 3
HCT	Human ileocecal adenocarcinoma
IAP	Inhibitors of apoptosis proteins
MAC	Mitochondrial apoptosis-induced channel
Maf	Musculoaponeurotic fibrosarcoma
MAPK	Mitogen-activated protein kinase
MC	Human breast cancer
MDR	Multidrug resistance
MDR1	Multidrug resistance protein 1
MEK	Mitogen-activated protein kinase
MMP	Matrix Metalloproteinase
MRP1	Multidrug resistance protein 1
MRP2	Multidrug resistance protein 2
mTOR	Mammalian target of rapamycin
NBDs	Nucleotide-binding domains
NF-κB	Nuclear factor κ light chain enhancer of activated B cells
Nrf2	Nuclear factor erythroid-2 p45-related factor 2
PDK1	PIP3 binds to kinase-1
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PIP3	Phosphatidylinositol 3,4,5-triphosphate
PTEN	Phosphatase and tensin homologue
TMDs	Transmembrane domains
TRIB2	Tribbles homologue 2
VEGF	Vascular Endothelial Growth Factor

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