Anatolian Journal of Biology
ISSN: 2687-444X
2020 2:1-51

Research Paper

Plant-Derived Natural Products as Multidrug Resistance Modulators in Cancer Therapy

Mine İsaoğlu [1,*], Medine Güllüce [2], Mehmet Karadayı [2]

[1] *Institute of Natural and Applied Sciences, Atatürk University, Erzurum, Turkey*
[2] *Faculty of Science, Department of Biology, Atatürk University, Erzurum, Turkey*

Received 21 December 2020; accepted 30 December 2020
Available online 31 December 2020

Abstract

Background: Cancer is the second leading cause of death worldwide and each year tens of millions of people are lost their lives due to different types of cancer. Despite all efforts in the treatment of cancer, the mortality and morbidity rates are still in high levels. Multidrug resistance (MDR) is one of the main impediments in the cancer treatment. MDR might result in tumor metastasis and recurrence, which is responsible for 90% of cancer-related deaths. Many intrinsic and extrinsic factors such as genetic and epigenetic modifications, drug efflux systems, DNA repair mechanisms, apoptotic and autophagic processes contribute drug resistance in cancer cells. To date, various types of molecules have been tested *in vitro* and *in vivo*, for MDR modulating activity but there is still no effective anticancer drug to completely overcome MDR. Phytochemicals, in alone or in combination with other chemotherapeutics, are potentially able to sensitize the cancer cells to conventional anticancer drugs in cancer patients with fewer side effects. In this review, we aimed to provide a general perspective about MDR-related mechanisms and novel therapeutic approaches including RNA interference (RNAi) therapy, nanotherapy and cancer stem cell treatments to combat MDR and to highlight the latest MDR reversing agents of plant origin based on their modulating effects on various proteins, enzymes, transcription factors, cell cycle regulators and survival and oncogenic pathways.

Conclusion: Plant-derived secondary metabolites may improve the therapeutic efficacy of anticancer drugs through targeting different MDR-related mechanisms and they serve as lead compounds to elicit better pharmacological results in the development of novel anticancer agents.

Keywords: Cancer; Multidrug resistance (MDR); Natural products; Plant secondary metabolites; Chemosensitizers.

1. Introduction

Cancer is a term used for diseases in abnormal cells that can divide uncontrollably and take over other tissues of the body [1]. It is a multi-step process and occurs as a result of loss of control of cell division, initially leading to tumor formation, followed by metastatic spread [2]. Metastasis is responsible for approximately 90% of cancer-related deaths [3].

Cancer is one of the leading causes morbidity and mortality in global [4]. In 2018, it was reported that the number of new cancer cases were 18.1 million and there were 9.5 million cancer-related deaths worldwide. Cancer mortality rate is higher in men (0.18%) than women (0.14%) [5]. While lung & bronchus, colon & rectum and pancreatic cancers are the estimated causes of death in the first, third and fourth place for both the sexes, respectively; prostate cancer in men and breast cancer in women take second place [6]. It is estimated by WHO that there will be 27 million new cancer cases and 17.1 million cancer-related deaths will occur in every year until 2050 [7].

Despite the remarkable scientific developments in the field of molecular oncology today, the fight against cancer is still one of the most important health problems across the world [8]. However, resistance of human tumors to chemotherapeutics greatly reduces the success rates in cancer therapy [9]. Apoptosis in cells occurs through mitochondria-mediated intrinsic pathway and/or receptor-mediated extrinsic pathway. Cells that cannot undergo apoptosis can change the

[*] *Correspondance: Mine İsaoğlu, Institute of Natural and Applied Sciences, Atatürk University, Erzurum, Turkey*
E-mail: mine.isaoglu@gmail.com

effectiveness of cancer treatment [10]. Multidrug resistance (MDR) is defined as cancer cells that are resistant to a chemotherapeutic are also resistant to other classes of cancer drugs that have different chemical structure and pharmacological activity. This concept was first described by Keld Dano in the literature in 1972 with the discovery of the extracellular transport of vinca alkaloids and anthracyclines from murine Ehrlich ascites carcinoma (EAC) cells through active transport [11]. MDR has been observed in many types of cancer including breast, lung, ovarian, blood and lower gastrointestinal system cancers by now and it also has an important role in the recurrence and metastasis of cancers [12,13]. Drug resistance in cancer cells may be natural (intrinsic resistance) or induced by drugs (extrinsic or acquired resistance) [14]. Acquired MDR is more difficult to treat due to lack of response to chemotherapeutics even when toxic doses are reached in drug therapy. When it comes to intrinsic MDR, cancer cells show resistance to chemotherapeutics when the first drug dose is taken [7]. To date, many mechanisms (e.g., increased drug excretion, decreased drug reuptake, change in drug metabolism (increased drug detoxification or drug inactivation), drug target modulation, activation of DNA repair pathways, inactivation of apoptotic mechanisms and induction of autophagy) have been associated with MDR (Figure 1) [15,16]. The main objectives of this review are to discuss the recent developments related to multidrug resistance in cancer therapy and to concentrate on potential MDR modulators from natural products of plant origin.

2. Multidrug Resistance in Cancer

Multidrug resistance is a process that antineoplastic drugs are pushed out of the tumor cells thus they show low pharmacological activity due to the decrease of drugs' concentration at the target sites [17]. MDR was first observed in antibiotic-resistant bacteria, then it was also seen in cancer [18]. It is a common clinical condition and it is actually the main factor that makes cancer therapies ineffective [19]. Researches have shown that the presence of drug-resistant cancer cells in patients who have received chemotherapy is responsible for the recurrence of tumors as well as poor prognosis [20]. Chemotherapy is the most frequently used treatment option in cancer [21].

Understanding how a cancer cell become resistant to a chemotherapeutic is a complex and challenging process. MDR occurs when the tumor does not respond to the drug in the presence of pre-existing resistance arising from internal factors in patients (intrinsic MDR) or when cancer cells become insensitive to the drug during chemotherapy (acquired MDR) [18]. There are three main categories of drug resistance which are drug dependent, target dependent and drug/target independent [22]. In the development of drug-induced MDR, drug metabolizing enzymes and drug carriers that are responsible for the transportation of drugs out of cells are overexpressed or the intake of drugs into cancer cells is reduced. Besides, changes at the gene level such as deletion, mutation, translocation and amplification play a crucial role in the emergence of target-dependent MDR. The drug/target independent mechanism arises from the modulation of cellular signaling cascades that inactivate the drug target as a result of genetic or epigenetic manipulations [11,23].

The cancerous cells become resistant to cell death and anticancer drugs owing to having different capabilities such as high adaptability, activation of survival and inactivation of death signaling pathways as well as escape from the growth suppressors. While genetic instability, heterogeneity, rapid mutation of tumor cells and cytogenetic changes make a slight contribution of the development of drug resistance, the efflux pumps and transporter proteins have a major role in the development of MDR [24,25]. Although many mechanisms that cause drug resistance have been identified today, these mechanisms have not been fully elucidated [18].

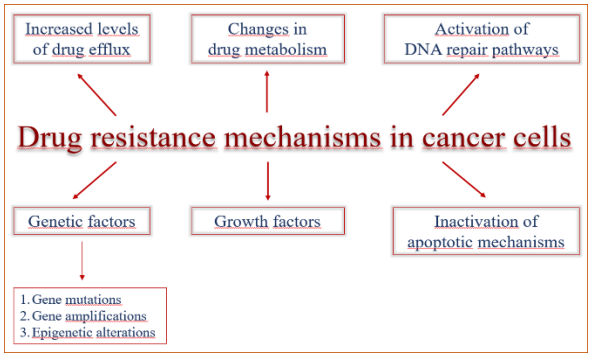

Figure 1. Mechanisms contributing to drug resistance in cancer cells [15,26]

2.1. Mechanisms of multidrug resistance

2.1.1. Drug efflux via ATP-binding cassette (ABC)-transporters

ABC-transporter membrane proteins, which can be expressed in both cancer and normal cells, consist of 48 members in humans and have 7 subfamilies from A to G. They can affect the pharmacokinetic (absorption, distribution, metabolism, excretion) and toxicokinetic activities of drugs [27]. More specifically, ABC superfamily has an important physiological role on protecting the human body from the harmful effects of xenobiotics and endogenous metabolites. These proteins contribute to the toxicity profile of many drugs and provide MDR in cancer cells related to poor prognosis in cancer patients [28].

To date, 15 ABC-transporter proteins (e.g., P-glycoprotein (P-gp), multidrug resistance-associated protein 2 (MRP2) and breast cancer resistance protein (BCRP)) are associated with MDR as drug efflux pumps [11]. The overexpression of ABC-transporters is one of the most important MDR mechanisms for the extracellular excretion of both cytotoxic agents and targeted anticancer drugs (Figure 2) [23]. Tumor cells

in which P-gp or other MDR-associated transporter proteins are highly expressed are usually resistant to chemotherapy [29].

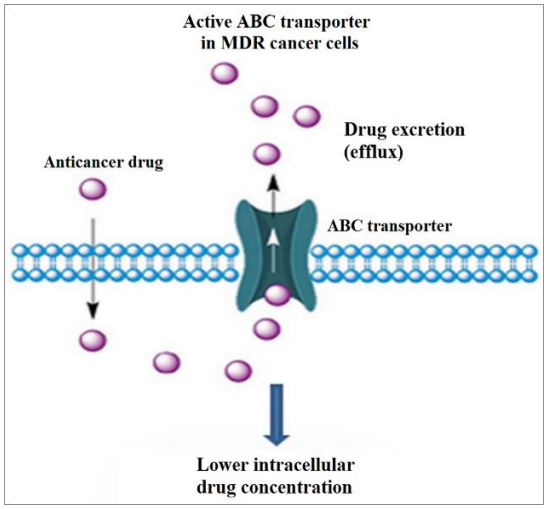

Figure 2. Diagram of drug efflux via ABC transporters in MDR cancer cells [18]

2.1.2. Deregulation of cell death mechanisms

2.1.2.a. Evasion of apoptosis

Apoptosis is a form of programmed cell death and it is regulated at the gene level. By this mechanism, damaged DNA cells in the body are destroyed regularly and efficiently. Many signaling pathways play important roles in the apoptosis process. In cells, intrinsic or caspase-mediated extrinsic pathways are involved in the induction of apoptosis [30]. Initiation of each pathway causes the activation cascade of caspases [31]. The balance between pro-apoptotic and anti-apoptotic proteins gives an idea of whether a cell undergoes apoptosis. Owing to the ability of cancer cells to escape apoptosis, the amount of anti-apoptotic proteins (B-cell lymphoma 2 (BCL-2), B-cell lymphoma-extra-large (BCL-XL) and myeloid cell leukemia 1 (MCL-1)) in the tumor tissue increases thus the cancer cells become resistant to chemotherapy. Aberrant apoptotic proteins are thought to play a role in the drug resistance of tumor cells [18,31-33].

By the induction of apoptosis as a result of DNA damage in cells that have not yet transformed into cancer cells, tumor formation can be eliminated in the body. According to the literature, deregulation of apoptosis process is associated with uncontrolled cell proliferation, cancer development and progression, and also resistance to anticancer drugs. Therefore, deregulation of apoptosis is considered as an important distinguishing feature in cancer. Developing therapeutic strategies targeting apoptotic resistance mechanisms with the intent of increasing the sensitivity of cancer cells to apoptosis and also enhancing the effectiveness of the cancer therapy is crucial in combating MDR. Many cancer drugs currently used in the clinic trigger apoptosis of cancer cells using intact apoptotic signaling pathways [33]. In addition, a number of plant-derived natural products such as aloe-emodin, curcumin, epigallocatechin-3-gallate (EGCG), genistein, juglone and quercetin show remarkable anticancer activites by inducing apoptosis in cancer cells [34].

2.1.2.b. Induction of autophagy

Autophagy is a conserved catabolic process that separates and degrades intracellular components in double-membrane vesicles called autophagosomes, and it has an important role in maintaining body homeostasis. Autophagy shares a common molecular pathway with apoptosis. It typically occurs irregular in cancer cells and can be triggered by various internal and external stress factors. In the end of the autophagy process, accumulation of damaged proteins and organelles that may be toxic to cells is prevented [35,36].

Autophagy plays a vital role in differentiation of some characteristics of cancer cells such as cell survival and cell death, metabolic decontrol, regulation of immune response, augmentation of cancer stem cells (CSC) and multidrug resistance [35]. It prevents multidrug resistant cancer cells from apoptosis and also increases the resistance of these cells to chemotherapy. The inhibition of autophagy can increase the sensitivity of MDR cells to anticancer agents and make MDR cells more liable to apoptosis [37,38].

Autophagy is one of the promising approaches in cancer treatment. Chemotherapeutics such as cyclosporine A, resveratrol (RES), tamoxifen (TAM) and arsenic trioxide show direct or indirect anticancer activities by inducing autophagic cell death [36]. Although inducing autophagy offers a valid therapy option in premalignant lesions, the inhibition of autophagy is a more effective treatment approach in many tumors and advanced cancer cases. Currently, researchers have focused on the discovery and development of drugs that inhibit autophagy, and there are several ongoing clinical trials for the treatment of cancer [39]. Silencing the autophagy-related genes (*Atgs*) and using the pharmacological autophagy inhibitors are the most popular approaches for the inhibition of autophagy [40]. The autophagy inhibitors (e.g., choloroquine, bafilomycin A1, 3-methyladenine, LY294002, SB202190 and SB203580) show their anticancer effects either targeting the nucleation and elongation of phagophore or inhibiting the endosome-lysosome system acidification [41].

2.1.2.c. Activation of DNA repair pathways

Various endogenous and exogenous genotoxic stresses (e.g., reactive oxygen species (ROS), ionizing radiation (IR), ultraviolet (UV) light, chemical agents and environmental pollutants) cause damage to human DNA at a certain rate on a daily basis. Damaged DNA molecules accumulated in cells are known to cause genomic instability. Unless DNA lesions are repaired, a cell cannot maintain its integrity and survive [42].

Repairing damaged DNA molecules also has a key role in the cancer prevention [43]. There are several

DNA repair mechanisms such as mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER) and double-stranded break repair (DSB) in human cells [42]. DNA molecules that are not properly repaired in cells can lead to mutations or chromosome abnormalities in tumor suppressor genes thus the oncogenic transformation process begins (Figure 3) [44]. The effect of DNA repair mechanisms in removing DNA lesions cannot be neglected in the patients receiving chemotherapy and radiotherapy because they significantly increase the abilities of cells to survive [42].

Activation of the cellular DNA damage response (DDR) is an important criterion in determining cell susceptibility to cisplatin (CIP) and other anticancer drugs that can eliminate tumor cells by inducing DNA damage. It is also necessary to understand the changes in DNA damage-signaling pathway in order to understand whether cancer cells are drug resistant and also MDR cells can be re-sensitized by any pharmacological intervention [45].

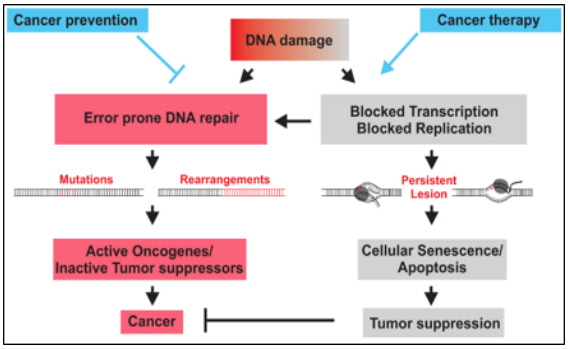

Figure 3. Cancer development process induced by increased level of DNA damage [44]

Although MDR cells have the ability to repair damaged DNA molecules, DNA is the most frequently targeted biomacromolecule in traditional cancer treatments [26]. Many anticancer drugs such as CIP, nucleoside analogs (cytarabine, gemcitabine, fludarabine), alkylating agents (nitrogen mustards, cyclophosphamide (CP), thiotepa, temozolomide (TMZ), nitrosoureas) and poly (ADP-ribose) polymerase 1 (PARP1) inhibitors (olaparib, rucaparib) which prevent cell proliferation, cause extensive DNA damage resulting in cell cycle arrest and apoptotic effects [44,46]. Recent studies showed that combining DNA-damaging agents and DNA damage response (DDR) inhibitors in cancer therapy, tumors can be selectively destroyed [42,47,48]. For example, Muvarak et. al. [49] reported that the use of DNA methyltransferase (DNMT) and PARP inhibitors together in the treatment of acute myeloid leukemia (AML) and breast cancer, has allowed PARP1 to bind tightly to chromatin thus such combinations have been reported to play an important role in order to enhance the effectiveness of PARP inhibitors. Liu et. al. [50] stated that ataxia telangiectasia and Rad3-related (ATR) protein have been associated with gemcitabine (GEM) resistance in pancreatic cancer cells and they showed the drug-resistant cells could be sensitized to GEM by the inhibition of ATR in anticancer therapy.

2.2. Therapeutic strategies for multidrug resistant cancers

Cancer chemotherapy resistance is a condition that makes the cancer treatment more complicated and it significantly reduces the effectiveness of existing anticancer drugs. MDR is directly related to the remission and progression of cancers. Resistance occurs due to pre-existing internal causes in patients (intrinsic resistance) or the desensitization of cancer cells to anticancer drugs during the treatment (acquired resistance). According to the information obtained from clinical data, at least two MDR mechanisms have found active in each of the cancer types thus cancers become more difficult to cure. Recent studies related to MDR have focused on both further investigation of MDR-related mechanisms and the development of novel therapeutic strategies, e.g., anticancer agents that can escape from the drug efflux pumps, MDR modulators and chemosensitizers, antisense oligonucleotides (ASOs), RNAi therapy, cytokine-based approaches, monoclonal antibodies, CSC technology, multifunctional nanocarriers as well as photodynamic therapy [11,13,18,51-55].

Overexpression of MDR transporters is one of the main factors contributing to drug resistance in chemotherapy. The most highly researched MDR transporters are the ABC superfamily. These proteins are responsible for preventing the accumulation of drugs in the cell, thereby reducing the toxicity of drugs [51]. Although ABC transporter modulators (Table 1) discovered up to the present have been successful in enhancing the sensitivity of tumor cells to anticancer drugs, there is no approved ABC transporter inhibitor in cancer-related MDR yet. This is due to severe side effects of inhibitor molecules and their lack of modern and innovative clinical study designs [7,56]. Therefore, there is an urgent need to discover new, more potent and less toxic ABC transporter inhibitors as MDR modulators and also new therapeutic opportunities in the field of cancer drug discovery and development [57].

3. The Rising Trends in MDR Modulators

ABC transporters contribute to the pharmacokinetics of various anticancer drugs and today we know that different types of cancers can be treated by modulation of ABC transporters. This protein family may also be beneficial in cancer prognosis. P-gp, multidrug resistance-associated protein 1 (MRP1), MRP2 and BRCA are well-known ABC transporters [7]. Among them, P-gp is still one of the most studied MDR-associated drug transporter and it has been known to interact with more than 200 MDR modulators [58,59].

The MDR-modulatory activities of many chemical compounds have so far been tested in clinical trials [60]. These molecules, given in Table 2, can be classi-

Table 1. Modulators of ABC transporters as chemosensitizers [7,60,61]

Target/ Gene encoding	Inhibitor Molecules
P-gp/*ABCB1*	Amlodipin, cyclosporine A, disulfiram, dofequidar, elacridar, nifedipine, quinidine, quinine, tariquidar, tetrandrine/CBT1®, verapamil, valspodar, zosuquidar
MRP1/*ABCC1*	3-*β*-Acetyl tormentic acid (3ATA), benzbromarone, *S*-decyglutathione, dofequidar, ibrutinib, leukotriene C4 (LTC4), probenecid, sulfinpyrazone, sulindac, tricyclic isoxazoles, verlukast
MRP2/*ABCC2*	Benzbromarone, curcumin, cyclosporine A, fluorescein, methotrexate, myricetin, PAK-104P, probenecid, sulfinpyrazone, thioridazine, verlukast, valspodar
BCRP/*ABCG2*	Biricodar, erlotinib, fumitremorgin C, gefitinib, GF12918, lapatinib, tariquidar

fied as first-, second-, third- and fourth- generations based on their affinity for drug transporters and the magnitude of their side effects [7,27]. The first-generation MDR modulators (Figure 4) had low binding affinities, required to administered in high doses so that they could be effective, and showed significant cardiotoxicity at higher doses. In addition, their unexpected pharmacokinetic interactions with other chemotherapeutics were another disadvantage.

Table 2. First-, second-, third-, and fourth-generation of ABC transporter modulators [7,27,59,60,62]

Generation	MDR modulatory compounds
1st	Calmodulin antagonists, cyclosporine A, quinidine, quinine, progesterone, reserpine, tamoxifen, toremifene, trifluoperazine, verapamil
2nd	Biricodar citrate, cyclosporine D, dexniguldipine, dexverapamil, valspodar
3rd	Annamycin, diarylimidazole, dofequidar, elacridar, erlotinib, laniquidar, lapatinib, mitotane, tariquidar, zosuquidar
4th	Curcumin, neochamaejasmin B

The second-generation MDR modulators (Figure 4) have been developed to overcome these problems. Although they had better pharmacological and toxicological profiles, their use was limited to clinical studies. Because they inhibited CYP450 enzymes, so drug-drug interactions were detected. They also seriously affected the metabolism and elimination of other drugs in the body. It should be noted that if second-generation MDR modulators are combined with other chemotherapeutics in the anticancer therapy, safe and ideal dose ranges should be well established due to pharmacokinetic interactions. These limitations have prompted researchers to discover novel, safer and highly effective MDR modulators. Third-generation MDR modulators (Figure 4) were derived from the structure-activity relationships and combinatorial chemistry studies of the second-generation MDR modulators. They were found to be 300 times more effective at nanomolar concentrations than the first- and second-generation MDR modulators. In addition, it has been stated that they do not interact with CYP450 enzymes and other ABC transporters. This has resulted in change of the general pharmacokinetic profiles of MDR modulators. Besides, the co-administration of third-generation MDR modulators and other anticancer drugs at lower doses has become possible in a chemotherapy regimen [59,63].

Different therapeutic strategies have also been developed to overcome MDR as an alternative to P-gp inhibitors. For instance, the expression of P-gp can be down-regulated in the cells through the inhibition of many pathways (e.g., extracellular-related kinase (ERK), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), V-ATPases/mammalian target of rapamycin (mTOR)/Hypoxia-inducible factor 1-alpha (HIF-1α)/P-gp and Janus kinase 2 (JNK2)/p-JNK/p-c Jun/P-gp pathways) by modulatory compounds [64]. In addition, Zhao et. al. [65] created silica nanoparticles modified by cancer cell membrane (CCM/CS/R-D) in the co-delivery of siRNA and doxorubicin (DOX) to the Ca^{2+} channel for effective treatment of multidrug resistant human cervical cancer. They found that the CCM/CS/R-D system was able to successfully target the tumor in preclinical studies, thus increasing the therapeutic efficacy of DOX on human cervical carcinoma (HeLa) cell line. Cho and Kim [55] reported that MDR mechanisms of CSCs (e.g., aldehyde dehydrogenases (ALDHs), epithelial-mesenchymal transition (EMT) and epigenetic modifications) could be targeted to overcome multidrug-resistant tumors. Sinha et. al. [66] stated that sirtuins (SIRTs) were the prognostic factors or biomarkers of metastatic and/or drug-resistant breast cancer cells and the sirtuin inhibitors/activators have been currently investigated in clinical trials. They suggested that the sirtuin modulators could be administered alone or in combination with other anticancer drugs in the treatment of drug-resistant cancers. Pramual et. al. [67] investigated the effectiveness of nanoparticle mediated photodynamic therapy (NPs/PDT) in lung cancer cells having both drug-selective MDR and metastasis-associated MDR mechanisms. They reported that the success of NPs/PDT strategy stemmed from the distribution ability of poly(lactic-*co*-glycolic acid) (PLGA)-lipid nanoparticles, which were described as photosensitizers or chemotherapeutic drugs, in reversing MDR resistance and these hybrid nanoparticles had the potential to be used in treating lung cancer cells with both MDR resistance mechanisms. Yang et. al. [68] reported that multidrug resistance proteins (MRPs) contributed to chemoresistance in cholangiocarcinoma (CCA) cells and they found that the *in vitro* cytotoxicity of GEM increased when they knocked out the human genes that synthesize MRPs. Dong et. al. [64] uncovered that RN486, which is a Bruton's tyrosine kinase (BTK) inhibitor, reversed the MDR mechanism caused by the overexpression of *ABCB1* transporters in Paclitaxel (PTX)- and DOX-resistant cancer cells. They concluded that the suppression of the drug-efflux activity of *ABCB1* could be achieved without making

any changes in its expression level or subcellular localization. Martinelli and Biglietti [69] discussed that the advantages and disadvantages of the use of various inorganic (iron oxide and metal oxide nanoparticles, gold nanoparticles, quantum dots, mesoporous silica nanoparticles and carbon-based nanocarriers) and organic (lipid-based nanoparticles, polymeric nanoparticles, polymeric micelles and dendrimers) nanocarriers as precise drug delivery and release systems in combating MDR. They emphasized that the biocompatibility and safety features of these systems needed to be further investigated prior to their clinical use. Lin et. al [70] identified that miRNA-765 has overexpressed in MDR-related gastric cancer cells and they showed that the down-regulation of miRNA-765 increased the sensitivity of gastric cancer cells to the anticancer drugs. Ma et. al. [71] developed self-targeting hyaluronate (HA) nanogels (^{CDDP}HANG/DOX) in order to release DOX and CIP simultaneously into the multidrug-resistant breast cancer cells for combating MDR. They concluded that ^{CDDP}HANG/DOX could remain in the bloodstream for a long time, accumulate excessively in tumor cells *in vivo*, effectively deliver drugs to drug-resistant MCF-7/ADR breast cancer cells, and exhibit good antitumor activity. Majidinia et. al. [72] mentioned that the applications of physical methods such as thermal (hyperthermia) and ultrasonic therapy, using different types of nanocarriers for successfully delivering multiple chemotherapeutics to MDR-related cancer cells. Yu et. al. [73] reported that programmed death-ligand 1 (PD-L1) moAb-conjugated PTX and tariquidar-loaded nanoliposomes (PD-PTLP) could reverse the multidrug resistance in SGC7901/ADR cells *in vitro* and had a significant MDR-reversal activity *in vivo*. Teng et. al. [74] designed three novel antimicrobial peptides with 13 amino acids and investigated the cytotoxic effects of these peptides on ABC transporter-overexpressing cancer cell lines having PTX- and DOX-resistance. They concluded that XH-14C (FIKRIARLLRKIWR) could reverse *ABCB1*-mediated MDR and its use in combination with conventional chemotherapeutic agents as an innovative strategy in cancer therapy. Hong et. al. [75] demonstrated that Y-320, a novel immunomodulator, when co-administered with other anticancer drugs, it significantly damaged drug-resistant breast cancer (BCap37, Bads-200 and Bats-72) cells. This indicates that Y-320 is an effective chemosensitizing agent that can be used in cancer-related MDR treatment with low toxicity.

The exploration of the usage of natural products as fourth-generation MDR modulators (Figure 4) in cancer therapy is of great interest today. Chemical natural compounds are known to have many advantages as drug leads in terms of chemical diversity, specific interactions with biological targets, especially proteins, as well as unique bioactivity and reduced toxicity profiles over the synthetic molecules. These properties make natural compounds a priority in drug discovery and development research [76-78]. Moreover, more than 70% of the anticancer drugs available on the market today are derived from or inspired by natural products [79].

Drug resistance in cancer generally develops due to the loss of functionality of several cellular mechanisms in the body and this encourages the researchers to investigate the potential use of multi-functional drugs in MDR-related cancer therapies. P-gp, MRP1 and BCRP are simultaneously expressed in many cancer cells thus the inhibition of each resistance mechanisms provided by these proteins results in one compensating the others. Accordingly, the idea of having broad-spectrum activity in MDR inhibitors makes more sense. From this point of view, natural compounds are a good alternative to the first three generations of MDR modulators for the reversal of drug resistance in cancer cells [60]. Seidel [80] reported that about 15% of the phytochemicals have been investigated so far and the pharmacological activities of only 6% of them have determined. This indicates that there is a great discovery field of the pharmaceutical potential of plant secondary metabolites.

Due to the limited clinical use of the third-generation MDR modulators based on their unexpected adverse side effects, the fourth-generation P-gp inhibitors have begun to the develop in order to take control of MDR in cancer therapy. These compounds have been natural products isolated from their biological source or natural product derivatives, peptidomimetics and dual ligands that have the potential to inhibit both P-gp and other MDR mediators. Despite years of effort, none of the MDR inhibitors developed to date have been found successful in clinical trials [64]. Natural products are a good starting point in drug development studies in order to reach more effective and safer drug molecules. Secondary metabolites from plants have tremendous potential for this aim, and it is urgently needed to investigate the potency of these natural compounds in reversing cancer resistance [81].

In this review, we aimed to provide an insight into the progress on plant-derived natural MDR modulators between the years of 2015-2020.

4. Natural MDR Modulators of Plant Origin

4.1. Plant secondary metabolites

Plant secondary metabolites are specific sources of drugs, food additives, flavors and industrially important biochemical substances. They are usually small organic molecules produced by plant cells. Secondary metabolites have no effect on the vital functions of plants such as growth, development and reproduction, but they play an important role in the adaptation of plants to the environmental conditions in which it is located. They are divided into three main classes as phenolics, alkaloids and terpenoids according to the pathways in which they are synthesized [82,83].

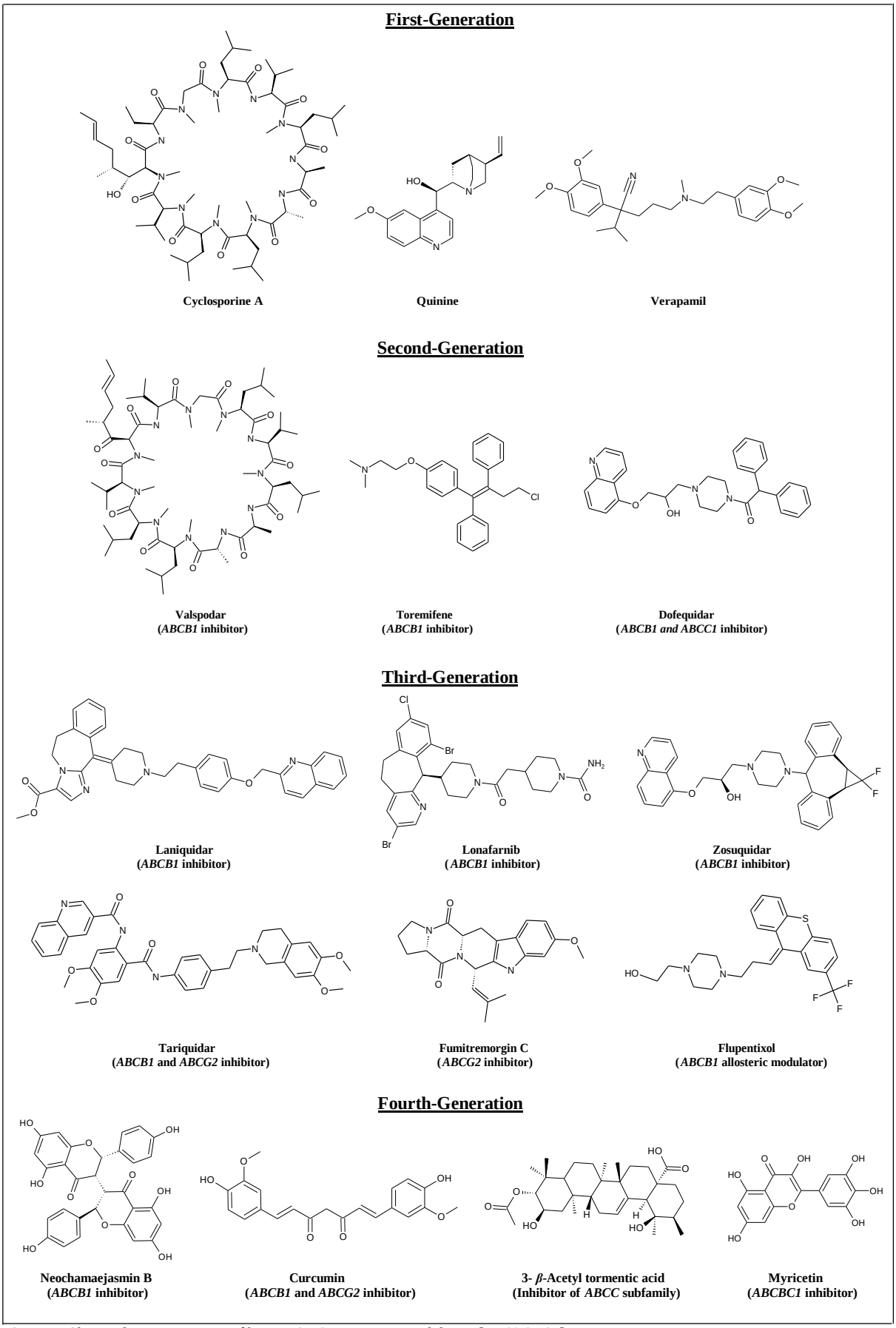

Figure 4. Chemical representations of known ABC transporter modulators [55,60,84,85]

4.1.1. Phenolic compounds

Phenolic compounds which do not contain nitogen atoms, have at least one aromatic ring to which one or more hydroxyl (-OH) groups are attached in their structures. They are naturally found conjugated to sugars or organic acids. Their antioxidant activity is due to their hydrogen atom or electron transfer ability, thus preventing the oxidation of various endogenous molecules in the body [86]. Polyphenols, phenolic acids, flavonoids, stilbens and lignans are phenolic compounds commonly found in plants [87].

Flavonoids are polyphenolic compounds bearing the benzo-γ-pyrone skeleton in their structure. They have low molecular weights and more than 8000 different flavonoids have been identified to date. Because of their selectivity profile and non-cytotoxic properites, they have a great potential to be P-gp inhibitors. In fact, they have shown comparable efficacy to classical P-gp inhibitors [88]. Apart from these, it has been reported that flavonoids have antioxidant, cardioprotective, anti-inflammatory, antiaging, immunomodulatory, antibacterial, antiviral, antiparasitic and antifungal activities [86].

Apigenin (AP) (**1**) (Figure 5) is a natural flavonoid present in many fruits and vegetables as well as medicinal plants *Salvia officinalis* (Lamiaceae), *Ocimum basilicum* (Lamiaceae) and *Tamarindus indica* (Fabaceae). It has been in the foreground for years with its chemoprotective effects. In addition, antioxidant, radical scavenging, antimutagenic, anti-inflammatory, antiviral and purgative activities of AP have also been reported [89]. Chen et. al. [90] demonstrated that apigenin combined with gefitinib (GEF) caused metabolism impairment and apoptotic cell death in H1975 lung cancer cells by inhibiting multiple oncogenic factors such as epidermal growth factor receptor (EGFR), c-Myc and HIF-1α, reducing the expression of glucose transporters (GLUTs) and monocarboxylate transporter 1 (MCT1) proteins as well as inactivating 5' AMP-activated protein kinase (AMPK) signaling. In another study, apigenin in combination with CIP has shown potential to sensitize human $CD44^+$ prostate CSCs by inducing apoptosis [91]. Gao et. al. [92] demonstrated that apigenin has significantly increased DOX sensitivity by inducing miR-520b expression and inhibiting autophagy related 7 (ATG7)-dependent autophagy in BEL-7402/ADM cells. Thus, it has a potential as a chemosensitizer for hepatocellular carcinoma (HCC).

Butein (**2**) (Figure 5) is a chalcone derivative that is produced by many botanical families such as Anacardiaceae, Asteraceae and Fabaceae. In addition to being a dietary polyphenol, butein can also inhibit the activity of protein tyrosine kinases, thereby playing an important role in the prevention and treatment of various types of cancers [93]. Zhang et. al. [94] investigated the anticancer effects of butein in HeLa cells and found that it sensitized these malignant cells to CIP *in vitro* and *in vivo*, by preventing the activation of the AKT and ERK/p38 mitogen-activated protein kinase (MAPK) pathways by targeting FoxO3a.

Curcumin (**3**) (Figure 5), is also called diferuloylmethane, is the major natural polyphenol compound found in the rhizome of *Curcuma longa* (turmeric). Turmeric has been traditionally used in Asian countries as a medicinal herb because of its antioxidant, anti-inflammatory, antimutagenic, antimicrobial and anticancer properties [95]. Curcumin alone, or in combination with other chemotherapeutics and/or phytochemicals, has the potential to inhibit the growth of various cancer cell lines and it might sensitize the tumor cells on the purpose of reversing MDR activity. Khatoon et. al. [96] has been reported different types of chemosensitizing effects of curcumin. In this review, it was emphasized that curcumin has played a remarkable role in the *in vitro* sensitization of leukemic cells to other anticancer agents, e.g., DOX, TAM, etoposide (ETP), methotrexate (MET), *L*-asparaginase (*L*-ASP), valproic acid and carnosic acid. Also, it was reported that the coadministration of curcumin and vincristine (VCR); or ETP, dasatinib, leucovorin, fluorouracil (5-FU)+oxaliplatin (OXP) resulted in a significant chemosensitizing effect in preclinical colon cancer models via regulating many cellular proteins and signal transduction pathways. They also mentioned that when curcumin has been co-administered with adriamycin (ADM), pterostilbene or DOX, the anticancer effects observed in HCC cells have increased due to the induction of caspase-3 activity and the decrease in the expression of Bcl-2, nuclear factor kappa B (NF-κB), lysyl oxidase (LOX), c-Myc, cellular inhibitor of apoptosis protein (cIAP) 2, *NAIP*, vascular endothelial growth factor (VEGF) and X-linked inhibitor of apoptosis (XIAP). Furthermore, they have been stated that curcumin has enhanced the anticancer activities of many chemotherapeutics such as DOX, ETP, VCR and 5-FU in gastric cancer cells, and also the cytotoxic effects of DOX, 5-FU, PTX in PC-3 and DU145 prostate cancer cells. In the same review, it has been reported that curcumin has a sensitization potential to different anticancer drugs and other compounds (e.g., CIP, DOX, docetaxel (DTX), GEM, GEF, irinotecan (IRT), mitomycin C (MMC), epicatechin, sulfinosine, and vinorelbine) in the lung cancer cells via the regulation of many signaling pathways. Besides, they have provided valuable information about the effectiveness of the curcumin alone or its combination therapies in order to increase the sensitivity of breast cancer cells. For example, they pointed out that curcumin in conjuction with carnosic acid, CIP, docosahexaenoic acid (DHA), DTX, retinoic acid, TOF, trichostatin A (TSA), valporic acid and genistein could successfully sensitize the breast cancer cells by interfering with many signal transduction pathways. Mahammedi et. al. [97] found that curcumin-DTX-prednisone (PDN) combination in metastatic prostate cancer patients who have not recieved chemotherapy, had good tolerability, high response rate and patient acceptability in a Phase II study.

Shabaninejad et. al. [98] reported that curcumin could arrest cell proliferation and induce apoptosis in colon, lung, breast, melanoma and glioblastoma (GBM) cancer cells. More specifically, it has the potential to inhibit the migration and invasion in human U87 glioblastoma cells via signal transducer and activator of transcription 3 (STAT3) pathway [99]. In a study conducted by Li et. al. [100], it was concluded that microRNA-378 has enhanced the inhibitory effect of curcumin in U87 cells *in vitro* and *in vivo*. Gersey et. al. [101] investigated that curcumin treatment in the subtoxic levels (2.5 μM) significantly decrease the proliferation of cancer cells by inducing ROS generation, promoting MAPK pathway activation and downregulating STAT3 activity in glioblastoma stem cells (GSCs). Shen et. al. [102] reported that curcumin has diminished autophagy by affecting the mechanism of autophagy to apoptosis switch and regulating Kelch-like ECH-associated protein 1 (Keap1) transcription in CIP-resistant A549 lung cancer cells. To eliminate the poor pharmacokinetic and low bioavailability properties of curcumin, many drug delivery systems has developed and this approach has been used as an alternative to the synthesis of curcumin derivatives. Keyvani-Ghamsari et. al. [103] reported that synthetic polymers such as PLGA is generally used in the delivery of curcumin *in vivo*. Wang et. al. [104] made a micelle formulation with curcumin and methoxy poly(ethylene glycol)-poly(lactide) copolymer (MPEG-PLA), and this combination has resulted in increasing the cytotoxic effects of curcumin by inducing apoptosis in melanoma cells.

Epigallocatechin-3-gallate (**4**) (Figure 5) is the most effective catechin compound abundantly found in green tea (*Camellia sinensis*) and accounts for over 50% of total polyphenols. Studies have proved that EGCG shows anticancer activity through different mechanisms such as cell cycle arrest and apoptosis [105]. In a study conducted by Kumar et. al. [106], it was reported that coadministration of EGCG and vandetanib (ZD6474) in a mesoporous silica gold cluster nano-drug delivery system, resulted in inhibiting EGFR2, VEGFR2 and Akt signalling pathways thus overcoming TAM resistance in TAM-resistant breast cancer cells. Zhang et. al. [107] reviewed the role of EGCG in the reversal of MDR in different types of cancers *in vivo* and *in vitro*. They concluded that EGCG has enhanced the chemotherapeutic activity of many anticancer agents (e.g., DOX, CIP and TAM), via inhibiting the multiple drug transporters, decreasing DNA methylation and histone acetylation, regulating the activity of miRNAs, controlling tumor microenvironment, balancing redox homeostasis, interfering multiple signaling pathways (down-regulation of AKT and mTOR), inducing MDR cancer cell death, modulating the properties of CSCs, and acting as a receptor tyrosine kinases inhibitor. Le et. al. [108] stated that EGCG had cytotoxic effects on various glioma cell lines *in vitro*, thus it has increased the efficacy of anti-glioma therapies.

Fisetin (**5**) (Figure 5), is an active flavonoid molecule found in fruits and vegetables such as strawberry, grape, kiwi, peach, onion and cucumber. The chemopreventive, chemotherapeutic and antioxidant effects of fisetin are well-known in the literature [110]. Lin et. al. [110] reported that fisetin had anticancer effects on cervical cancer and glioma. In the same study, it was also demonstrated that the combination therapy of fisetin and sorafenib against HeLa cells was effective by interfering apoptosis signaling pathways, both *in vitro* and *in vivo*. In another study, the chemosensitizing effects of fisetin in both IRT- and OXP-resistant colon cancer cells *in vitro* and *in vivo* through promoting caspase-8 and cytochrome-C expressions likely by inhibiting the insulin-like growth factor 1 receptor (IGF-1R) and Akt proteins and also suppressing the tumor growth has been reported by Jeng et. al. [111].

Genistein (**6**) (Figure 5), is a soy derived isoflavonoid compound that is first isolated from *Genista tinctoria* in 1899. In the literature, it has been reported that genistein has antioxidant, anticancer, cardioprotective, hepatoprotective and immunosuppressive activities [112]. The combination of genistein, as a chemosensitizing agent, and FOLFOX or FOLFOX-Bevacizumab is found safe and tolerable in patients with metastatic colorectal cancer (CRC) in a Phase I/II trial [113]. Huang et. al. [114] demonstrated that genistein could overcome MDR in PTX-resistant ovarian cancer (SKOV3) cells by inhibiting androgen receptor (AR) activation and suppression of AR-driven genes *in vitro*.

Hesperetin (**7**) (Figure 5), which is a derivative of hesperidin, is extracted from tangerine peel and exhibits multiple antitumor activities. It has been reported that this flavanone compound has MDR-reversal activity against P-gp-mediated CIP resistance on CIP-resistant human lung cancer (A549/DDP) cells *in vivo*.

Isorhamnetin (IH) (**8**) (Figure 5) is a plant-derived secondary metabolite isolated from *Hippophaer hamnoides* L. and *Oenanthe javanica*. This compound has hepatoprotective, antioxidant, antimicrobial, antidiabetic, anti-inflammatory and anticancer activities [115]. Manu et. al. [116] stated that IH has enhanced the antitumor effect of capecitabine by eliminating the activation of NF-κB pathway and suppressing the expression of various NF-κB regulated gene products in gastric cancer cell (AGS, SNU-5 and SNU-16) lines.

Kaempferol (Kae) (**9**) (Figure 5) is the major flavonoid obtained from *Zingiberaceae Kaempferia* rhizome and it is generally presented in glycosidic form in nature. It has important biological functions such as cardiovascular, antioxidant, antidiabetic, anti-inflammatory, hepatoprotective and neuroprotective effects [117]. Moradzadeh et. al. [118] reported that Kae has increased apoptosis in human acute promyelocytic leukemia (HL60 and NB4) cells and also inhibited the MDR-related *ABCB1* and *ABCC1* gene

expressions *in vitro*. In another study, Nair et. al. [119] investigated the interaction energy of Kae with MRP1 protein using an *in silico* method. After that, they tested the MDR-reversal activity of Kae in liver cancer (HepG2 and N1S1) cells *in vitro* and they concluded that Kae has sensitized HepG2 and N1S1 to sorafenib via decreasing the overexpression of P-gp.

Licochalcone A (LCA) (**10**) (Figure 5) is a natural chalcone that can be isolated from the root of *Glycyrrhiza inflata* (licorice). This compound has antiprotozoal, antiviral, antifungal, antimicrobial and anti-inflammatory activities. Also, LCA reverses *ABCG2*-mediated MDR in human multidrug-resistant cancer cell lines in a concentration-dependent manner. This activity was confirmed by *in silico* docking analysis from the interactions of the human *ABCG2* protein with LCA at the drug binding site [120].

Quercetin (**11**) (Figure 5), is a bioflavonoid that cannot be produced in human body. It is widely found in different types of fruits and vegetables such as fennel, tea, coriander, grape, onion and pepper. Quercetin has been reported as an antioxidative, anti-inflammatory, antihypertensive, antiobesity, anti-hypercholesterolemic, anti-atherosclerotic, anticancer and antitumor agent. However, it is mostly used in the treatment of metabolic and inflammatory disorders [121,122]. Sun et. al. [123] reported that quersetin acted synergistically with metformin (MET), by inhibiting the growth, migration and invasion of human prostate cancer (PC3 and LNCaP) cells through modulating the VEGF/Akt/PI3K pathway both *in vitro* and *in vivo*. In another study, Maruszewska and Tarasiuk [124] found that quercetin has induced the apoptotic and lysosomal cell death of sensitive HL60 and MDR-leukemia (HL60/VINC and HL60/MX2) cells acting upon caspase-3, -8 and lysosome membrane permeabilization-dependent mechanisms *in vitro*. Several studies have revealed that quercetin play an important role in reversing MDR activity in many cancer cells such as hepatoma cells (by inhibiting the Frizzled homolog protein 7 (FZD7)/*β*-catenin pathway), KB/VCR oral cancer cell (triggering apoptosis by inhibiting Bax and inducing caspase-3 and Bcl-2 expressions), K562 leukemia cell (by affecting MAPK/ERK/JNK signaling pathway). Unfortunately, the mechanism of MDR reversal activity of quercetin has not yet been fully explored [125].

Tea polyphenols (*Theaceae*) (Figure 5) such as gallic acid (GA), epigallocatechin (EGC), catechin (C), EGCG, epicatechin gallate (ECG), and epicatechin (EC), have been reported as chemosensitizing agents in Bleomycin-resistant cervical cancer (SiHa) cells as well as CIP-resistant breast cancer (MCF-7) and non-small cell lung cancer (A549) cells [126].

δ-Tocotrienol (δ-T3) (**12**) (Figure 5), is an important component of vitamin E, is obtained from rice and has multiple physiological functions, such as anticancer and anti-inflammatory activites [127]. Thomsen et. al. [128] showed that δ-T3 and bevacizumab combination therapy has been effective in multiresistant ovarian cancer in a phase II trial. Another study demonstrated δ-tocotrienols synergistically enhance the anticancer activity of ethyl acetate extract (9EA) of *Acalypha wilkesiana* at lower dose by inducing apoptosis in lung cancer cells [129]. Khatoon et. al. [96] reported that there were numerous studies indicating that the combination of T3 and celecoxib (CXB), or erlotinib, ferulic acid, RES, DHA, sesamin has been found successful in chemosensitizing the breast cancer cells by downregulating the expression of Akt, NF-κB and STAT3, and their related gene products.

Lignans are a group of phenolic compounds that are widely found in the plant kingdom and today they are known for their antitumor properties [130].

Arctium lappa (burdock) is a well-known medicinal plant that is used in Traditional Chinese medicine (TCM) and Europe due to its potential for treating arthritis, baldness and cancer. Su et. al. isolated six lignan compounds (arctigenin (**13**), matairesinol (**14**), arctiin (**15**), (iso)lappaol A (**16**), lappaol C (**17**), and lappaol F (**18**)) given the formulas in Figure 5, from *A. lappa* seeds and they tested their MDR reversal potentials in the MDR cancer cell (CaCo2 and CEM/ADR 5000) lines overexpressing P-gp and other ABC transporters. When they applied each lignans in combination with DOX to MDR cancer cells, they observed that all compounds showed synergistic effects in CaCo2 cells as well as matairesinol, arctiin, lappaol C and lappaol F displayed synergistic activity in CEM/ADR 5000 cells. They even revealed that the MDR reversing activity has enhanced when they applied each of the lignans together with DOX and digitonin (a steroidal saponin). Moreover, they concluded that the isolated lignan compounds could only inhibit the activity of P-gp except lappaol C. Lappaol C showed inhibition potential on both P-gp and other ABC transporters [131].

Honokiol (**19**) (Figure 5), is an anticancer biaryl-type lignan compound isolated from *Magnolia* plants. It has recently been popular for its immune boosting and cancer regulating properties. This phytochemical can interfere with many cancer-related pathways such as sonic hedgehog (SHH), STAT3, NF-κB, mTOR, EGFR and MAPK. Thus, it can induce apoptosis, suppress the cell proliferation, and decrease the expression of CSC markers and P-gp *in vitro* and *in vivo* [132]. Ong et. al. [133] stated that the down-regulation of the P-gp expression in MDR breast (MCF-7/ADR) and MDR ovarian cancer (NCI/ADR-RES) cells by honokiol was achieved.

Phenolic acids are another phytochemicals obtained from natural sources. They get much attention because of their multiple pharmacological actions such as antioxidant and antitumor properties. Caffeic, gallic, rosmarinic, carnosic, ferulic, *p*-coumaric and vanillic acid are naturally occurring phenolic acids in plants [134]. Among them, caffeic acid stands out with its anti-inflammatory, antibacterial and antiviral effects. It has also reported that caffeic acid has MDR reversal

activity on human cervical epithelioid carcinoma (HeLaS3) cells [135].

Stilbenoids are naturally occurring phenolic compounds found in plants such as *Morus alba*, *Pterocarpus marsupium*, *Vitis* sp., *Gnetum* spp., *Rheum* sp. and *Passiflora* species. They are phytoalexins with antimicrobial activities to protect the plants against various fungal pathogens and toxins. Also, their cardioprotective, anti-atherosclerotic, anticancer, antidiabetic and anti-obesity activities have been reported in the literature [136].

Resveratrol (**20**) (Figure 5), that is found in more than 70 plant species, contains two phenol rings linked to each other with an ethylene bridge. Its anticancer activity has been showed in several *in vitro* and *in vivo* studies at different carcinogenesis stages such as the initiation, promotion and progression [137]. Guo et. al. [138] reported that the co-delivery of RES and DTX at a ratio of 1:1 (w/w) to human MCF-7 cells via a polymeric MPEG-poly-*D*-lactide (PDLA) nanocarrier has increased the cytotoxicity of each compound, therefore this combination has offered a promising approach to treat drug-resistant tumors. In a review published by Sameiyan and her colleagues [139], it has been stated that RES reduced the cell survival by inducing autophagy in drug-resistant K562/ADM cells. Also, it triggered the autophagic cell death via the inhibition of Akt and enhancement of AMPK signaling in CIP-resistant human oral cancer (CAR) cells. RES has also been found beneficial in many *in vitro* and *in vivo* studies in order to defeat MDR by inhibiting drug-metabolizing enzymes such as CYP1A1 and CY1B1, inducing DNA breakage, regulation of cell cycle activity, evasion of apoptosis acting upon different metabolic pathways and reducing the function or expression of drug transporters [140]. Wang et. al. [141] mentioned that RES could downregulate the MDR1 expression by inhibiting NF-κB signaling pathway in OXP-resistant colorectal cancer cells (CRCs).

4.1.2. Alkaloids

Alkaloids are low-molecular-weight compounds containing nitrogen atoms in their structures. These compounds are basic in character since they have a nitrogen-containing heterocyclic ring and many of them are toxic. They are known for their antimicrobial, antifungal, anti-inflammatory, antipsychotic, antihypertensive, anti-diuretic, adrenolytic and hepatoprotective activities, also their cytotoxic effects on human healthy and cancer cells lines in the literature. Alkaloid compounds are divided into more than 20 different subclasses such as pyrrolidine alkaloids, piperidine alkaloids, quinolizidine alkaloids and tropane alkaloids according to their bioprecursors [87,142,143].

Berberine (**21**) (Figure 6), an isoquinoline alkaloid purified from the *Berberis* species, is known for its multiple pharmacological properties such as antibacterial, anti-hypertensive, and anti-arrhythmic activities [144]. There are several studies demonstrating that berberine has MDR reversal activity in many cancer cell lines *in vitro* and *in vivo* [144-146]. Liu et. al. [147] indicated that the combination treatment of berberin and CIP could inhibit the proliferation of human ovarian cancer (OVCAR3) cells in a dose- and time-dependent manner via inducing necroptosis and apoptosis in these cells. Another study conducted by Pan et. al. [148] has revealed that low-dose berberin sensitizes the MCF-7/hypoxia cells to DOX, besides its higher doses directly induce apoptosis in MCF-7/hypoxia cells *in vitro* and *in vivo* through the AMPK-HIF-1α-P-gp pathway.

Dioncophylline A (**22**), **Dioncophylline C** (**23**) and **Mbandakamine A** (**24**) (Figure 6) are naphthylisoquinoline alkaloids, which are present in Dioncophyllaceae and Ancistrocladaceae families, have significant antiproliferative effects in breast cancer (MCF-7 and MDA-MB-231) cell lines by the mechanism of inducing the apoptotic cell death via intrinsic pathway. They are potential drug candidates in the treatment of MDR-resistant breast cancers as well [149].

Dregamine (**25**) and **Tabernaemontanine** (**26**) (Figure 6), two major epimeric alkaloids isolated from *Tabernaemontana elegans*, are from the class of monoterpene indole alkaloids. Their MDR-reversing activity was reported by Cardoso et. al. [150] related to their P-gp inhibitory effects in resistant human colon cancer (COLO 320) and mouse T-lymphoma (L5178Y, MDR) cells *in vitro*.

Nuciferine (27) (Figure 6), an alkaloid from *Nelumbo nucifera* and *Nymphaea caerulea*, can sentisitize HCT-8/T and A549/T cancer cells to PTX, DOX, DTX and daunorubicin (DRB). Also, it suppresses the colony formation of MDR cells *in vitro* and the tumor growth in A549/T xenograft mice *in vivo* [151].

Piperine (28) (Figure 6), an alkaloid from black (*Piper nigrum* L.) and long peppers (*Piper longum* L.), has a great antitumor potential *in vitro* and *in vivo*. Piperin enhaces the anticancer effect of MMC by blocking p-STAT3/p65 and Bcl-2 activation in MDR-resistant cervical cancer (HeLa/MMC) cells *in vitro* and *in vivo* [152].

Piperlongumine (**29**) (Figure 6) is an amide alkaloid obtained from *P. longum*, has the potential to inhibit various multidrug-resistant cancer cells. It enhances the therapeutic sensitivity and suppresses the cell migration, invasion, EMT and proliferation in oral cancer (SAS and CGHNC8) cell lines and also inhibits the tumor growth ability at 2.4 mg/kg dose in SAS mice xenograft by inhibiting cancer stemness and the expression of stem cell regulatory proteins [153].

Reserpine (**30**) (Figure 6) is an indole alkaloid from *Rauwolfia serpentina*, shows a great antitumor activity

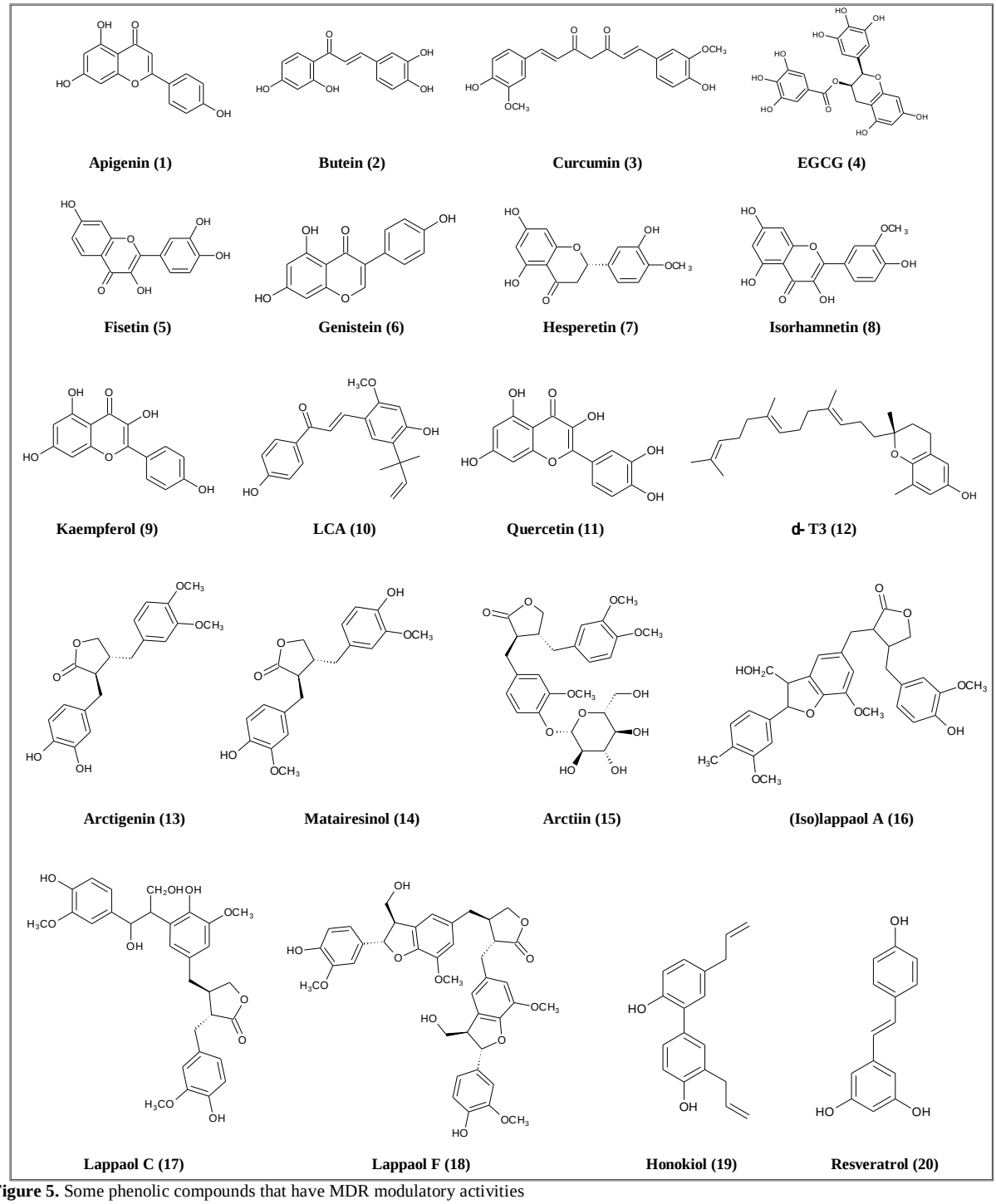

Figure 5. Some phenolic compounds that have MDR modulatory activities

against cancer cells *in vitro* and *in vivo*. It sensitizes the resistant leukemia (CEM/ADR5000), breast (MDA-MB-231BCRP), colon (HCT116 $p53^{-/-}$) and glioblastoma (U87MG.Δ*EGFR*) cells to anticancer drugs through inhibiting the efflux function of P-gp [154].

Tetrandrine (31) (Figure 6) isolated from the root of *Stephania tetrandra* S Moore, has been traditionally used in Chinese Medicine in the treatment of autoimmune disorders, inflammatory pulmonary diseases, cardiovascular diseases and hypertension. Tetrandrine is a good chemical starting point for developing new MDR-reversing agents due to its potent inhibition properties on P-gp. It has been stated that tetrandrine is a chemosensitizing agent in multidrug-resistant cancer cells such as human epidermoid carcinoma (KBυ200), leukemia (CEM/ADR5000), human T lymphoblastoid leukemia (MOLT-4/DNR) and human chronic myeloid leukemia (K562/A02) cells. Moreover, it increases the cytotoxicity of CIP in ovarian cancer cells by suppressing the cell growth and induction of apoptosis via the modulation of the Wnt/cadherin signaling pathway. Another MDR-overcoming mechanisms of tetrandrine are reducing the

migration and invasion in HCT116 cells and also triggering the apoptotic cell death in human HeLa, hepatoma (Huh7 and FHCC98), human glioma (U87 and U251) and human lung (Calu-1 and A549) cells via ROS production and cyclin-dependent kinase inhibitor 1 ($p21^{CIP1/WAF1}$) expression [155].

Wilforine (**32**) (Figure 6) is a sesquiterpene pyridine alkaloid from *Tripterygium wilfordii*. Hook. F. that possess many therapeutic functions in order to treat rheumatoid arthritis, HIV/AIDS, Crohn's disease and cancers. It has been reported that Wilforine competitively and effectively inhibits the efflux activity of P-gp in a concentration-dependent manner in human cervical cancer (HeLaS3 and KBvin) cells and it also promotes PTX-induced apoptosis in multidrug-resistant KBvin cells [156].

4.1.3. Terpenoids and steroids

Terpenoids, consist of C_5H_8 isoprene units, are the largest family of natural products that include more than 40.000 oxygen-containing terpene analogues. They are widely found in plants [157]. To date, numerous terpenoid compounds have been found to show cytotoxic and anticancer activities against various tumor cells in preclinical animal models [158]. According to the number of isoprene units, terpenoids are named as monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}) and triterpenes (C_{30}), respectively [87].

Carotenoids also called tetraterpenoids (C_{40}), are the organic pigments that are widely distributed in plants. They are divided into two main groups as carotenes (*β*-carotene) and xanthophylls (crocin, canthaxanthin and fucoxanthin) based on the presence or absence of oxygen atom in the structure. Their antioxidant capacities are well-known in the literature. The MDR modulatory activity of capsanthin, lycopene, lutein, antheraxanthin, violaxanthin, zeaxanthin and capsanthin have been reported against MDR1 in different types of cancer cell lines [159]. Carotenoids can inhibit the expression of oncogenes and angiogenesis as well as induce the apoptosis [160]. Recently, Eid et. al. [161] demonstrated that fucoxanthin (**33**) (Figure 7) could sensitize the multidrug-resistant breast (MCF-7/ADR), liver (HepG-2/ADR) and ovarian (SKOV-3/ADR) cancer cells to DOX by the induction of apoptosis *in vitro*. On the other hand, *β*-carotene displayed a synergistic MDR reversal activity with DOX on KB-vin and NCI-H460/MX20 cell lines via inhibiting human P-gp efflux function without altering *ABCB1* mRNA expression [162].

Diterpenes are a large class of isoprenoid-derived compounds that are widely distributed in plants. While diterpene compounds facilitate the adaptation of the plants to the environmental conditions, diterpenoid plant hormones such as gibberellin, stimulate the growth and development of plant species. However, most of these compounds have specialized functions specific to a single plant genus, family or species. They have multiple therapeutic actions including antimicrobial, anticancer (Taxol from *Taxus brevifolia*), psychotropic (Salvinorin A from *Salvia divinorum*), keratosis (Ingenol mebutate from *Euphorbia sp.*), antioxidant (carnosic acid from *Rosmarinus officinalis*) and cAMP modulatory (forskolin from *Coleus forskohlii*) activities [163].

Ingol-3,7,12-triacetate-8-benzoate (**34**) (Figure 7) is a diterpenoid isolated from *Euphorbia royleana*, acted as an inhibitor of P-gp and potentiated the efficacy of DOX at 10 μM in DOX-resistant human HCC (HepG2/DOX) cell line [164].

Yang et. al. [165] reported that three lathyrane diterpene compounds (compound **35**, **36** and **37**) (Figure 7) from *Euphorbia lathyris* seeds, showed potent MDR reversal activity in HepG2/ADR cells likely via suppressing P-gp overexpression or decreasing the efflux of P-gp regulated by chemotherapeutic drugs. Similarly, lathyrane-type diterpenoid **EM-E-11-4 (38)** (Figure 7) extracted from *Euphorbia micractina*, had good chemosensitizing activity in PTX-resistant tumor (A549/Tax) cells overexpressing either P-gp or *β*III-tubulin *in vitro* [166].

The MDR modulatory activities of Jatrophane diterpenoids from *Pedilanthus tithymaloides*, were tested on HepG2/ADR and MCF-7/ADR cancer cells by Zhu et. al. [167] and they reported that (1*S*,2*S*,3*S*,4*S*,7*R*,9*R*,13*R*,14*R*,15*S*)-9,15-fiacetoxy-3,7-dibenzoyloxy-1,13,14-trihydroxyjatropha-5*E*-ene (compound **39)** (Figure 7) exhibited remarkable *in vitro* stability as well as a favourable antitumor activity *in vivo*, thus compound **39** was specified as a promising lead molecule for new MDR-reversing anticancer agents. In another study, nicaeenin F and nicaeenin G (jatrophane diterpenoids from the latex of *Euphorbia nicaeensis*) have been found to show a significant inhibitory effect in two MDR cancer (NCI-H460/R and DLD1-TxR) cells [168].

Segetane and ingenane skeletons were first discovered from the methanol extract of *Euphorbia taurinensis* All. by Redei et. al. [169]. Among the isolated diterpenoids, ingenanes (**40**, **41**) and segetane (**42**) (Figure 7) showed remarkable *ABCB1*-modulating activities at 20 μM concentration in mouse T-lymphoma cells (PAR).

Epoxylathyrane derivatives obtained from the derivatization of epoxyboetirane A which is a lathyrane-type macrocyclic diterpene isolated from *Euphorbia boetica*, were evaluated against mitoxantrone (MTX)- or DRB-resistant human gastric, pancreatic and colon cancer cells by Reis et. al. [170]. They concluded that compounds epoxyboetirane P, methoxyboetirane B and methoxyboetirane C had the best potential as MDR-modifying agents. In addition, methoxyboetirane B (**43**) and methoxyboetirane C (**44**) (Figure 7) induced apoptosis via caspase-3 activation in MDR cancer cell lines.

Royleanone derivatives from *Plectranthus* spp. has been reported that as a novel class of P-gp inhibitors

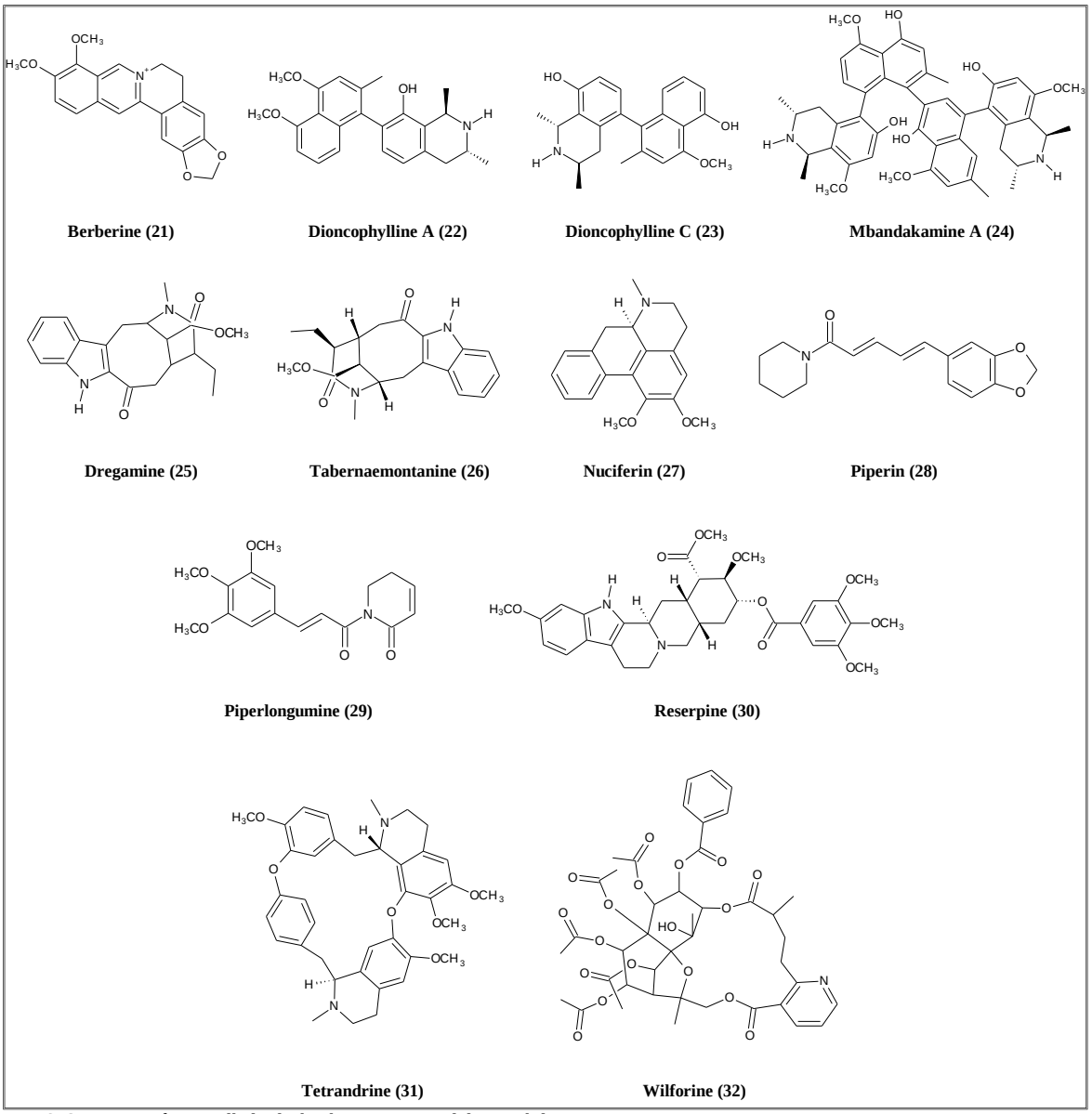

Figure 6. Structures of some alkaloids that have MDR modulation abilities

against human non-small cell lung carcinoma (NCI-H460 and NCI-H460/R) cells. Of these diterpenoids, compound **45** (Figure 7) showed significant P-gp inhibitory activity and it also sensitized the resistant NCI-H460/R cells to DOX *in vitro* [171].

Ginsenosides, triterpene saponin components of *Panax ginseng* that is one of the most reliable medicinal plants used in Asia and North America, contain a four trans-ring steroid skeleton divided into several groups. Ginsenosides have multiple pharmacological actions such as anticancer, antidiabetic, immunomodulatory, cardioprotective, neuroprotective, antiamnestic and antistress effects. Nonetheless, they stand out for their chemoprotective and chemotherapeutic activities both *in vitro* and *in vivo* [172,173]. The combination therapy of ginsenoside Rg5 (**46**) (Figure 7) and DTX was reported as a promising strategy in order to suppress the expression of Nrf2 and phosphorylation of AKT as well as induce apoptosis in PTX-resistant lung and ovarian cancer cells *in vitro* and *in vivo.*

Limonoids are abundant in the Meliaceae plants and they have a wide variety of potent bioactivities such as antibacterial, antimalarial, anti-multidrug resistance (MDR), insecticidal, antifeedant and anti-inflammatory activities. Ciliatasecone F (**47**) and 7-acetylneotrichilenone (**48**) (Figure 7), limonoid compounds isolated from the barks of *Toona ciliate* var. *yunnanensis* (Meliaceae), found to be highly effective in reversing resistance in MCF-7/DOX cells at a non-cytotoxic concentration of 50 μM [174]. Another novel limonoid, tooniliatone A (**49**) (Figure 7) was isolated from the air-dried stem bark of *Toonaciliata* Roem, and it showed MDR-reversal activity in K562/MDR and MCF-7/MDR cell lines by decreasing Bcl-xL via activation of JNK MAPK signaling [175].

Monoterpenes are a very large and diverse subclass of natural products, consisting of two isoprene units connected to each other. They are generally found in the composition of essential oils and these compounds have antifungal, antimicrobial, antiviral, anti-

inflammatory, antitumor, antioxidant, anxiolytic and analgesic activities. Geraniol, linalool, nerol (acyclic), thymol, (-)-mentol, eugenol (monocyclic), α-pinene, (+)-camphor, (-)-borneol are very familiar monoterpenes nowadays [176]. Thymoquinone (**50**) (Figure 7) (from *Nigella sativa* seeds) is a monoterpene that enhances the antitumor activity of CIP in human gastric cancer (SGC-7901, HGC-27 and MGC-803) cells by down-regulating P-gp and up-regulating *PTEN* gene *in vitro* and *in vivo* [177]. Similarly, thymoquinone shows antitumor activity in combination with PTX in mouse breast cancer (4T1) cells *in vitro* via increasing the cleaved caspase -3, -7, -12 protein levels and reducing phosphorylated p65 and Akt1. These data are also supported by the fact that thymoquinone increases the sensitivity of cancer cells to PTX *in vivo* [178].

Triterpenes are natural alkene derivatives that are presented in vegetables, animals and fungi. Due to their structural diversity, they have various pharmacological properties such as anticancer, anti-inflammatory, antioxidative, antiviral and antimicrobial activities. To date, the anticancer activity of many natural triterpenoids (e.g., betulinic acid, oleanolic acid, ursolic acid and lupeol) has been reported in the literature [179].

Betulinic acid (**51**) (Figure 7) is a pentacyclic triterpenoid obtained from the bark of the white birch (*Betula pubescens*). It was able to reverse the MDR of tested MCF-7/taxol and MDA-MB-231/taxol cells *in vitro* as well as MDA-MB-231 cells in mice xenograft by triggering ER stress-mediated apoptosis via directly targeting glucose regulatory protein 78 (GRP78) [180]. Furthermore, betulinic acid showed potent antitumor activity on PTX-resistant human lung carcinoma (H460) cells by the induction of mitochondrial apoptosis and cell cycle arrest at G_2/M phase [181]. From another point of view, Jin et. al. reported that [182] DOX/betulinic acid micelles enabled each molecule together to successfully reach the ovarian cancer cells, increased the anticancer activity and decreased off-target effects in the target tissue. In addition, these micelles showed less cardiac toxicity and leukocyte counts in Skov3 subcutaneous xenograft models.

Celastrol (**52**) (Figure 7), purified from the plant *Tripterygium wilfordii*, is a pentacyclic triterpenoid whose MDR modulatory activity has been extensively investigated in recent years. Celastrol overcomes multidrug resistance in many cancer cell lines (e.g., non-small cell lung cancer (PC-9/GR and H1975), anaplastic thyroid carcinoma (8505C and SW1736), oral cancer (SASV16), multiple myeloma (U266, H929 and KMS11) and HCC (Hepa1-6) cells) in combination with tyrosine kinase inhibitors or other chemotherapeutics *in vitro* and/or *in vivo* [183-188].

Lupeol (**53**) (Figure 7), is a dietary triterpene, presented in many medicinal plants (*Zanthoxylum* genus), various fruits and vegetables. Lupeol was found to restore the DOX sensitivity of culture multidrug-resistant CEM/ADR5000 leukemia, MDA-MB-231-BCRP breast, HCT116 $p53^{-/-}$ colon and U87MG.Δ*EGFR* glioblastoma cancer cells via multiple mechanisms *in vitro* [189]. In another study conducted by Chen et. al. [190], it was demonstrated that lupeol altered endoplasmic reticulum (ER) stress-signaling pathway via down-regulating *ABCG2* expression with the aim of apoptosis induction in OXP-resistant colorectal cancer (LoVo) cell line.

Oleanolic acid (**54**) (Figure 7), is another plant-derived triterpene which has potent pharmacological properties, especially anticancer activities. Oleanolic acid inhibits the growth of multidrug-resistant liver cancer (HepG2) cells by the induction of apoptosis and deactivation of JNK/p38 signalling pathway *in vitro* [191]. Additionally, Mbaveng et. al. [192] have revealed that *N*-acetylglycoside of oleanolic acid (aridanin) (**55**) (Figure 7) is a promising MDR modifier due to its apoptotic, ferroptotic and necroptotic effects on human leukemic cell (CCRF-CEM) line and its vast potential in combating multifactorial resistance in CEM/ADR5000 cells.

Ursolic acid (**56**) (Figure 7), a pentacyclic triterpene, is found in many fruits, vegetables and medicinal herbs such as *Eriobotrya japonica, R. officinalis,* apple peels and cranberries. It exhibits MDR modulatory effect on P-gp transporter in MCF-7/ADR cells and also it disrupts the energy metabolism and related amino acids *in vitro* [193]. Another anti-MDR activity of ursolic acid has been reported by Prasad et. al. [194] due to its inhibition potential on human pancreatic cancer (AsPC-1 and MIA PaCa-2) cells and the sensitizing effect to GEM *in vivo*.

Momordica balsamina triterpenoids have a chemosensitizing effect on drug-resistant gastric (EPG85-257RNOV, EPG85-257RDB), pancreatic (EPP85-181RNOV, EPP85-181RDB) and colon (HT-29RNOV, HT-29RDB) cancer cells via the modulation of P-gp function [195].

Steroids are an important class of compounds that contain a cyclopentanoperhydrophenanthrene ring and some rearranged forms. They are structural components of the cell membranes and are involved in many physiological functions. Steroid compounds are known to be highly lipophilic and they have great enhancement potential due to their low cytotoxicity and high bioavailability properties as in abiraterone. They have been shown in the literature to be effective in many types of cancer, including MDR-related cancers due to their steroid sulfatase inhibitory, aromatase inhibitory, 17*β*-hydroxysteroid dehydrogenase inhibitory activities [196]. Xiao et. al. [197] reported that aglaiasterols D (**57**) (Figure 8), isolated from *Aglaia abbreviate* stems, showed good antitumour activity against drug-resistant K562/A02, MCF-7/ADM, KB/VCR cancer cell lines at a micromolar concentration range. In another study conducted by Kong et. al. [198], guggulsterone (**58**) (Figure 8), a phytosterol isolated gum resin of the tree *Commiphora mukul*, has been found to be an efficient chemosensiti-

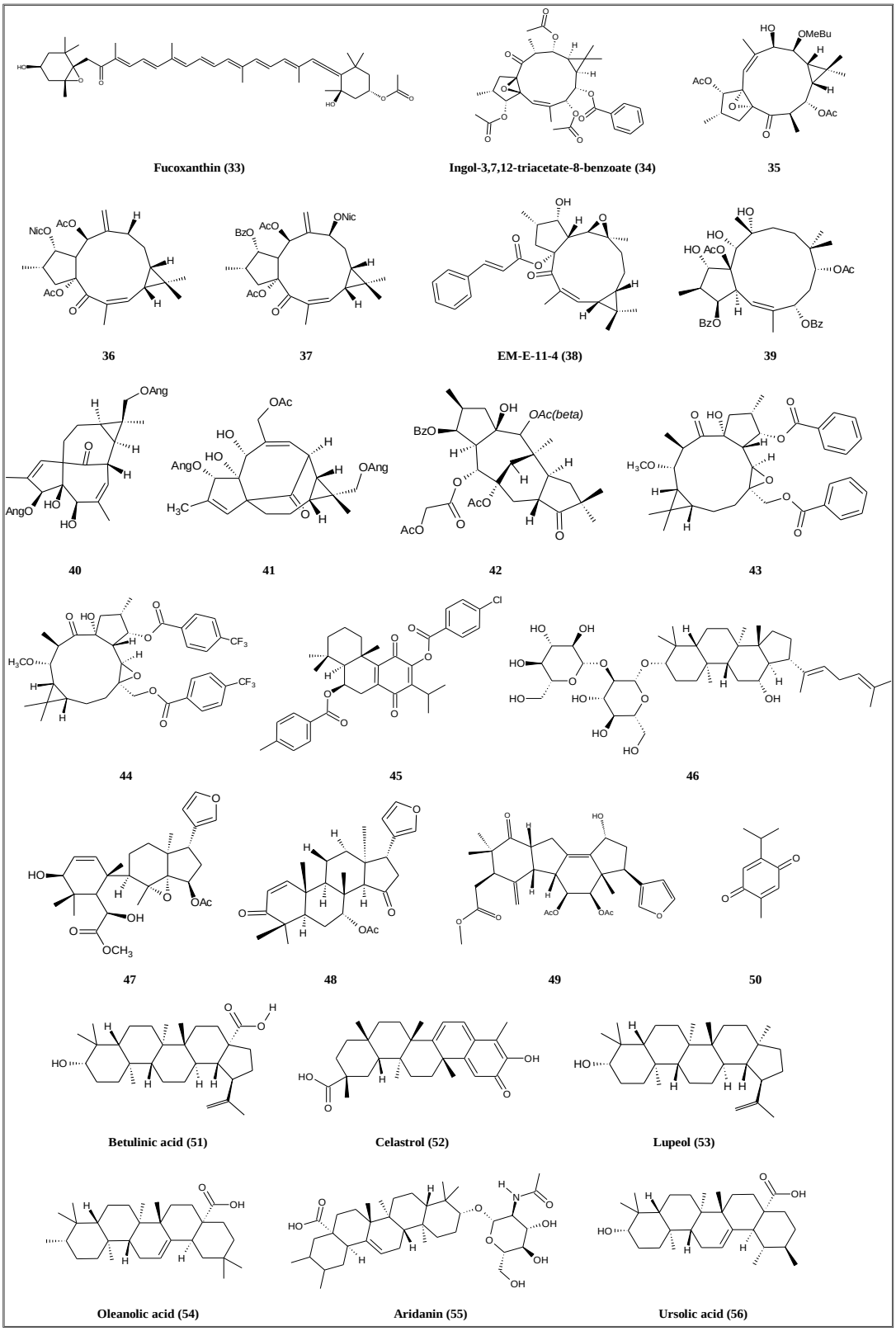

Figure 7. Chemical structures of some selected terpenoids as MDR reversal agents

zer against DOX when combined with bexarotene (retinoid X receptor agonist) in MDA-MB-231 breast cancer cells [199]. Ku et. al. [200] reported that Cucurbitacin D induced apoptosis via Stat3 and NF-κB signaling in human DOX-resistant breast cancer (MCF7/ADR) cells. Withanolide E (**59**) (Figure 8) from the indigenous South American plant *Physalis peruviana*, has a great potential in sensitizing human renal adenocarcinoma (ACHN, CAKI-1 and SN12-C) cells to tumor necrosis factor-related apoptosis inducing ligand (TRAIL)-mediated apoptosis *in vitro* and *in vivo* by the specific modulation of heat shock

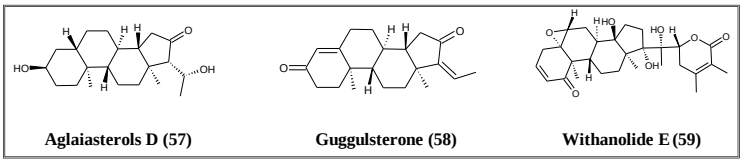

Figure 8. Chemical structures of aglaiasterols D, guggulsterone and withanolide E

protein 90 (HSP90) function resulting in cFLIP (an anti-apoptotic regulator) degradation [201].

4.1.4. Miscellaneous secondary metabolites

4.1.4.a. Organosulfur compounds

Organosulfur compounds are generally present in cruciferous vegetables such as onion, garlic, broccoli, brussel sprouts and cauliflower. Sulfur atoms in their structure are attached to a cyanate group or a carbon atom in a cyclic or noncyclic configuration. Various isocyanates consist of glucosinates in cruciferous vegetables as a result of the activity of myrosinase enzyme. Their chemopreventive and anticancer activities have been well-known in the literature [202]. Yang et. et. [203] demonstrated that sulforaphane (**60**) (Figure 9), in combination with DOX, induced autophagy by down-regulating the expression of *HDAC6* in triple negative breast cancer (BT549 and MDA-MB-468) cells *in vitro*. Also, *in vivo* assay results indicated that sulforaphane and DOX combination had a significant inhibitory activity in MDA-MB-231 xenografts. Pawlik et. al. [204] also reported that *R*, *S*-sulforaphane and erucin (**61**) (Figure 9) potentiated the anticancer effect of 4-hydroxytamoxifen at low concentrations in TAM-resistant breast cancer (MCF-7 tamR and T47D tamR) cells via down-regulation of anti-apoptotic proteins such as Bcl-2 and survivin and induction of cell death.

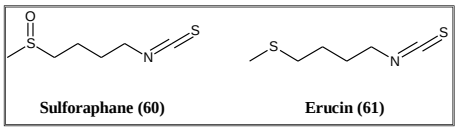

Figure 9. Examples of organosulfur compounds as chemosensitizers

The detailed list of natural molecules of plant origin whose preclinical properties have been investigated in 2015-2020 is given in Table 3.

5. Conclusion and Future Perspectives

Chemoresistance is one of the major obstacles in the treatment of various cancer types. As the frequency of cancer cases has increased around the world and the relatively low success rates have been achieved in traditional drug treatments, there has been a trend towards multitargeted drug therapies that enable minimizing adverse effects in the field of oncology.

Plant secondary metabolites have a unique potential for the discovery of novel anticancer agents that possess a wide range of structural and chemical diversity, good drug-like properties, most likely better toxicity profiles and multitargeted pharmacological actions [205,206]. The use of plant-derived compounds as chemosensitizing agents, alone or in combination with another anticancer drug, reflects a clinically relevant approach to overcome MDR by modulating one or more resistance mechanisms [96]. To date, MDR-modulatory effects of different types of secondary plant metabolites such as phenolics, alkaloids, terpenoids and steroids on various cancer cells have been evaluated in the preclinical experiments, but clinical studies are needed to fully understand the *in vivo* activities of these phytochemicals. In addition to *in vitro* and *in vivo* studies, the analysis of structure-activity relationships of biologically active secondary metabolites and integrating of *in silico* models to drug development process may be good alternatives to traditional drug design methods in terms of achieving more potent and less toxic drug leads and revealing the mechanisms of interaction with biomolecular targets related to MDR [79,207]. Another common approach to reverse the MDR effect is to use the nanocarriers such as liposomes, dendrimers, carbon nanotubes and dendrimeric micelles in order to deliver anticancer drugs to their biological targets, with or without chemosensitizing agents. Nanocarriers are superior in eliminating the unfavourable properties of different chemotherapeutics such as nonspecific biodistribution and targeting, low solubility and low therapeutic index values [208].

In the last ten years, more than 3000 antimicrobial peptides (AMPs) have been isolated and identified from different types of species, including higher plants. Many AMPs are known for their anticancer properties today and some of them have already entered clinical trials. They attract attention for offering a new therapeutic approach in the treatment of MDR-related cancers by acting through different mechanisms [209,210].

One of the most important MDR mechanism in cancer is the overexpression of ABC transporters. However, there are no clinically approved ABC modulators to reverse drug resistance caused by ABC transporter proteins [211]. Researches for discovering novel ABC modulators from phytochemicals make significant contributions to the development of new therapeutic approaches that will effectively destroy drug-resistant cancer cells.

To summarize, the use of natural plant-derived molecules as mostly chemosensitizers to overcome multidrug resistance in cancer is a new therapeutic approach. Therefore, there is an urgent need to discover novel chemosensitizing agents that will allow the anticancer drug to remain in the tumor tissues for a longer time, initiate DNA damage, stimulate apoptosis

via upregulation of pro-apoptotic proteins or regulate the expression of drug targets [96]. Additionally, it is also important to define the synergistic or antagonistic effects of phytochemicals using in combination with anticancer drugs.

The *in vivo* efficacy and safety profiles of newly discovered natural molecules of plant origin need to be well-defined in clinical studies. More effort should be made to identify novel drug resistance mechanisms in various cancer cell types and also explore the vast potential of plant-based natural products for the development of novel MDR modulating agents in cancer therapies.

Table 3. Plant-derived natural products and their *in vitro* and *in vivo* effects on various cancer cells

Phenolic Compounds					
Compound	**Source**	**Combination**	**Experimental Model**	**Mechanisms of Overcoming MDR**	**References**
Acacetin	*Turnera diffusa* & *Robinia pseudoacacia*	DOX	A549 and H1299	↓ Cell proliferation, ↑ G_2/M cell cycle arrest, ↑ DOX uptake, ↓ MDR1 expression	[212]
2-Acetyl-7-methoxynaphtho[2,3-*b*]furan-4,9-quinone (AMNQ)	*Milletia versicolor*	-	CEM/ADR5000, MDA-MB-231-BCRP, HCT116 $p53^{-/-}$ and U87MG.Δ*EGFR*	↓ Cell proliferation, ↑ apoptosis, ↓ mitochondrial membrane potential, ↑ ROS levels	[213]
Apigenin	*S. officinalis*, *Lawsonia inermis*, *Turnera aphrodisiaca*, *O. basilicum*, *T. indica*, *Matricaria chamomilla*	CIP	$CD44^+$ stem cells from human PC3	↑ Apoptosis, ↑ cell migration, ↓ Bcl-2, ↑ Apaf-1, P21 and p53, ↓ PI3K/Akt and NF-κB signaling pathway, ↑ sensitivity to CIP	[91]
		DOX	CEM/ADR5000, HEK293-ABCB5 and MDA-MB-231-BCRP	↑ Autophagy, ↓ P-gp and BCRP expressions, ↑ cellular uptake of DOX	[89]
		miR-520b mimics/ inhibitor	BEL-7402/ADM	↓ Autophagy, ↑ miR-520b expression, ↓ ATG7, ↑ sensitivity to DOX	[92]
			miR-520b mice xenograft		
		GEF	NCI-H1975	Metabolism distruption, ↑ cell migration, ↑ G_0/G_1 cell cycle arrest, ↑ apoptosis ↑ E-cadherin, matrix metallopeptidase (MMP)-2 and MMP-9 expressions, ↓ AMPK pathway and autophagy flux, ↓ p-EGFR, HIF-1α, c-Myc, Glut1, and MCT, ↓ Bcl-2 expression, ↑ Bax expression	[90]
Alpinumisoflavone	*Rinorea welwitschii*	-	CEM/ADR5000, MDA-MB-231-BCRP, HCT116 $p53^{-/-}$ and U87MG.Δ*EGFR*	↑ Apoptosis, ↓ mitochondrial membrane potential, ↑ ROS production	[214]
Baicalein	*Radix Scutellariae*	5-FU or Epirubicin	BEL-7402/5-FU	↑ Apoptosis, ↑ autophagy, ↓ P-gp and Bcl-xL expressions	[215]

Table 3. *Cont.*

Baicalin	*Scutellaria baicalensis Georgi (Huang Qin)*	ADM	HL-60/ADM	↓ MDR-related gene expression, ↑ MRP1, LRP and Bcl-2 gene expression, ↓ PI3K/Akt signalling pathway	[216]
Bavachinin	*Psoralea corylifolia* L.	DRB and MTX	EPG85.257RDB and MCF7/MX	↓ Efflux activity of ABC transporters	[217]
Bergapten	*Dorstenia kameruniana*	-	CEM/ADR5000, MDA-MB-231-BCRP, HCT116 $p53^{-/-}$ and U87MG.Δ*EGFR*	↓ Cell proliferation	[218]
Butein	*Semecarpus anacardium*, *Dalbergia odorifera*, *Caragana jubata* & *Rhus verniciflua*	-	HCC827GR	↑ Apoptosis-related protein expression, ↓ phosphorylation and kinase activity of EGFR and MET, ↑ PARP and caspase-3 cleavage, ↓ Bcl-2 expression	[219]
			HCC827GR mice xenograft		
		CIP	HeLa	↑ Percentage of apoptotic cells, ↑ G1 phase arrest, ↓ activation of AKT, ERK/p38 MAPK pathways, ↓ tumor growth, ↑ FoxO3a expression, ↑ sensitivity to CIP	[94]
			HeLa mice xenograft		
Caffeic acid	Herb yerba mate, thyme, *Eucalyptus globulus* and *Cephalaria* sp.	VCR, PTX or DOX	ABCB1/Flp-In™ -293 and KB/VIN	↓ P-gp efflux function	[135]
Cardamonin	*Alpinia* spp.	5-FU	BGC-823/5-FU	↓ Wnt/β-catenin signaling pathway, ↑ apoptosis and cell cycle arrest, ↓ P-gp, *β*-catenin and TCF4 expressions, ↑ sensitivity to 5-FU	[220]
			BGC-823/5-FU mice xenograft		
Carvacrol	*Origanum vulgare*, *Thyme vulgaris* & *Satureja hortensis*	-	PC3	↓ IL-6 protein level, ↓ pSTAT3, pERK1/2 and pAKT signaling proteins, ↓ cell survival, proliferation and invasion	[221,222]
Chrysin	Thai propolis	-	SW48, SW480, SW620, HT-29 and HCT-116	↓ Cell viability, ↑ ROS production, ↑ autophagy, ↑ LC3-II levels, ↓ the phosphorylation of protein kinase B (Akt) and mammalian target of rapamycin (mTOR)	[223]
Chrysoeriol	*Arnebia euchroma* (Royle) Johnst.	-	A549	↓ Cell growth, migration and invasion, ↑ Beclin-1 and LC3-II expressions, ↓ p62 expression, ↑ sub-G_1/G_0 cell cycle arrest, ↓ MAPK/ERK signalling pathway	[224]
			A549 mice xenograft		

Table 3. *Cont.*

Curcumin	Spice turmeric (*C. longa*)	-	Glio3, Glio4, Glio9, Glio11 and Glio14	↓ cell proliferation, ↑ ROS production, ↑ MAPK pathway activation, ↓ STAT3 activity	[101]
		miRNA-378	U87	↓ Cell proliferation, ↑ apoptosis, ↑ P38 signaling pathway	[100]
		-	U87-miR-378 mice xenograft		
		CIP	A549/CDDP	Autophagy/apoptosis switch, ↓ Keap1 transcription, ↑ sensitivity to CIP	[102]
		-	TRAMP C1 mice prostate cells	Reversing CpG methylation at the promoter region of Neurog1 and the hypermethylation of Nrf2	[225]
		EGCG + RES (TriCurin)	UMSCC47 and UPCI:SCC090 HPV16-positive HNSCC	↓ Cell proliferation, ↓ oncogene E6 expression, ↑ p53 levels	[226]
			UMSCC47 mice xenograft		
		5-FU	Mice-bearing human gastric cancer xenografts	Preventing tumor growth, ↓ NF-κB and COX-2 levels	[227]
		Quercetin + Green tea + RES + Cruciferex	Fanconi anemia HNSCC	↓ Cell proliferation, migration and invasion, ↓ MMP-2 and -9 secretion	[228]
			OHSU-974 mice xenograft		
		TSA	Hepa 1-6	↓ Cell growth, ↑ apoptosis, ↓ DNMT1 gene expression	[229]
Curcumin analogues (diketone- and cyclohexanone-)	derived from *C. longa*	VCR or PTX	K562/Adr	↓ P-gp function and/ or expression, ↑ DOX accumulation	[230]
Daidzein	*Glycine max* L., *Trifolium pretense*, *Medicago sativa* L. and *Genista* sp.	*R*-equol + *S*-equol	MDA-MB-231 $BCRP^{+}$	↓ BRCP activity, ↑ sensitivity to MTX	[231,232]
	Hypericum roeperanum Schimp. p. ex A. Rich	-	CCRF-CEM, CEM/ADR5000, MDA-MB-231-BCRP, HCT116 $p53^{-/-}$ and U87MG.Δ*EGFR*	↓ Cell proliferation, ↑ autophagy, ↑ apoptosis, ↓ mitochondrial membrane potential, ↑ ROS production	[233]
Dihydromyricetin	*Vitis heyneana*	OXP or VCR	HCT116/OXA and HCT8/VCR	↓ MRP2 expression and its promoter activity, ↓ NF-κB-Nrf2 signaling	[234]
		OXP	HCT116/OXA mice xenograft		
	Ampelopsis grossedentata	5-FU	SGC7901/5-FU	↓ Cell growth, ↓ MDR1 expression, ↑ apoptosis, ↑ sensitivity to 5-FU	[235]
Ellagic acid	*Fragaria* × *ananassa*, *genus Vaccinium* & *genus Rubus*	Gallic acid	HL60/VINC and HL60/MX2	↑ Apoptotic cell death, ↑ caspase-3 and -8 activation, ↑ ROS levels, ↑ DNA fragmentation	[236]

Table 3. *Cont.*

Embelin	*Embelia ribes*	DRB	K562/D	↓ Caspase-3, XIAP and BCL-2 mRNA expressions, ↑ BAX mRNA expression	[237]
		-	K562 and U937	↑ Apoptosis, ↓ AKT phosphorylation and activation levels, ↓ XIAP expression	[238]
		Olaparib	CAL-120 and MDA-MB-231	↓ Cell growth, ↑ apoptosis, ↓ XIAP and PARP expressions	[239]
			MDA-MB-231 mice xenograft		
Emodin	Rheumatic palm leaves	GEM	PANC-1	↓ Expression of MDR1/P-gp and other MRPs	[240]
			PANC-1 mice xenograft		
EPCG	*C. sinensis*	-	U251 and U87	↑ Cell death, ↓ cell proliferation and invasion, ↓ P-gp levels	[108]
		Sulforaphane	ERα-negative MDA-MB-231 and MDA-MB-157	↑ Epigenetic *ERα* reactivation, ↑ TAM-dependent anti-estrogen chemosensitivity	[105]
			MDA-MB-231 mouse xenograft		
		Vandetanib (via ZEAuSSi nanocarriers)	MCF 7/TAM and T-47D/TAM	Sensitizing the cells to apoptosis, ↓ phosphorylation of EGFR, VEGFR2 and Akt	[106]
			MCF 7/TAM mice xenograft		
Fisetin	Anacardiaceae, *Acacia* spp. (Fabaceae), *Butea frondosa* & *Gleditsia triacanthos*	-	OXP-resistant OR and IRT-resistant CPT11	↑ Apoptosis, ↑ caspase-8 and -3 cleavage, ↓ tumor growth	[111,241]
			OR and CPT11 mice xenografts		
		Cabazitaxel	PrEC, 22Rυ1 and C4-2	↓ Cell proliferation, ↑ apoptosis, ↓ CD31, PCNA, Ki67 and MMP-9 expressions	[242]
			22Rυ1 and PC-3M-luc-6 mice xenografts		
		Sorafenib	HeLa	Activation of death receptor-5 mediated caspase-8/caspase-3 and the mitochondria-dependent apoptotic pathways	[110]
			HeLa mice xenograft		
			A375	Activation of MMP-2 and -9 expressions via EMT transcription factors, ↓ cell invasion and metastasis	[243]
			A375 mice xenograft		
Galangin	*Alpinia galangal*	CIP	A549/DDP	↓ Cell migration and colony formation, ↑ apoptosis, ↑ Bcl-2 suppression ↓ p-STAT3/p65 pathway	[244]
			A549/DDP mice xenograft		

Table 3. *Cont.*

Gambogic acid	*Garcinia hanburyi*	PTX	PTX-resistant Mda-MB-231 and Mda-MB-468	↓ Cell proliferation, ↑ apoptosis ↓ SHH signaling pathway, ↓ Bcl-2 expression, ↑ caspase-3 and BaX cleavage	[245]
			Mda-MB-231R mice xenograft		
		GEM	BxPC-3, PANC-1, MIA PaCa-2 and SW1990	↓ ERK/ E2F transcription factor-1 (E2F1) / ribonucleotide reductase subunit-M2 (RRM2) signaling pathway activation	[246]
			BxPC-3 mice xenograft		
		DOX	MCF-7/ADR	↓ P-gp and survivin expressions	[247,248]
Hesperetin	*Citrus x sinensis* & *Cordia sebestena*	CIP or JSH-23	A549/DDP	↓ P-gp expression, ↓ NF-κB signaling pathway, ↑ sensitivity to CIP	[249]
			A549/DDP mice xenograft		
Hispidulin	*Eupatorium littorale Cabrera*, *Artemisia vulgaris* L. & *Arnica Montana* L.	MTX	HepG2	↓ *ABCG2* activity, ↑ apoptosis	[250]
	Salvia involucrata	GEM or 5-FU	GBC-SD	↓ HIF-1α/P-gp signaling, ↑ apoptosis, ↑ G_0/G_1 cell cycle arrest	[251]
			GBC-SD mice xenograft		
Honokiol	*Magnolia x soulangiana* (Chinese Magnolia tree)	Cetuximab	Cetuximab-resistant H226	↓ HER family related to its proliferation (MAPK) and survival (AKT) pathways, ↓ phosphorylation of DRP1, and change in mitochondrial function	[252]
			UW-SCC1 PDX mice xenograft		
		Magnolol	KKU-100 and KKU-213	↓ CCA cell proliferation, adhesion, migration and invasion, ↑ cell death at high concentrations, ↑ G_0/G_1 cell cycle arrest, ↑ apoptosis, ↓ MMP-9 and -2 activity	[253]
Icaritin	*Herba Epimedii*	DOX	MG-63/DOX	↑ DOX accumulation, ↓ mRNA and protein levels of MDR1 and MRP1, ↓ STAT3 phosphorylation	[254]
		TRAIL	U87MG and U373	Sensitizing TRAIL-induced tumor cell apoptosis via suppression of NF-κB-dependent c-FLIP expression	[255]
Isoliquiritigenin	*Glycyrrhiza glabra*	DOX	DOX-resistant MES-SA/Dx5 and MES-SA/Dx5-R	↓ Cell growth, ↑ G_2/M and sub-G1 cell cycle arrest, ↑ apoptotic cell death, ↓ m-TOR pathway	[256]

Table 3. *Cont.*

Isorhamnetin	*Hippophae rhamnoides* L.	Capecitabine	AGS, SNU-5 and SNU-16	↓ Cell viability, ↑ apoptosis, ↓ Expression of NF-κB and NF-κB regulated proteins (Cyclin D1, COX-2, survivin, Bcl-xL, XIAP, ICAM-1, MMP-9, and VEGF)	[116]
			SNU-5 mice xenograft		
		CIP + Carboplatin	A-549	↓ Cancer cell growth, ↑ apoptosis, ↓ mitochondrial membrane potential, ↑ caspase-3 and -9 and PARP activation	[257]
Iso-sinensetin	*Cordyceps militaris*	-	MDR1-MDCKII and Taxol-resistant MX-1/T	↓ P-gp-mediated transport	[258]
			Rat xenograft		
Licochalcone A	*Glycyrrhiza inflata*	Topotecan	S1-M1-80 and H460-MX20	↓ *ABCG2* function, ↑ apoptosis	[120]
Luteolin	*Apium graveolens*, *Daucus carota subsp. sativus* & *Lonicera Caprifolium* Mill.	CIP	SKOV3	↓ PARP1 expression, ↓ PARP1-mediated autophagy	[259]
Mangiferin	*Mangifera indica* L.	ADM, VCR or Melphalan	IM9 and RPMI8226	↓ Cell viability, ↓ the nuclear translocation of NF-κB, ↑ p53 and Noxa expressions, ↓ XIAP, surviving and Bcl-xL expressions, ↑ sub-G1 cell cycle arrest, ↑ apoptosis via activating caspase-3	[260]
		CIP	SKRC-45	↑ Apoptosis, ↑ ROS production, ↑ cleaved caspase-3, ↓ mitochondrial membrane potential, ↑ Nrf-2 expression via the activation of PI3K	[261]
			EAC swiss albino mice xenograft		
Medicarpin and Millepurpan	*M. sativa*	-	Murine P388/DOX	↓ Cell growth, ↑ mitochondrial-mediated, caspase-dependent-apoptosis, ↑ DOX cytotoxicity and uptake, ↑ P-gp expression	[262]
Myricetin	*Solanum lycopersicum*, *Citrus × sinensis*, *C. sinensis* & genus *Vaccinium*	PTX	A2780 and OVCAR3	Modulation of pro- and anti-apoptotic markers, ↑ apoptosis, ↓ MDR-1 in lower doses, ↑ PTX cytotoxicity	[263,264]
Naringenin	*Citrus × paradisi*	-	SKBR3	↓ Cell proliferation and pro-apoptotic effects, ↓ HER2-TK activity	[265]
			A549	↓ Cell migration via suppression of AKT activity, ↓ MMP-2 and -9 activities	[266]
		U0126 (a MAPK inhibitor)	HTB-22	↓ Cell proliferation, ↑ apoptosis	[267]
Neochamaejasmin B	*Stellera chamaejasme* L.	-	MDCK and MDCK-hMDR1	↓ P-gp expression and P-gp-mediated drug efflux	[85]

Table 3. *Cont.*

Nobiletin	Citrus fruits (Rutaceae)	PTX	A2780/T and A549/T	↓ *ABCB1* activity, ↓ AKT/ERK/Nrf2 pathway, ↑ p53	[268]
			A549/T xenograft model	↓ *ABCB1*-mediated efflux, ↓ AKT/ERK/Nrf2 pathway, ↑ sensitivity to DOX	[269]
Oroxylin A	*S. baicalensis*	-	MDR1-MDCKII and Taxol-resistant MX-1/T	↓ P-gp-mediated transport	[258]
			Rat xenograft		
Plumbagin	Genus *Plumbago*	-	T24 and UMUC3	↓ PI3K/AKT/mTOR signaling pathway, ↑ G_1 cell cycle arrest, ↑ apoptosis	[270]
			T24 mice xenograft		
Pycnanthulignene A	*Pycnanthus angolensis* (Welw.) Ward	-	CEM/ADR5000	↑ Apoptosis, ↓ mitochondrial membrane potential, ↑ ROS production	[214]
Quercetin	*Allium cepa* L., *Brassica oleracea* var. *italica*, *Malus domestica*, *Vitis vinifera* & genus *Vaccinium*	ADM	T-ALL mice xenograft	↓ Cell proliferation, ↑ cell survival	[96]
		DOX, PTX or VCR	MCF-7 and MCF-7/dox	↓ P-gp expression, ↓ breast CSCs	[271]
		Cathepsin inhibitors	HL60/VINC and HL60/MX2	↑ Apoptosis, ↑ ROs production, ↓ cellular GSH level, ↑ programmed cell death	[124]
		MET	PC-3 and LNCaP	↓ Cell growth, migration and invasion, ↑ apoptosis, ↓ VEGF/Akt/PI3K pathway	[123]
			PC-3 mice xenograft		
Resveratrol	*Vitis vinifera*, *Arachis hypogaea*, genus *Vaccinium* & *Polygonum cupsidatum*	-	K562/ADM	↑ Autophagic apoptosis via the lysosomal cathepsin D pathway	[272]
		-	CIP-resistant CAR	↑ Autophagy and apoptosis by regulating the AMPK, Akt and autophagy-related protein levels	[273]
		5-FU	HCT116 and HCT116R	Chemosensitizing cells to 5-FU in TNF-β-induced inflammatory tumor microenvironment	[274]
Rosmarinic acid	*O. vulgare* ssp. hirtum, *O. vulgare* & *O. syriacum*	CIP	A549DDP	↓ Cell growth, ↑ cell cycle arrest, ↑ apoptosis by activating MAPK, ↓ P-gp and MDR1 expressions	[275]
			A549DDP mice xenograft		
Rutin	*Styphnolobium japonicum* L., genus *Eucalyptus*, genus *Ginkgo* & *Hypericum perforatum*	DOX	$KBCH^R8$-5 and MCF7/ADR	Modulating Wnt/β-catenin signaling, ↓ *ABCB1* overexpression, ↑ G_2/M cell cycle arrest	[276]
		CP and MET	MB-MDA-231 and MCF-7	↓ P-gp and BCRP activities, ↑ cell cycle arrest, ↑ apoptosis	[277]
Sciadopitysin	*Ginkgo biloba*	-	MDR1-MDCKI and MX-1/T	↓ P-gp-mediated transport	[258]
			Rat xenograft		
Scutellarin	*Scutellaria altissima* L.	CIP	PC3	↓ Cell proliferation, ↑ G_2/M cell cycle arrest, ↑ apoptosis, ↑ DNA damage, ↑ cleaved-caspase-3 and -9 levels, ↑ sensitivity to CIP	[278]

Table 3. *Cont.*

Shikonin	*Lithospermum erythrorhizon*	CIP	HCT116, HT29 and SW620	Mitochondrial dysfunction, ↓ cell growth, ↑ G_2/M cell cycle arrest, ↑ apoptosis, ↑ ROS accumulation	[279]
			HCT116 mice xenograft		
Silybin A, Silybin B and Silybin AB	*Silybum marianum* L.	DOX	A2780/DOX	↓ P-gp ATPase activity, ↑ sensitivity to DOX	[280]
Sinapic acid	Brassicaceae (Cruciferae) plants	-	PC-3 and LNCaP	↓ CDH2, MMP-2 and -9 expressions, ↑ caspase-3 activity, ↓ cell invasion	[281]
Sinensetin	*Orthosiphon aristatus*	-	MDR1-MDCKI and MX-1/T	↓ P-gp-mediated transport	[258]
			Rat xenograft		
Tangeretin	*Citrus sinensis*	-	MDR1-MDCKI and MX-1/T	↓ P-gp-mediated transport	[258]
			Rat xenograft		
Taxifolin	*Larix sibirica*, *Pinus roxburghii* & *Cedrus deodara*	DOX, PTX or VCR	HeLaS3 and MDR KB-vin	Resensitizing MDR cancer cells to chemotherapeutic agents, ↓ *ABCB1* expression	[282]
Tetrahydrocurcumin	derived from *C. longa*	-	Ara-C-resistant HL60	↑ R-HL60 cell death via autophagy	[283]
Tephrosin	*Tephrosia candida*	DRB and MTX	MCF7/MX and EPG85.257RDB	↓ Efflux activity of ABC transporters, ↑ DRB and MTX accumulation	[217]
Theaflavin	*C. sinensis*	DOX	$KBCH^R8$-5 and MCF7/ADR	Modulating Wnt/*β*-catenin signaling, ↓ *ABCB1* overexpression	[276]
Thymol	*Thymus vulgaris* L.	-	HCT116 and Lovo	↓ EMT, ↓ cell invasion and metastasis via inhibiting the activation of the Wnt/β-catenin pathway, ↑ PI3K/AKT and ERK pathways	[284]
			HCT116 mice xenograft		
		-	A549	↑ Mitochondrial pathway-mediated apoptosis via ROS generation, ↑ G_0/G_1 cell cycle arrest, ↑ macromolecular damage, ↑ Bax, ↓ Bcl-2 and ↓ superoxide dismutase (SOD) levels	[285]
		Oliveria essential oil (OEA)	MDA-MB231	↑ Apoptosis, ↑ caspase-3, ↓ mitochondrial membrane potential, ↑ DNA damage, ↑ S-phase cell cycle arrest	[286]
δ-T3	*Elaeis guineensis*, *Oryza* spp., *Triticum aestivum*, *Hordeum vulgare* & *Avena sativa*	Bevacizumab	Phase II study (23 patients)	↑ HOXA9 meth-ctDNA marker	[128,287]
		Ethyl acetate extract of *A. wilkesiana*	A549	↑ Apoptosis	[129]
Vitexin	*Vitex agnus-castus*, *Phyllostachys nigra*, *Passifloraceae* spp. & *Crataegus* spp. (hawthorn)	-	$HCT\text{-}116^{DR}$	↑ Apoptosis via suppressing autophagy, ↓ MDR-1 expression, ↑ cleaved caspase-9 and -3, ↑ BID and Bax, ↓ ATG5, Beclin-1 and LC3-II expressions	[288]
			$HCT\text{-}116^{DR}$ mice xenograft		

Table 3. *Cont.*

Wallichinine	*Piper wallichii*	VCR, DOX or CIP	KB_{V200}	↓ Cell growth, ↑ cell cycle arrest, ↑ apoptosis, ↓ *ABCB1* drug efflux function	[289]
Wogonin	*S. baicalensis* Georgi.	ADM	Imatinib-resistant K562/A02 36 and K562R 37	↓ Nrf2 signaling via Stat3/NF-κB inactivation	[290]
Xanthohumol	*Humulus lupulus* L.	Colchicin	MCF-7/ADR	↓ *ABCB1*-mediated transport of DOX, ↑ *ABCB1* ATPase activity	[291]
Alkaloids					
Compound	**Source**	**Combination**	**Experimental Model**	**Mechanisms of Overcoming MDR**	**References**
Berberine	*Coptis chinensis*	CIP	OVCAR3	↓ Cell proliferation and growth, ↑ G_0/G_1 cell cycle arrest, ↑ necroptosis, ↑ apoptosis	[147]
		DOX	MCF-7/MDR	↑ AMPK activation, ↓ HIF and P-gp expression, ↑ DOX sensitivity (in low dose) ↑ AMPK activation, ↑ p53 expression (in high dose)	[144]
			MCF-7/MDR mice xenograft		
			NCI-H460 and NCI-H1975	↓ Cell proliferation, ↑ apoptosis, ↓ phosphorylated and total levels of STAT3, ↑ STAT3 degradation	[146]
			MCF-7/hypoxia	↑ Inhibition of AMPK, ↓ HIF-1α and P-gp expression, ↑ DOX sensitivity (in low dose) ↑ p53 expression, ↓ AMPK-HIF-1α signaling pathway (in high dose)	[148]
			MCF-7/hypoxia mice xenograft		
		-	SW620 and LoVo	↓ Cell growth, migration, invasion and metastasis ↓ COX-2/PGE_2-JAK2/STAT3 signaling pathway	[145]
			SW620 and LoVo mice xenografts		
Capsaicin	*Capsicum frutescens*	5-FU	QBC939, SK-ChA-1 and MZ-ChA-1	↓ autophagy by activating PI3K/AKT/mTOR pathway, ↑ sensitivity to 5-FU	[292]
			CCA mice xenograft		
		Piperin	Caco-2 and CEM/ADR5000	↓ P-gp activity, ↑ DOX cytotoxicity	[293]
		CIP	MG63, 143B and HOS	↑ Apoptosis, ↑ G_0/G_1 cell cycle arrest, ↓ cell invasion, ↑ autophagy, ↑ ROS/JNK and p-AKT/mTOR signaling	[294]
			143B mice xenograft		
		DTX	PC3 and LNCaP	↓ Cell growth, ↓ PI3K/Akt/mTOR signaling pathway, ↓ AMPK activation	[295]
			PC3 and LNCaP mice xenografts		
		Sorafenib	LM3, Hep3B and HuH7	↓ Cell invasion and metastasis, ↑ E-cadherin, ↓ N-cadherin, MMP-2 and MMP-9, ↓ EGFR and PI3K/Akt/mTOR signaling, ↑ apoptosis and autophagy	[296]
			LM3 mice xenograft		

Table 3. *Cont.*

Cepharanthin	*Stephania cepharantha* Hayata	Dacomitinib	NCI-H1975, NCI-H1650, HCC827, A549 and NCI-H1299 NCI-H1975 mice xenograft	↑ Accumulation of autophagy markers, ↑ autophagic flux, ↓ Akt/mTOR pathway, ↓ autophagosome-lysosome fusion, ↓ lysosomal cathepsin B and cathepsin D maturation	[297]
Diindolylmethane	Cruciferous (Brassicaceae) vegetables	DTX	MDA-MB231 and SK-BR-3	↓ Cell viability, ↑ apoptosis, ↑ ROS generation	[298]
Dioncophylline A, Dioncophylline C and Mbandakamine A	Dioncophyllaceae & Ancistrocladaceae	-	MDA-MB-231 and MCF-7	↓ Cell proliferation by causing deformations in the nuclear membrane, ↑ ROS production, ↑ apoptotic cell death, ↓ mitochondrial membrane potential	[149]
Glaucine	*Corydalis yanhusuo*	ADM or MTX	MCF-7/Adr	↓ P-gp and MRP1 expressions, ↑ sensitivity to ADM and MTX	[299]
Hernandezine	*Thalictrum glandulosissimum*	-	Taxol-resistant HCT-8	↑ Autophagy, ↑ AMPK kinase, ↑ cell death	[300]
Indole-3-carbinol	Cruciferous vegetables	Fludarabine	Fludarabine-resistant chronic lymphocytic leukemia (CLL) cells CLL mice xenograft	↓ XIAP and cIAP1/2 levels ↑ caspase 9-dependent apoptosis	[301]
		Sorafenib	HepG2 and Huh-7	↑ NOX-1 expression, ↑ G_0/G_1 cell cycle arrest, ↑ apoptosis, ↓ p-Akt, p-ERK and HIF-1α levels, ↓ NOX-1 expression, ↓ VEGF and EGFR gene expressions, ↑ E-cadherin gene expression	[302]
		Vemurafenib	G-361, SK-MEL-2, SK-MEL-24 and RPMI-7951 G-361 mice xenograft	↓ Cell proliferation, ↓ micropthalmia-associated transcription factor (MITF-M) protein levels, ↓ phosphorylated ERK/MAPK	[303]
Liensinine	*N. nucifera* Gaertn.	DOX	MDA-MB-231, MCF-7 and A549 MDA-MB-231 mice xenograft	↓ Autophagic degradation, ↓ autophagosome-lysosome fusion ↑ mitochondrial fission via dephosphorylation and mitochondrial translocation of DNM1L, ↑ sensitivity to DOX	[304]
Neferine	*N. nucifera* (Lotus)	-	PTX- and DOX-resistant MCF-7, A549 and HCT-8	↓ P-gp-mediated efflux	[305]
Nuciferine	*N. nucifera*	PTX	PTX-, HCT-8/T and A549/T A549/T mice xenograft	↓ PI3K/AKT and MAPK/ERK signaling pathway, ↓ Activation of Nrf2 and HIF-1α ↓ P-gp expression and function, ↓ BCRP expression	[151]

Table 3. *Cont.*

Piperin	*P. nigrum* L. & *P. longum* L.	MMC	Hela/MMC Hela/MMC mice xenograft	↓ Cell proliferation, ↓ p-STAT3/p65, ↓ Bcl-2 activation, ↑ apoptosis, ↑ Bax and Bid, ↑ caspase cleavage	[152]
Piperlongumine	*P. longum*	CIP	A549/Cis A549/Cis mice xenograft	↓ Phosphorylation of Akt via the accumulation of ROS, ↓ drug efflux, ↑ apoptosis	[306]
		OXP	HCT-116 and LoVo HCT-116 mice xenograft	↑ ROS-mediated ER stress and mitochondrial function impairment	[307]
Reserpine	*R. serpentina*	-	CEM/ADR5000, MDA-MB-231-BCRP, HCT116 $p53^{-/-}$ and U87MG.Δ*EGFR*	↓ P-gp efflux function	[154]
Sanguinarine	*Sanguinaria canadensis*	-	U266, MM1S, IM9 and RPMI-8226	↑ Apoptosis via inhibition of the JaK2/STAT3 signaling, ↑ ROS generation, ↓ IL 6 secretion	[308]
		CIP	CIP-resistant A2780/R	↑ Apoptosis, ↑ sensitivity to CIP, ↓ intracellular GSH content	[309]
		-	CEM/ADR5000	↓ P-gp transporter activity, ↓ NF-κB activation	[310]
Wilforine	*Tripterygium wilfordii.* Hook. F.	PTX	KBvin	↓ P-gp efflux activity	[156]
Terpenoids and Steroids					
Compound	**Source**	**Combination**	**Experimental Model**	**Mechanisms of Overcoming MDR**	**References**
Acetyl-11-keto-*β*-boswellic acid	*Boswellia serrata*	-	Human PC3 and murine RM-1 RM-1 and RM-1/Doc mice homografts	↓ Cell proliferation, ↑ apoptosis, ↓ expression of stemness-associated genes, ↓ Akt and Stat3 signaling pathways	[311]
			A2780 and A2780/Taxol A2780/Taxol mice xenograft	↑ Apoptosis, ↑ G_2/M cell cycle arrest, ↓ cell migration and invasion, ↓ P-gp, LRP, BCRP and MRP protein expressions	[312]
			HCT-8/VCR	↓ Cell proliferation, ↓ P-gp activity, ↓ MDR1 gene expression	[313]
7-Acetylneotrichilenone	*T. ciliata* var. *yunnanensis*	DOX	MCF-7/DOX	Regulating mitochondrial expression of Bcl-2 family proteins through JNK/cJun pathway, ↑ sensitivity to DOX	[174]
Aguerin B	*Centaurea drabifolia* subsp. *detonsa*	-	DOX-resistant CEM/ADR5000	Low degrees of anticancer drug resistance, ↓ cell proliferation	[314]
Aridanin	*Tetrapleura tetraptera* (Schum. & Thonn) Taub	DOX	CEM/ADR5000 cells	↑ Apoptosis, ↑ ROS levels, ↓ mitochondrial membrane potential, ↓ ferroptotic and necroptotic cell death	[192]

Table 3. *Cont.*

Betulinic acid	White-barked birch tree, *Vitex negundo*, *Quisqualis fructus*, *Berlinia grandiflora*, *Tetracentron sinense*, *Orthosiphon stamineus*, *Eucalyptus camaldulensis*, *Syncarpa glomulifera* & *Betula pubescens*	-	CEM/ADR5000 and MDA-MB-231-BCRP	↓ P-gp, BCRP, *ABCB5* and mutation activated EGFR overexpressing cells, ↓ autocrine motility factor receptor (AMFR) activity	[315]
		-	RCC4	↓ Cell viability, ↑ cell death, ↑ caspase-mediated apoptosis pathway, ↑ Bax and PuMA expressions, ↓ Bcl-2 and XIAP,	[316]
		5-FU, ETP or TMZ		↓ PARP expression, ↑ MDR1 expression	
		PTX	MCF-7/taxol and MDA-MB-31/taxol	↓ Cell proliferation, ↑ apoptosis, ↑ G_2/M cell cycle arrest, ↑ ER stress	[180]
			MDA-MB-231 mice xenograft		
		-	PTX-resistant H460	↑ Apoptosis, ↑ cell cycle arrest, ↑ Bax/Bcl-2 ratio, ↓ mitochondrial membrane potential	[181]
Boswellic acid	*B. serrata*	MET (in nanoparticle formulation)	MiaPaCa-2	↓ Cell proliferation, ↑ apoptosis via DNA fragmentation, ↓ mitochondrial membrane potential	[317]
		Curcumin	HCT116, RKO, SW480, SW620, HT29, Caco2 and HCT116 $p53^{-/-}$	↓ Cell proliferation, ↑ G_2/M cell cycle arrest, ↑ apoptosis, ↑ tumor-suppressive miR-34a, ↓ miR-27a	[318]
			HCT116 mice xenograft		
B5G1 (novel betulinic acid analog)	derived from *B. serrata*	-	HepG2/ADM, MCF-7/ADR	↑ Cell death via mitochondrial-apoptosis pathway, ↓ PTEN-induced putative kinase 1 (PINK1)/Parkin-dependent mitophagy	[319]
			HepG2/ADM mice xenograft		
Celastrol	*Trypterygium wilfordii.*	-	VCR-resistant SASV16	↑ Apoptotic cell death via inducing cell cycle arrest at the G_2/M phase, ↑ Bax, Bim and tBid expressions, ↓ Bcl-2 expression, ↑ JNK1/2 activation, ↓ ERK1/2 and p38 activation	[320]
			Taxol-resistant A549, MCF-7, A2780, HCT-8, CIP-resistant SGC7901 and DOX-resistant MCF-7	↓ Sarcoplasmic/ ER Ca^{2+} ATPase (SERCA), ↓ P-gp function, ↑ calcium-mediated autophagy and ATP depletion, ↑ autophagy	[321]
			LLC-1 mice xenograft		
		Bortezomib	U266, H929 and KMS11	↓ Cell proliferation, migration and invasion, ↑ apoptosis, ↑ caspase-3, ↓ NF-κB activation, ↓ CXCR4 and MMP-9 gene products, ↓ tumor growth, ↓ serum IL-6 and TNF-α levels	[187]
			U266 mice xenograft		

Table 3. *Cont.*

Celastrol	*T. wilfordii.*	GEF	PC-9/GR	↓ Cell proliferation and migration, ↓ Axl protein levels	[183]
		GEF or Erlotinib	Mutant H1975	↓ Cell migration and invasion, ↓ p-EGFR pathway	[184]
			H1975 mice xenograft		
		Lapatinib	MDA-MB-453	↓ Cell proliferation, ↑ apoptosis, ↓ HER2 membrane protein expression	[322]
		PTX	8505C and SW1736	↑ Cell death via modulation of NF-κB, Akt and MAPK pathways, ↑ ER stress, ↑ ROS production	[185]
		Sorafenib	HepG2 and Hepa1-6	↓ Cell growth, ↑ VEGF autocrine, ↑ AKT pathway, ↑ apoptosis	[188]
			Hepa1-6 mice xenograft		
		VCR	SASV16	↓ Cell viability, ↑ G_2/M cell cycle arrest, ↑ apoptosis, ↑ cleaved caspase-8, -9, -3 and PARP, ↓ Bcl-2 expression, ↑ JNK1/2 activation	[186]
		DOX (in nanoparticle formulation)	MCF-7/ADR	↓ P-gp expression, ↑ apoptosis and autophagy via ROS/JNK signaling pathway	[323]
Ciliatasecone F	*T. ciliata* var. *yunnanensis*	DOX	MCF-7/DOX	Regulating mitochondrial expression of Bcl-2 family proteins via JNK/cJun pathway	[174]
Cucurbitacin B	Cucurbitaceae plants	DOX	MCF-7/Adr	↓ Cell proliferation, ↓ phosphorylation of Akt (pAkt), ↑ protein phosphatase 2A, ↓ cancerous inhibitor of protein phosphatase 2A (CIP2A)	[324]
Cucurbitacin D	*Trichosanthes kirilowii*	DOX	MCF7/ADR	↑ Apoptosis, ↑ G_2/M cell cycle arrest, ↓ Stat3 expression, ↓ NF-κB signaling pathway	[200]
Cynaropicrin	*Centaurea drabifolia* subsp. *detonsa*	-	CEM/ADR5000	↓ Cell proliferation	[314]
α-Carotene	*Daucus carota* subsp. *sativus*, *Ipomoea batatas*, *Cucurbita pepo* & *Brassica oleracea* var. *italica*	PTX	LLC, BCRC 60050	↓ Primary tumor growth, ↓ metastasis, ↑ TIMP-1, TIMP-2 and PAI-1 expressions	[325]
			LLC mice xenograft		
β-Carotene	Compositae, Umbelliferae & Chenopodiaceae plants	5-FU	EC1 and Eca109	↓ Cell proliferation, ↓ AKT/mTOR/p70S6K pathway, ↓ Bcl-2/Bax protein ratio, ↑ caspase-3	[326]
			Eca109 mice xenograft		
		DOX	KB-vin and NCI-H460/MX20	↓ P-gp transport, ↑ ATPase activity	[162]
Crocin	*Crocus sativus*	DOX	A2780/RCIS	↓ MRP1 and MRP2 gene expressions	[327]

Table 3. *Cont.*

β-Elemene	*Curcuma wenyujin*	-	SGC7901/ADR	↑ Cbl-b expression, ↓ MMP-2 and -9 expressions, ↓ ZEB1 and ZEB2 expressions, ↓ miR-1323, ↓ Cbl-b/EGFR/ERK/ AKT pathway	[328]
			SGC7901/ADR mice xenograft		
EM-E-11-4	*E. micractina*	PTX	A549/Tax	↑ G_2/M cell cycle arrest, ↑ apoptosis, ↓ P-gp ATPase activity	[166]
β-Escin	*Aesculus hippocastanum* L. (horse chestnut seeds)	5-FU	MCF-7	↑ p53 gene expression, ↓ Bcl-2, ↑ apoptosis	[329]
(1*S*,2*S*,3*S*,4*S*,7*R*,9*R*,13*R*,14*R*,15*S*)-9,15-Fiacetoxy-3,7-dibenzoyloxy-1,13,14-trihydroxyjatropha-5*E*-ene	*P. tithymaloides*	ADR	HepG2/ADR and MCF-7/ADR	↓ Pgp-mediated efflux	[167]
			HepG2/ADR mice xenograft		
Fucoxanthin	*Undaria pinnatifida*, *Eisenia bicyclis*, *Hijikia fusiformis*, *Laminaria Japonica* and *Sargassum fulvellum*	DOX	MCF-7/ADR, HepG-2/ADR and SKOV-3/ADR	↓ *ABCC1*, *ABCG2* and ABCB1 expressions, ↑ levels and activity of caspases (CASP3, CASP8) and p53, ↑ apoptosis	[161]
Ginsenoside Rg5	*P. ginseng*	DTX	PTX-resistant A2780/T and A549/T	↑ Apoptosis, ↑ G_2/M cell cycle arrest, ↓ Nrf2/PI3K/AKT pathways	[330]
			A549/T mice xenograft		
Guggulsterone	*Commiphora wightii*	Bexarotene	MDA-MB-231	↑ Exosome-associated BCRP secretion, ↑ apoptosis, ↑ sensitivity to DOX	[198]
2*α*-Hydroxyalantolactone	*Pulicaria undulata*	-	CEM/ADR5000, MDA-MB-231-BCRP, HCT116 $p53^{-/-}$ and U87MG.Δ*EGFR*	↓ PI3K/AKT pathway, ↑ DNA damage, ↑ G_2/M cell cycle arrest	[331]
Isopetasin and *S*-Isopetasin	*Petasites formosanus* Kitamura	DOX	CEM/ADR5000, MDA-MB-231-BCRP	↑ P-gp inhibition, ↑ ROS generation, ↑ apoptosis	[332]
Isotenulin and Tenulin	*Helenium amarum*	PTX, DOX or VCR	KB-vin	↓ P-gp efflux function via stimulating P-gp ATPase activity	[333]
Ingol-3,7,12-triacetate-8-benzoate	*E. royleana*	DOX	HepG2/DOX	↓ P-gp transporter activity, ↑ sensitivity to DOX	[164]
Lupeol	*Zanthoxylum gilletii*	-	LoVo	↓ Cell viability, ↑ apoptosis, ↓ *ABCG2*, ↑ ER stress	[190]
			LoVo mice xenograft		
		5-FU	SGC7901 and BGC823	↓ Cell growth, ↑ apoptosis, ↑ Bax and p53 expressions, ↓ survivin and Bcl-2 expressions	[334]
			BGC823 mice xenograft		
Methoxyboetirane B, Methoxyboetirane C	*E. boetica*	-	EPG85-257RNOV, EPG85-257RDB, EPP85-181RNOV, EPP85-181RDB, HT-29RNOV, HT-29RDB	Modulating P-gp/ *ABCB1* efflux, ↑ apoptosis	[170]
Nicaeenin G	*E. nicaeensis*	DOX	NCI-H460/R and DLD1-TxR	↑ P-gp inhibition, ↑ sensitivity to DOX	[168]

Table 3. *Cont.*

Oleanolic acid	*Carpobrotus edulis*	-	MDA-MB-231 and HepG2 Zebrafish (*Danio rerio*) model	↑ P-gp inhibition	[335]
			A549, NCI-H460 and NCI-H1299	↓ Cell proliferation, ↑ miR-122, ↑ cell cycle arrest through miR-122/Cyclin G1/MEF2D pathway	[336]
			A549, NCI-H460 and NCI-H1299 mice xenografts		
			HepG2	↓ Cell growth, migration and invasion, ↑ apoptosis, ↓ G_2/M cell cycle arrest, ↓ JNK/p38 signalling pathway	[191]
Saikosaponin A	*Radix Bupleuri*	DOX, PTX or VCR	MCF-7/ADR and HepG2/ADM	↓ P-gp expression	[337]
Thymoquinone	*N. sativa*	CIP	GC-7901, HGC-27 and MGC-803	↓ Cell growth, ↑ PTEN, ↑CIP-induced apoptosis, ↓ PI3K/AKT signaling pathway, ↑ mitochondrial pathway, ↓ P-gp expression	[177]
			GC-7901 mice xenograft		
		PTX	Mouse 4T1 and EAC cells	↓ Cell migration, ↓ cell growth, ↑ apoptosis, ↑ cleaved caspase-3, -7 and -12, ↓ phosphorylated p65 and Akt1	[178]
			EAC mice xenograft		
			MCF-7 and T47D	↑ Apoptotic/necrotic cell death, ↑ autophagy, ↓ breast cancer-associated stem cell clone (CD44+/CD24-cell, ↓ TWIST-1 gene, ↑ SNAIL-1 and SNAIL-2 genes	[338]
		Melatonin	EMT6/P mice xenograft	↑ Apoptosis rate, ↑ extensive necrosis, ↓ VEGF expression	[339]
		Ferulic acid	MDA-MB-231	↓ Cell proliferation (each compound in low doses)	[340]
Tooniliatone A	*T.* Roem	DOX	K562/MDR and MCF-7/MDR	↓ Bcl-xL, ↑ SAPK/JNK pathway, ↓ cJun protein, ↑ JNK MAPK signaling, ↑ sensitivity to DOX	[175]
Ursolic Acid	*M. domestica*, *Vaccinium* spp. *Eriobotrya japonica* & *R. officinalis*	DOX	MCF-7/ADR	Disruption of energy metabolism, ↓ P-gp function	[193]
		GEM	AsPC-1 and MIA PaCa-2	↓ Cell proliferation, ↑ apoptosis, ↓ NF-κB activation and its regulated gene products, ↓ colony formation ability, ↓ XIAP, Bcl-2, cIAP-1, cIAP-2, cyclin D1, cMyc, ICAM-1, MMP-9 and VEGF expressions	[194]
			Panc-28 orthotopic mouse model		
		PTX	PTX-resistant MDA-MB-231	↑ miR-149-5p expression, ↓ MyD88 expression	[341]
			231/PTX mice xenograft		

Table 3. *Cont.*

Walsurin A	*Walsura robusta*	DOX	MCF-7/DOX	↓ P-gp function, ↑ sensitivity to DOX	[342]
Withaferin A	*Withania somnifera*	CIP	H441, CL97 and H1975	↓ Cell growth, ↓ mTOR/STAT3 signaling	[343]
			H441 mice xenograft		
		OXP	Panc-1, MIAPaCa-2 and SW1990	ROS-mediated mitochondrial dysfunction, ↓ PI3K/AKT signaling	[344]
			Panc-1 mice xenograft		
Withanolide E	*Physalis peruviana*	Drozitumab	ACHN, CAKI-1 and SN12-C	↑ TRAIL-induced apoptosis, ↑ cFLIP degradation and modulation of HSP90 function	[201]
			ACHN mice xenograft		

Miscellaneous Compounds					
Compound	**Source**	**Combination**	**Experimental Model**	**Mechanisms of Overcoming MDR**	**References**
Erucin	Cruciferous vegetables	4-OH TAM	T47D tamR, MCF-7 tamR	↓ Cell viability, ↓ Bcl-2/Bax ratio, ↓ surviving levels, ↑ PARP cleavage, ↑ mitochondrial stress marker (ADRP)	[204]
Garcinol	*Guttiferae* plants	-	PANC-1 SP	↓ Mcl-1, EZH2, *ABCG2*, Gli-1 and Notch1 expression, ↑ several tumor suppressor miRNAs and also miR-200c	[345]
		Erlotinib or CIP	A549M	↑ several key EMT-regulating miRNAs, such as miR-200b, miR-205, miR-218 and let-7c, ↑ sensitivity to Erlotinib and CIP	[346]
		PTX	Mouse T41 (CRL-2539)	↓ Caspase-3/$iPLA_2$ and NF-κB/Twist1 signaling pathways	[347]
			4T1-Luc mice xenograft		
Oblongifolin C	*Garcinia yunnanensis*	GEM	MIA PaCa-2, PANC-1, BxPC-3, Capan-1 and SW1990	↓ Src/MAPK/ERK pathway, ↑ sensitivity to GEM	[348]
			MIA-RES mice xenograft		
Podophyllotoxin	*Podophyllum peltatum*	-	HCC827GR	↓ Kinase activity, ↓ cell viability, ↑ apoptosis, ↑ G_2/M cell cycle arrest, ↓ MCL-1, survivin and Bcl-xl expression	[349]
Podophyllotoxin derivative: GMZ1	-	-	ADM-resistant K562/A02	↓ Cell viability, ↑ apoptosis, ↓ MDR gene expression	[350]
Sulforaphane	Cruciferous vegetables	DOX	BT549 and MDA-MB-468	↓ Cell growth, ↑ autophagy, ↓ activation of PTEN via attenuation of HDAC6 expression	[203]
			MDA-MB-231 mice xenograft		

Conflict of Interest

The authors declare no conflict of interest.

References

[1] World Health Organization. "Cancer". Who.int. https://www.who.int/health-topics/cancer#tab=tab_1 (accessed November 27, 2020).

[2] D. Hanahan and R. A. Weinberg, "Hallmarks of Cancer: The Next Generation," *Cell*, vol. 144, no. 5, pp. 646-674, Mar. 2011, doi: 10.1016/j.cell.2011.02.013.

[3] Z. Abbas and S. Rehman, "An Overview of Cancer Treatment Modalities," in *Neoplasm*, H. N. Shahzad, Ed. United Kingdom: IntechOpen, 2018, pp. 139-157.

[4] P. Kanavos, "The rising burden of cancer in the developing world," *Ann. Oncol.*, vol. 17, no. 8, pp. viii15-viii23, Jul. 2006, doi: 10.1093/annonc/mdl983.

[5] National Cancer Institute. "Cancer Statistics". Cancer.gov. https://www.cancer.gov/about-cancer/understanding/statistics (accessed November 28, 2020).

[6] American Cancer Society, "Cancer Facts & Figures 2020," 2020. [Online]. Available: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020 (accessed November 28, 2020).

[7] A. Kumar and V. Jaitak, "Natural products as multidrug resistance modulators in cancer," *Eur. J. Med. Chem.*, vol. 176, pp. 268-291, May 2019, doi: 10.1016/j.ejmech.2019.05.027.

[8] I. Valle, D. Tramalloni, N. L. Bragazzi, "Cancer prevention: state of the art and future prospects," *J. Rev. Med. Hyg.*, vol. 56, no. 1, pp. E21-E27, Mar. 2015.

[9] M. F. Ullah, "Cancer Multidrug Resistance (MDR): A Major Impediment to Effective Chemotherapy," *Asian Pac. J. Cancer Prev.*, vol. 9, no. 1, pp. 1-6, Jan.-Mar. 2008.

[10] R. Briffa, S. P. Langdon, G. Grech, D. J. Harrison, "Acquired and Intrinsic Resistance to Colorectal Cancer Treatment", in *Colorectal Cancer-Diagnosis, Screening and Management*, J. Chen, Ed. United Kingdom: IntechOpen, 2017, pp. 57-81.

[11] S. K. Gupta, P. Singh, V. Ali, M. Verma, "Role of membrane-embedded drug efflux ABC transporters in the cancer chemotherapy," *Oncol. Rev.*, vol. 14, no. 2, p. 448, Jul. 2020. doi: 10.4081/oncol.2020.448.

[12] R-J. Ju, L-M. Mu, W.-L. Lu, "Targeting drug delivery systems for circumventing multidrug resistance of cancers," *Ther. Deliv.* vol. 4, no. 6, pp. 667-671, Jun. 2013. doi: 10.4155/tde.13.39.

[13] M. Saraswathy and S. Gong, "Different strategies to overcome multidrug resistance in cancer," *Biotechnol. Adv.*, vol. 31, no. 8, pp. 1397-1407, Dec. 2013. doi: 10.1016/j.biotechadv.2013.06.004.

[14] T. H. Lippert, H.-J. Ruoff, M. Volm, "Intrinsic and Acquired Drug Resistance in Malignant Tumors," *Arzneimittelforschung*, vol. 58, no. 6, pp. 261-264, Feb. 2008. doi: 10.1055/s-0031-1296504.

[15] A. Rose-James, T. T. Sreelekha, S. K. George, "Nano strategies in the war against multidrug resistance in leukemia," *OncoDrugs*, vol. 1, no. 1, pp. 3e-9e, Dec. 2013.

[16] J. Wang, N. Seebacher, H. Shi, Q. Kan, Z. Duan, "Novel strategies to prevent the development of multidrug resistance (MDR) in cancer," *Oncotarget*, vol. 8, no. 48, pp. 84559-84571, Jul. 2017. doi: 10.18632/oncotarget.19187.

[17] S. Tuncer, "Drug Delivery With Nanoparticles To Multi-Drug Resistance Cancer Cell Line," M.Sc. dissertation, Dept. Nanotechnology and Nanomedicine, Hacettepe Univ., Ankara, 2014.

[18] O. Fapohunda and D. C. Ajayi, "Cancer cell metabolism resulting in multidrug resistance to chemotherapy and possible ways out," *J. Cancer Prev. Curr. Res.*, vol. 11, no. 3, pp. 64-70, Jun. 2020. doi: 10.15406/jcpcr.2020.11.00429.

[19] A. Zargar, S. Chang, A. Kothari, A. M. Snijders, J.-H. Mao *et. al.*, "Overcoming the challenges of cancer drug resistance through bacterial-mediated therapy," *CDTM*, vol. 5, no. 4, pp. 258-266, Dec. 2019. doi: 10.1016/j.cdtm.2019.11.001.

[20] X.-J. Liang, C. Chen, Y. Zhao, P. C. Wang, "Circumventing Tumor Resistance to Chemotherapy by Nanotechnology," *Methods Mol Biol.*, vol. 596, pp. 467-488, Mar. 2010. doi: 10.1007/978-1-60761-416-6_21.

[21] V. Schirrmacher, "From chemotherapy to biological therapy: A review of novel concepts to reduce the side effects of systemic cancer treatment (Review)," *Int. J. Oncol.*, vol. 54, no. 2, pp. 407-419, Dec. 2019. doi: 10.3892/ijo.2018.4661.

[22] S. A. Mirzaei, S. Reiisi, P. G. Tabari, A. Shekari, F. Aliakbari *et. al.*, "Broad blocking of MDR efflux pumps by acetylshikonin and acetoxyisovalerylshikonin to generate hypersensitive phenotype of malignant carcinoma cells," *Sci. Rep.*, vol. 8, no. 1, p. 3446, Feb. 2018. doi: 10.1038/s41598-018-21710-5.

[23] Z. Chen, T. Shi, L. Zhang, M. Deng, C. Huang, "Mammalian drug efflux transporters of the ATP binding cassette (ABC) family in multidrug resistance: A review of the past decade," *Cancer Lett.*, vol. 370, no. 1, pp. 153-164, Jan. 2016. doi: 10.1016/j.canlet.2015.10.010.

[24] T. Haider, V. Pandey, N. Banjare, P. N. Gupta, V. Soni, "Drug resistance in cancer: mechanisms and tackling strategies," *Pharmacol. Rep.*, vol.

72, pp. 1125-1151, Jul. 2020. doi: 10.1007/s43440-020-00138-7.

[25] C. S. Chambers, J. Viktorová, K. Řehořová, D. Biedermann, L. Turková, "Defying Multidrug Resistance! Modulation of Related Transporters by Flavonoids and Flavonolignans," *J. Agric. Food Chem.*, vol. 68, no. 7, pp. 1763-1779, Feb. 2020. doi: 10.1021/acs.jafc.9b00694.

[26] K. Bukowski, M. Kciuk, R. Kontek, "Mechanisms of Multidrug Resistance in Cancer Chemotherapy," *Int. J. Mol. Sci.*, vol. 21, no. 9, p. 3233, May 2020. doi: 10.3390/ijms21093233.

[27] S. Wu and L. Fu, "Tyrosine kinase inhibitors enhanced the efficacy of conventional chemotherapeutic agent in multidrug resistant cancer cells," *Mol. Cancer*, vol. 17, no. 1, p. 25, Feb. 2018. doi: 10.1186/s12943-018-0775-3.

[28] A. C. Jaramillo, F. A. Saig, J. Cloos, G. Jansen, G. J. Peters *et. al.*, "How to overcome ATP-binding cassette drug efflux transporter-mediated drug resistance?", *Cancer Drug Resist.*, vol. 1, pp. 6-29, Mar. 2018. doi: 10.20517/cdr.2018.02.

[29] M. Liscovitch and Y. Lavie, "Cancer multidrug resistance: a review of recent drug discovery research, *IDrugs*, vol. 5, no. 4, pp. 349-355, Apr. 2002.

[30] W. An, H. Lai, Y. Zhang, M. Liu, X. Lin, "Apoptotic Pathway as the Therapeutic Target for Anticancer Traditional Chinese Medicines," *Front. Pharmacol.*, vol. 10, p. 758, Jul. 2019. doi: 10.3389/fphar.2019.00758.

[31] S.-T. Pan, Z.-L. Li, Z.-X. He, J.-X. Qiu, S.-F. Zhou, "Molecular mechanisms for tumour resistance to chemotherapy," *Clin. Exp. Pharmacol. Physiol.*, vol. 43, no. 8, pp. 723-737, Apr. 2016. doi: 10.1111/1440-1681.12581.

[32] B. L. Y. Kwan and V. W. K. Wai, "Autophagy in Multidrug-Resistant Cancers," in *Autophagy in Current Trends in Cellular Physiology and Pathology*, N. V. Gorbunov, Ed. United Kingdom: IntechOpen, 2016, pp. 435-454.

[33] G. Pistritto, D. Trisciuoglio, C. Ceci, A. Garufi, G. D'Orazi, "Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies," *Aging*, vol. 8, no. 4, pp. 603-619, Apr. 2016. doi: 10.18632/aging.100934.

[34] C. M. Pfeffer and A. T. K. Singh, "Apoptosis: A Target for Anticancer Therapy," *Int. J. Mol. Sci.*, vol. 19, no. 2, p. 448, Feb. 2018. doi: 10.3390/ijms19020448.

[35] J. G. Alvarez-Meythaler, Y. Garcia-Mayea, C. Mir, H. Kondoh, M. E. LLeonart, "Autophagy Takes Center Stage as a Possible Cancer Hallmark," *Front. Oncol.*, vol. 10, p. 586069, Oct. 2020. doi: 10.3389/fonc.2020.586069.

[36] X. Hou, J. Jiang, Z. Tian, L. Wei, "Autophagy and Tumour Chemotherapy," in *Autophagy: Biology and Diseases - Clinical Science*, W. Le, Ed. Singapore: Springer, 2020, pp. 351-374.

[37] Y.-J. Li, Y.-H. Lei, N. Yao, C.-R. Wang, N. Hu *et. al.*, "Autophagy and multidrug resistance in cancer," *Chin. J. Cancer*, vol. 36, p. 52, Jun. 2017. doi: 10.1186/s40880-017-0219-2.

[38] J. M. M. Levy and A. Thorburn, "Autophagy in cancer: moving from understanding mechanism to improving therapy responses in patients," *Cell Death Differ.*, vol. 27, no. 3, pp. 1-15, Dec. 2019. doi: 10.1038/s41418-019-0474-7.

[39] S. Nagini, P. Manikandan, R. R. Malla, "The Autophagy Conundrum in Cancer Development, Progression and Therapeutics," in *Autophagy in Tumor and Tumor Microenvironment*, S. K. Bhutia, Ed. Singapore: Springer, 2020, pp. 223-247.

[40] H. Chang and Z. Zou, "Targeting autophagy to overcome drug resistance: further developments," *J. Hematol. Oncol.*, vol. 13, p. 159, Nov. 2020. doi: 10.1186/s13045-020-01000-2.

[41] F. Cuomo, L. Altucci, G. Cobellis, "Autophagy Function and Dysfunction: Potential Drugs as Anti-Cancer Therapy," *Cancers (Basel)*, vol. 11, no. 10, p. 1465, Sep. 2019. doi: 10.3390/cancers11101465.

[42] A. S. Rodrigues, B. C. Gomes, C. Martins, M. Gromicho, N. G. Oliveira *et. al.*, "DNA Repair and Resistance to Cancer Therapy," in *New Research Directions in DNA Repair*, C. Chen, Ed. United Kingdom: IntechOpen, 2013, pp. 489-528.

[43] C. J. Link Jr. and V. A. Bohr, "DNA repair in drug resistance: Studies on the repair process at the level of the gene," in *Molecular and Clinical Advances in Anticancer Drug Resistance*, R. F. Ozols, Ed. New York: Springer, 1991, pp. 209-232.

[44] A. Torgovnick and B. Schumacher, "DNA repair mechanisms in cancer development and therapy," *Front. Genet.*, vol. 6, p. 157, Apr. 2015. doi: 10.3389/fgene.2015.00157.

[45] L. Wang, A. J. Mosel, G. G. Oakley, A. Peng, "Deficient DNA damage signaling leads to chemoresistance to cisplatin in oral cancer," *Mol. Cancer. Ther.*, vol. 11, no. 11, pp. 2401-2409, Nov. 2012. doi: 10.1158/1535-7163.MCT-12-0448.

[46] J.-P. Gillet and M. M. Gottesman, "Mechanisms of Multidrug Resistance in Cancer," in *Cancer, Methods in Molecular Biology*, J. M. Walker, Ed. United States: Springer, 2010, pp. 47-76.

[47] S. Sato and H. Itamoch, "DNA Repair and Chemotherapy," in *Advances in DNA Repair*, C. C. Chen, Ed. United Kingdom: IntechOpen, 2015, pp. 359-380.

[48] N. Hosoya and K. Miyagawa, "Targeting DNA damage response in cancer therapy," *Cancer Sci.*, vol. 105, pp. 370-388, Jan. 2014. doi: 10.1111/cas.12366.

[49] N. E. Muvarak, K. Chowdhury, L. Xia, C. Robert, E. Y. Choi *et. al.*, "Enhancing the Cytotoxic Effects of PARP Inhibitors with DNA

Demethylating Agents - A Potential Therapy for Cancer," *Cancer Cell*, vol. 30, pp. 637-650, Oct. 2016. doi: 10.1016/j.ccell.2016.09.002.

[50] S. Liu, Y. Ge, T. Wang, H. Edwards, Q. Ren *et. al.*, "Inhibition of ATR potentiates the cytotoxic effect of gemcitabine on pancreatic cancer cells through enhancement of DNA damage and abrogation of ribonucleotide reductase induction by gemcitabine," *Oncol. Rep.*, vol. 37, pp. 3377-3386, Mar. 2017. doi: 10.3892/or.2017.5580.

[51] X. An, C. Sarmiento, T. Tan, H. Zhu, "Regulation of multidrug resistance by microRNAs in anti-cancer therapy," *Acta Pharm. Sin. B.*, vol. 7, no. 1, pp. 38-51, Jul. 2017. doi: 10.1016/j.apsb.2016.09.002.

[52] V. S. Jones, R.-Y. Huang, L.-P. Chen, Z.-S. Chen, L. Fu *et. al.*, "Cytokines in cancer drug resistance: Cues to new therapeutic strategies," *Biochim. Biophys. Acta*, vol. 1865, pp. 255-265, Mar. 2016. doi: 10.1016/j.bbcan.2016.03.005.

[53] E. C. Aniogo, B. P. A. George, H. Abrahamse, "The role of photodynamic therapy on multidrug resistant breast cancer," *Cancer Cell Int.*, vol. 19, p. 91, Apr. 2019. doi: 10.1186/s12935-019-0815-0.

[54] T. Ozben, "Mechanisms and strategies to overcome multiple drug resistance in cancer," *FEBS Lett.*, vol. 580, pp. 2903-2909, Feb. 2006. doi: 10.1016/j.febslet.2006.02.020.

[55] Y. Cho and Y. K. Kim, "Cancer Stem Cells as a Potential Target to Overcome Multidrug Resistance," *Front Oncol.*, vol. 10, p. 764, Jun. 2020. doi: 10.3389/fonc.2020.00764.

[56] S. M. Stefan, "Multi-target ABC transporter modulators: what next and where to go?," *Future Med.Chem.*, vol. 11, no. 18, pp. 2353-2358, Sept. 2019. doi: 10.4155/fmc-2019-0185.

[57] M. Falasca and K. J. Linton, "Investigational ABC transporter inhibitors," *Expert Opin. Investig. Drugs*, vol. 21, no. 5, pp. 657-666, May 2012. doi: 10.1517/13543784.2012.679339.

[58] A. K. Nanayakkara, C. A. Follit, G. Chen, N. S. Williams, P. D. Vogel *et. al.*, "Targeted inhibitors of P-glycoprotein increase chemotherapeutic-induced mortality of multidrug resistant tumor cells," *Sci. Rep.*, vol. 8, p. 967, Jan. 2018. doi: 10.1038/s41598-018-19325-x.

[59] I. S. Mohammad, W. He, L. Yin, "Understanding of human ATP binding cassette superfamily and novel multidrug resistance modulators to overcome MDR," *Biomed. Pharmacother.*, vol. 100, pp. 335-348, Apr. 2018. doi: 10.1016/j.biopha.2018.02.038.

[60] B. M. F. Gonçalves, D. S. P. Cardoso, M.-J. U. Ferreira, "Overcoming Multidrug Resistance: Flavonoid and Terpenoid Nitrogen-Containing Derivatives as ABC Transporter Modulators," *Molecules*, vol. 25, p. 3364, Jul. 2020. doi: 10.3390/molecules25153364.

[61] Y. H. Choi, A.-M. Yu, "ABC Transporters in Multidrug Resistance and Pharmacokinetics, and Strategies for Drug Development," *Curr. Pharm. Des.*, vol. 20, no. 5, pp. 793-807, Jan. 2014.

[62] A. R. Hamed, N. S. Abdel-Azim, K. A. Shams, F. M. Hammouda, "Targeting multidrug resistance in cancer by natural chemosensitizers," *Bull. Natl. Res. Cent.*, vol. 43, p. 8, Jan. 2019. doi: 10.1186/s42269-019-0043-8.

[63] H. M. Coley, "Overcoming Multidrug Resistance in Cancer: Clinical Studies of P-Glycoprotein Inhibitors," in *Cancer, Methods in Molecular Biology*, J. M. Walker, Ed. United States: Springer, 2010, pp. 341-358.

[64] X.-D. Dong, M. Zhang, X. Ma, J.-Q. Wang, Z.-N. Lei *et. al.*, "Bruton's Tyrosine Kinase (BTK) Inhibitor RN486 Overcomes *ABCB1*-Mediated Multidrug Resistance in Cancer Cells," *Front. Cell Dev. Biol.*, vol. 8, p. 865, Aug. 2020. doi: 10.3389/fcell.2020.00865.

[65] Z. Zhao, M. Ji, Q. Wang, N. He, Y. Li, "Ca^{2+} signaling modulation using cancer cell membrane coated chitosan nanoparticles to combat multidrug resistance of cancer," *Carbohydr. Polym.*, vol. 238, p. 116073, Feb. 2020. doi: 10.1016/j.carbpol.2020.116073.

[66] S. Sinha, S. Sharma, J. Vora, N. Shrivastava, "Emerging role of sirtuins in breast cancer metastasis and multidrug resistance: Implication for novel therapeutic strategies targeting sirtuins," *Pharmacol. Res.*, vol. 158, p. 104880, May 2020. doi: 10.1016/j.phrs.2020.104880.

[67] S. Pramual, K. Lirdprapamongkol, V. Jouan-Hureaux, M. Barberi-Heyob, C. Frochot *et. al.*, "Overcoming the diverse mechanisms of multidrug resistance in lung cancer cells by photodynamic therapy using pTHPP-loaded PLGA-lipid hybrid nanoparticles," *Eur. J. Pharm. Biopharm.*, vol. 149, pp. 218-228, Feb. 2020. doi: 10.1016/j.ejpb.2020.02.012.

[68] J. Yang, D. Sontag, Y. Gong, G. Y. Minuk, "Enhanced Gemcitabine Cytotoxicity with Knockdown of Multidrug Resistance Protein Genes in Human Cholangiocarcinoma Cell Lines," *J. Gastroenterol. Hepatol.*, Oct. 2020. doi: 10.1111/jgh.15289.

[69] C. Martinelli and M. Biglietti "Nanotechnological approaches for counteracting multidrug resistance in cancer" *Cancer Drug Resist.*, Oct. 2020. doi: 10.20517/cdr.2020.47.

[70] W. Lin, Y. Miao, X. Meng, Y. Huang, W. Zhao *et. al.*, "miRNA-765 mediates multidrug resistance via targeting BATF2 in gastric cancer cells," *FEBS Open Bio.*, vol. 10, no. 6, pp. 1021-1030, Jun. 2020. doi: 10.1002/2211-5463.12838.

[71] W. Ma, Q. Chen, W, Xu, M, Yu, Y. Yang *et. al.*, "Self-targeting visualizable hyaluronate nanogel for synchronized intracellular release of doxorubicin and cisplatin in combating

multidrug-resistant breast cancer," *Nano Res.*, Nov. 2020. doi: 10.1007 / s12274-020-3124-y.

[72] M. Majidinia, M. Mirza-Aghazadeh-Attari, M. Rahimi, A. Mihanfar, A. Karimian *et. al.*, "Overcoming multidrug resistance in cancer: Recent progress in nanotechnology and new horizons," *IUBMB Life.*, vol. 72, no. 5, pp. 855-871, May 2020. doi: 10.1002/iub.2215.

[73] J. Yu, F. Hu, Q. Zhu, X. Li, H. Ren *et. al.*, " PD-L1 monoclonal antibody-decorated nanoliposomes loaded with Paclitaxel and P-gp transport inhibitor for the synergistic chemotherapy against multidrug resistant gastric cancers," *Nanoscale Res. Lett.*, vol. 15, no. 1, p. 59, Mar. 2020. doi: 10.1186/s11671-019-3228-z.

[74] Q.-X. Teng, X. Luo, Z.-N. Lei, J.-Q. Wang, J. Wurpel *et. al.*, "The Multidrug Resistance-Reversing Activity of a Novel Antimicrobial Peptide," *Cancers (Basel)*, vol. 12, no. 7, p. 1963, Jul. 2020. doi: 10.3390/cancers12071963.

[75] J. Hong, S. Jing, Y. Zhang, R. Chen, K. G. Owusu-Ansah *et. al.*, "Y-320, a novel immune-modulator, sensitizes multidrug-resistant tumors to chemotherapy," *Am. J. Transl. Res.*, vol. 12, no. 2, pp. 551-562, Feb. 2020.

[76] M. Lahlou, "The Success of Natural Products in Drug Discovery," *J. Pharm. Pharmacol.*, vol. 4, pp. 17-31, Jun. 2013. doi: 10.4236/pp.2013.43A003.

[77] A. A. Koparde, R. C. Doijad, C. S. Magdum, "Natural Products in Drug Discovery," in *Pharmacognosy - Medicinal Plants*, S. Perveen and A. Al-Taweel, Eds. United Kingdom: IntechOpen, 2019, pp. 1-19.

[78] E. E. Carlson, "Natural Products as Chemical Probes", *ACS Chem. Biol.*, vol. 5, no. 7, pp. 639-653, Jul. 2010. doi: 10.1021/cb100105c.

[79] S. Dalavelle, V. Dobričić, L. Lazzarato, E. Gazzano, M. Machuqueiro *et. al.*, "Improvement of conventional anti-cancer drugs as new tools against multidrug resistant tumors," *Drug Resist. Updat.*, vol. 50, p. 100682, May 2020. doi: 10.1016/j.drup.2020.100682.

[80] V. Seidel, "Plant-Derived Chemicals: A Source of Inspiration for New Drugs," *Plants (Basel)*, vol. 9, no. 11, p. 1562, Nov. 2020. doi: 10.3390/plants9111562.

[81] S. Karthikeyan and S. L. Hoti, "Development of Fourth Generation ABC Inhibitors from Natural Products: A Novel Approach to Overcome Cancer Multidrug Resistance," *Anticancer Agents Med. Chem.*, vol. 15, no. 5, pp. 605-615, Jan. 2015. doi: 0.2174/1871520615666150113103439.

[82] A. Ramakrishna and G. A. Ravishankar, "Influence of abiotic stress signals on secondary metabolites in plants," *Plant Signal. Behav.*, vol. 6, no. 11, pp. 1720-1731, Nov. 2011. doi: 10.4161/psb.6.11.17613.

[83] A. M. L. Seca and D. C. G. A. Pinto, "Plant Secondary Metabolites as Anticancer Agents: Successes in Clinical Trials and Therapeutic Application," *Int. J. Mol. Sci.*, vol. 19, no. 1, p. 263, Jan. 2018. doi: 10.3390/ijms19010263.

[84] X. Xue, J.-L. Yu, D.-Q. Sun, W. Zou, F. Kong *et. al.*, "Curcumin as a multidrug resistance modulator - A quick review," *Biomed. Prev. Nutr.*, vol. 3, no. 2, pp. 173-176, Apr. 2013. doi: 10.1016/j.bionut.2012.12.001.

[85] L. Pan, H. Hu, X. Wang, L. Yu, H. Jiang, "Inhibitory Effects of Neochamaejasmin B on P-Glycoprotein in MDCK-hMDR1 Cells and Molecular Docking of NCB Binding in P-Glycoprotein," *Molecules*, vol. 20, pp. 2931-2948, Feb. 2015. doi: 10.3390/molecules20022931.

[86] M. M. Jucá, F. M. S. C. Filho, J. C. de Almeida, D. da Silva Mesquita, J. R. de Moraes Barriga *et. al.*, "Flavonoids: biological activities and therapeutic potential," *Nat. Prod. Res.*, vol. 34, no. 5, pp. 692-705, Mar. 2020. doi: 10.1080/14786419.2018.1493588.

[87] J. Dinic, A. Podolski-Renic, T. Stankovic, J. Bankovic, M. Pesic, "New Approaches With Natural Product Drugs for Overcoming Multidrug Resistance in Cancer," *Curr. Pharm. Des.*, vol. 21, no. 38, pp. 5589-5604, Oct. 2015. doi: 10.2174/1381612821666151002113546.

[88] A. Ferreira, M. Rodrigues, A. Fortuna, A. Falcão, G. Alves, "Flavonoid compounds as reversing agents of the P-glycoprotein-mediated multidrug resistance: An *in vitro* evaluation with focus on antiepileptic drugs," *Food Res. Int.*, vol. 103, pp. 110-120, Jan. 2018. doi: 10.1016/j.foodres.2017.10.010.

[89] M. Saeed, O. Kadioglu, H. Khalid, Y. Sugimoto, T. Efferth, "Activity of the dietary flavonoid, apigenin, against multidrug-resistant tumor cells as determined by pharmacogenomics and molecular docking," *J. Nutr. Biochem.*, vol. 26, no. 1, pp. 44-56, Jan. 2015. doi: 10.1016/j.jnutbio.2014.09.008.

[90] Z. Chen, D. Tian, X. Liao, Y. Zhang, J. Xiao, "Apigenin Combined With Gefitinib Blocks Autophagy Flux and Induces Apoptotic Cell Death Through Inhibition of HIF-1α, c-Myc, p-EGFR, and Glucose Metabolism in EGFR L858R+T790M-Mutated H1975 Cells," *Front. Pharmacol.*, vol. 10, p. 260, Mar. 2019. doi: 10.3389/fphar.2019.00260.

[91] S. Erdogan, K. Turkekul, R. Serttas, Z. Erdogan, "The natural flavonoid apigenin sensitizes human $CD44^+$ prostate cancer stem cells to cisplatin therapy," *Biomed. Pharmacother.*, vol. 88, pp. 210-217, Apr. 2017. doi: 10.1016/j.biopha.2017.01.056.

[92] A.-M. Gao, X.-Y. Zhang, J.-N. Hu, Z.-P. Ke, "Apigenin sensitizes hepatocellular carcinoma cells to doxorubic through regulating miR-520b/ATG7 axis," *Chem. Biol. Interact.*, vol. 280,

pp. 45-50, Jan. 2018. doi: 10.1016/j.cbi.2017.11.020.

[93] R. B. Semwal, D. K. Semwal, S. Combrinck, A. Viljoen, "Butein: From ancient traditional remedy to modern nutraceutical," *Phytochem. Lett.*, vol. 11, pp. 188-201, Dec. 2014. doi: 10.1016/j.phytol.2014.12.014.

[94] L. Zhang, X. Yang, X. Li, C. Li, L. Z. Barriga *et. al.*, "Butein sensitizes HeLa cells to cisplatin through the AKT and ERK/p38 MAPK pathways by targeting FoxO3a," *Int. J. Mol. Med.*, vol. 36, no. 4, pp. 957-966, Oct. 2015. doi: 10.3892/ijmm.2015.2324.

[95] S. J. Hewlings and D. S. Kalman, "Curcumin: A Review of Its Effects on Human Health," *Foods.*, vol. 6, no. 10, p. 92, Oct. 2017. doi: 10.3390/foods6100092.

[96] E. Khatoon, K. Banik, C. Harsha, B. L. Sailo, K. K. Thakur *et. al.*, "Phytochemicals in cancer cell chemosensitization: Current knowledge and future perspectives," *Semin. Cancer Biol.*, vol. 28, p. S1044-579X(20)30150-4, Jun. 2020. doi: 10.1016/j.semcancer.2020.06.014.

[97] H. Mahammedi, E. Planchat, M. Pouget, X. Durando, H. Curé *et. al.*, "The New Combination Docetaxel, Prednisone and Curcumin in Patients with Castration-Resistant Prostate Cancer: A Pilot Phase II Study," *Oncology*, vol. 90, no. 2, pp. 69-78, Jan. 2016. doi: 10.1159/000441148.

[98] S. H. Shahcheraghi, M. Zangui, M. Lotfi, M. Ghayour-Mobarhan, A. Ghorbani *et. al.*, "Therapeutic Potential of Curcumin in the Treatment of Glioblastoma Multiforme," *Curr. Pharm. Des.*, vol. 25, no. 3, pp. 333-342, Jan. 2019. doi: 10.2174/1381612825666190313123704.

[99] K. S. Park, S. Y. Yoon, S. H. Park, J. H. Hwang, "Anti-Migration and Anti-Invasion Effects of Curcumin via Suppression of Fascin Expression in Glioblastoma Cells," *Brain Tumor Res. Treat.*, vol. 7, no. 1, pp. 16-24, Apr. 2019. doi: 10.14791/btrt.2019.7.e28.

[100] W. Li, W. Yang, Y. Liu, S. Chen, S. Chin *et. al.*, "MicroRNA-378 enhances inhibitory effect of curcumin on glioblastoma," *Oncotarget*, vol. 8, no. 43, pp. 73938-73946, May 2017. doi: 10.18632/oncotarget.17881.

[101] Z. C. Gersey, G. A. Rodriguez, E. Barbarite, A. Sanchez, W. M. Walters *et. al.*, "Curcumin decreases malignant characteristics of glioblastoma stem cells via induction of reactive oxygen species," *BMC Cancer*, vol. 17, no. 1, p. 99, Feb. 2017. doi: 10.1186/s12885-017-3058-2.

[102] J. Shen, Y.-J. Chen, Y.-W. Jia, W.-Y. Zhao, G.-H. Chen *et. al.*, "Reverse effect of curcumin on CDDP-induced drug-resistance via Keap1/p62-Nrf2 signaling in A549/CDDP cell," *Asian Pac. J. Trop. Med.*, vol. 10, no. 12, pp. 1190-1196, Dec. 2017. doi: 10.1016/j.apjtm.2017.10.028.

[103] S. Keyvani-Ghamsari, K. Khorsandi, A. Gul, "Curcumin effect on cancer cells' multidrug resistance: An update," *Phytother. Res.*, vol. 34, no. 10, pp. 2534-2556, Oct. 2020. doi: 10.1002/ptr.6703.

[104] B. Wang, X. Liu, Y. Teng, T. Yu, J. Chen *et. al.*, "Improving anti-melanoma effect of curcumin by biodegradable nanoparticles," *Oncotarget*, vol. 8, no. 65, pp. 108624-108642, Aug. 2017. doi: 10.18632/oncotarget.20585.

[105] Y. Li, S. M. Meeran, T. O. Tollefsbol, "Combinatorial bioactive botanicals re-sensitize tamoxifen treatment in ER-negative breast cancer via epigenetic reactivation of ERα expression," *Sci. Rep.*, vol. 7, no. 1, p. 9345, Aug. 2017. doi: 10.1038/s41598-017-09764-3.

[106] B. N. Prashanth Kumar, N. Puvvada, S. Rajput, S. Sarkar, M. K. Mahto *et. al.*, "Targeting of EGFR, VEGFR2, and Akt by Engineered Dual Drug Encapsulated Mesoporous Silica-Gold Nanoclusters Sensitizes Tamoxifen-Resistant Breast Cancer," *Mol. Pharm.*, vol. 15, no. 7, pp. 2698-2713, Jul. 2018. doi: 10.1021/acs.molpharmaceut.8b00218.

[107] W. Zhang, W. Zhang, L. Sun, L. Xiang, X. Lai *et. al.*, "The effects and mechanisms of epigallocatechin-3-gallate on reversing multidrug resistance in cancer," *Trends Food Sci. Technol.*, vol. 93, pp. 221-233, Sept. 2019. doi: 10.1016/j.tifs.2019.09.017.

[108] C. T. Le, W. P. J. Leenders, R. J. Molenaar, C. J. F. van Noorden *et. al.*, "Effects of the Green Tea Polyphenol Epigallocatechin-3-Gallate on Glioma: A Critical Evaluation of the Literature," *Nutr. Cancer*, vol. 70, no. 3, pp. 317-333, Apr. 2018. doi: 10.1080/01635581.2018.1446090.

[109] N. Khan, D. N. Syed, N. Ahmad, H. Mukhtar, "Fisetin: a dietary antioxidant for health promotion," *Antioxid. Redox Signal.*, vol. 19, no. 2, pp. 151-162, Jul. 2013. doi: 10.1089/ars.2012.4901.

[110] M.-T. Lin, C.-L. Lin, T.-Y. Lin, C.-W. Cheng, S.-F. Yang *et. al.*, "Synergistic effect of fisetin combined with sorafenib in human cervical cancer HeLa cells through activation of death receptor-5 mediated caspase-8/caspase-3 and the mitochondria-dependent apoptotic pathway," *Tumour Biol.*, vol. 37, no. 5, pp. 6987-6996, May 2016. doi: 10.1007/s13277-015-4526-4.

[111] L.-B. Jeng, B. K. Velmurugan, M.-C. Chen, H.-H. Hsu, T.-J. Ho *et. al.*, "Fisetin mediated apoptotic cell death in parental and Oxaliplatin/irinotecan resistant colorectal cancer cells *in vitro* and *in vivo*," J. *Cell Physiol.*, vol. 233, no. 9, pp. 7134-7142, Sept. 2018. doi: 10.1002/jcp.26532.

[112] A. A. Ganai and H. Farooqi, "Bioactivity of genistein: A review of *in vitro* and *in vivo* studies," *Biomed. Pharmacother.*, vol. 76, pp. 30-38, Dec. 2015. doi: 10.1016/j.biopha.2015.

[113] S. Pintova, S. Dharmupari, E. Moshier, N. Zubizarreta, C. Ang *et. al.*, "Genistein combined with FOLFOX or FOLFOX-Bevacizumab for the treatment of metastatic colorectal cancer: phase I/II pilot study," *Cancer Chemother. Pharmacol.*, vol. 84, no.3, pp. 591-598, Sept. 2019. doi: 10.1007/s00280-019-03886-3.

[114] S.-L. Huang, T.-C. Chang, C. C. K. Chao, N.-K. Sun, "Role of the TLR4-androgen receptor axis and genistein in taxol-resistant ovarian cancer cells," *Biochem. Pharmacol.*, vol. 177, p. 113965, Jul. 2020. doi: 10.1016/j.bcp.2020.113965.

[115] S. Kandakumar and V. Manju, "Pharmacological Applications of Isorhamnetin: A Short Review," *Int. J. Trend Res. Dev.*, vol. 1, no. 4, pp. 672-678, Jun. 2017.

[116] K. A. Manu, M. K. Shanmugam, L. Ramachandran, F. Li, K. S. Siveen *et. al.*, "Corrigendum on "Isorhamnetin augments the anti-tumor effect of capeciatbine through the negative regulation of NF-κB signaling cascade in gastric cancer," *Cancer Lett.*, vol. 28, no. 420, p. 259, Apr. 2018. doi: 10.1016/j.canlet.2018.01.003.

[117] J. Wang, X. Fang, L. Ge, F. Cao, L. Zhao *et. al.*, "Antitumor, antioxidant and anti-inflammatory activities of kaempferol and its corresponding glycosides and the enzymatic preparation of kaempferol," *PLoS One*, vol. 13, no. 5, p. e0197563, May 2018. doi: 10.1371/journal.pone.0197563.

[118] M. Moradzadeh, A. Tabarraei, H. R. Sadeghnia, A. Ghorbani, A. Mohamadkhani *et. al.*, "Kaempferol increases apoptosis in human acute promyelocytic leukemia cells and inhibits multidrug resistance genes," *J. Cell Biochem.*, vol. 119, no. 2, pp. 2288-2297, Feb. 2018. doi: 10.1002/jcb.26391.

[119] B. Nair, R. J. Anto, S. M. L. R. Nath, "Kaempferol-Mediated Sensitization Enhances Chemotherapeutic Efficacy of Sorafenib Against Hepatocellular Carcinoma: An *In Silico* and *In Vitro* Approach," *Adv. Pharm. Bull.*, vol. 10, no. 3, pp. 472-476, Jul. 2020. doi: 10.34172/apb.2020.058.

[120] C.-P. Wu, S. Lusvarghi, S.-H. Hsiao, T.-C. Liu, Y.-Q. Li *et. al.*, "Licochalcone A Selectively Resensitizes *ABCG2*-Overexpressing Multidrug-Resistant Cancer Cells to Chemotherapeutic Drugs," *J. Nat. Prod.*, vol. 83, no. 5, pp. 1461-1472, May 2020. doi: 10.1021/acs.jnatprod.9b01022.

[121] A. V. A. David, R. Arulmoli, S. Parasuraman, "Overviews of Biological Importance of Quercetin: A Bioactive Flavonoid," *Pharmacogn. Rev.*, vol. 10, no. 20, pp. 84-89, Jul.-Dec. 2016. doi: 10.4103/0973-7847.194044.

[122] H. G. Ulusoy and N. Sanlier, "A minireview of quercetin: from its metabolism to possible mechanisms of its biological activities," *Crit. Rev. Food Sci. Nutr.*, vol. 60, no. 19, pp. 3290-3303, Nov. 2020. doi: 10.1080/10408398.2019.1683810.

[123] S. Sun, F. Gong, P. Liu, Q. Miao, "Metformin combined with quercetin synergistically repressed prostate cancer cells via inhibition of VEGF/PI3K/Akt signaling pathway," *Gene*, vol. 664, pp. 50-57, Jul. 2018. doi: 10.1016/j.gene.2018.04.045.

[124] A. Maruszewska and J. Tarasiuk, "Quercetin Triggers Induction of Apoptotic and Lysosomal Death of Sensitive and Multidrug Resistant Leukaemia HL60 Cells," *Nutr. Cancer*, pp. 1-18, Apr. 2020. doi: 10.1080/01635581.2020.1752745.

[125] Y. Zhou, J. Zhang, K. Wang, W. Han, X. Wang *et. al.*, "Quercetin overcomes colon cancer cells resistance to chemotherapy by inhibiting solute carrier family 1, member 5 transporter," *Eur. J. Pharmacol.*, vol. 881, p. 173185, Aug. 2020. doi: 10.1016/j.ejphar.2020.173185.

[126] J. Cao, J. Han, H. Xiao, J. Qiao, M. Han, "Effect of Tea Polyphenol Compounds on Anticancer Drugs in Terms of Anti-Tumor Activity, Toxicology, and Pharmacokinetics," *Nutrients*, vol. 8, no. 12, p. 762, Dec. 2016. doi: 10.3390/nu8120762.

[127] J. Shen, T. Yang, Y. Xu, Y. Luo, X. Zhong, "δ-Tocotrienol, Isolated from Rice Bran, Exerts an Anti-Inflammatory Effect via MAPKs and PPARs Signaling Pathways in Lipopolysaccharide-Stimulated Macrophages," *Int. J. Mol. Sci.*, vol. 19, no. 10, p. 3022, Oct. 2018. doi: 10.3390/ijms19103022.

[128] C. B. Thomsen, R. F. Andersen, K. D. Steffensen, P. Adimi, A. Jakobsen, "Delta tocotrienol in recurrent ovarian cancer. A phase II trial," *Pharmacol. Res.*, vol. 141, pp. 392-396, Mar. 2019. doi: 10.1016/j.phrs.2019.01.017.

[129] I. B. Abubakar, S.-W. Lim, H.-S. Loh, "Synergistic Apoptotic Effects of Tocotrienol Isomers and *Acalypha wilkesiana* on A549 and U87MG Cancer Cells," *Trop. Life Sci. Res.*, vol. 29, no. 1, pp. 229-238, Mar. 2018. doi: 10.21315/tlsr2018.29.1.15.

[130] J. Saguez, J. Attoumbré, P. Giordanengo, S. Baltora-Rosset, "Biological activities of lignans and neolignans on the aphid *Myzus persicae* (Sulzer)," *Arthropod Plant Interact.*, vol. 7, pp. 225-233, Nov. 2013. doi: 10.1007/s11829-012-9236-x.

[131] S. Su, X. Cheng, M. Wink, "Natural lignans from *Arctium lappa* modulate P-glycoprotein efflux function in multidrug resistant cancer cells," *Phytomedicine*, vol. 22, no. 2, pp. 301-307, Feb. 2015. doi: 10.1016/j.phymed.2014.12.009.

[132] A. Rauf, S. Patel, M. Imran, A. Maalik, M. U. Arshad *et. al.*, "Honokiol: An anticancer lignan," *Biomed. Pharmacother.*, vol. 107, pp. 555-562, Nov. 2018. doi: 10.1016/j.biopha.2018.08.054.

[133] C. P. Ong, W. L. Lee, Y. Q. Tang, W. H. Yap, "Honokiol: A Review of Its Anticancer Potential and Mechanisms," *Cancers (Basel)*, vol. 12, no. 1, pp. 48, Dec. 2019. doi: 10.3390/cancers12010048.

[134] S. Kiokias, C. Proestos, V. Oreopoulou, "Phenolic Acids of Plant Origin-A Review on Their Antioxidant Activity *In Vitro* (O/W Emulsion Systems) Along with Their *in Vivo* Health Biochemical Properties," Foods, vol. 9, no. 4, p. 534, Apr. 2020. doi: 10.3390/foods9040534.

[135] Y.-N. Teng, C. C. N. Wang, W.-C. Liao, Y.-H. Lan, C.-C. Hung, "Caffeic Acid Attenuates Multi-Drug Resistance in Cancer Cells by Inhibiting Efflux Function of Human P-glycoprotein, *Molecules*, vol. 25, no. 2, p. 247, Jan. 2020. doi: 10.3390/molecules25020247.

[136] B. C. Akinwumi, K.-A. M. Bordun, H. D. Anderson, "Biological Activities of Stilbenoids," *Int. J. Mol. Sci.*, vol. 19, no. 3, p. 792, Mar. 2018. doi: 10.3390/ijms19030792.

[137] B. Salehi, A. P. Mishra, M. Nigam, B. Sener, M. Kilic, "Resveratrol: A Double-Edged Sword in Health Benefits," *Biomedicines*, vol. 6, no. 3, p. 91, Sept. 2018. doi: 10.3390/biomedicines6030091.

[138] X. Guo, Z. Zhao, D. Chen, M. Qiao, F. Wan, "Co-delivery of resveratrol and docetaxel via polymeric micelles to improve the treatment of drug-resistant tumors," *Asian J. Pharm. Sci.*, vol. 14, no. 1, pp. 78-85, Jan. 2019. doi: 10.1016/j.ajps.2018.03.002.

[139] E. Sameiyan, A. W. Hayes, G. Karimi, "The effect of medicinal plants on multiple drug resistance through autophagy: A review of *in vitro* studies," *Eur. J. Pharmacol.*, vol. 852, pp. 244-253, Jun. 2019. doi: 10.1016/j.ejphar.2019.04.001.

[140] N. S. Alamolhodaei, A. M. Tsatsakis, M. Ramezan, A. W. Hayes, G. Karim, "Resveratrol as MDR reversion molecule in breast cancer: An overview," *Food Chem. Toxicol.*, vol. 103, pp. 223-232, May 2017. doi: 10.1016/j.fct.2017.03.024.

[141] L.-Y. Wang, S. Zhao, G.-J. Lv, X.-J. Ma, J.-B. Zhang, "Mechanisms of resveratrol in the prevention and treatment of gastrointestinal cancer," *World J. Clin. Cases*, vol. 8, no. 12, pp. 2425-2437, Jun. 2020. doi: 10.12998/wjcc.v8.i12.2425.

[142] H. N. Matsuura and A. G. Fett-Neto, "Plant Alkaloids: Main Features, Toxicity, and Mechanisms of Action," in *Plant Toxins*, P. Gopalakrishnakone, C. R. Carlini, R. Ligabue-Braun, Eds. Switzerland: Springer, 2017, pp. 243-261.

[143] B. Debnath, W. S. Singh, M. Das, S. Goswami, M. K. Singh *et. al.*, "Role of plant alkaloids on human health: A review of biological activities," *Mater. Today Chem.*, vol. 9, pp. 56-72, May 2018. doi: 10.1016/j.mtchem.2018.05.001.

[144] Y. Pan, F. Zhang, Y. Zhao, D. Shao, X. Zheng *et. al.*, "Berberine Enhances Chemosensitivity and Induces Apoptosis Through Dose-orchestrated AMPK Signaling in Breast Cancer," *J. Cancer*, vol. 8, no. 9, pp. 1679-1689, Jun. 2017. doi: 10.7150/jca.19106.

[145] X. Liu, Q, Ji, N, Ye, H, Sui, L. Zhou *et. al.*, "Berberine Inhibits Invasion and Metastasis of Colorectal Cancer Cells via COX-2/PGE_2 Mediated JAK2/STAT3 Signaling Pathway," *PLoS One*, vol. 10, no. 5, p. e0123478, May 2015. doi: 10.1371/journal.pone.0123478.

[146] T. Zhu, L.-L. Li, G.-F. Xiao, Q.-Z. Luo, Q.-Z. Liu *et. al.*, "Berberine Increases Doxorubicin Sensitivity by Suppressing STAT3 in Lung Cancer," *Am. J. Chin. Med.*, vol. 43, no. 7, pp. 1487-1502, Oct. 2015. doi: 10.1142/S0192415X15500846.

[147] L. Liu, J. Fan, G. Ai, J. Liu, N. Luo *et. al.*, "Berberine in combination with cisplatin induces necroptosis and apoptosis in ovarian cancer cells," *Biol. Res.*, vol. 52, no. 1, p. 37, Jul. 2019. doi: 10.1186/s40659-019-0243-6.

[148] Y. Pan, D. Shao, Y. Zhao, F. Zhang, X. Zheng *et. al.*, "Berberine Reverses Hypoxia-induced Chemoresistance in Breast Cancer through the Inhibition of AMPK-HIF-1α," *Int. J. Biol. Sci.*, vol. 13, no. 6, pp. 794-803, Jul. 2017. doi: 10.7150/ijbs.18969.

[149] P. P. Kushwaha, A. K. Singh, K. S. Prajapati, M. Shuaib, S. Fayez *et. al.*, "Induction of apoptosis in breast cancer cells by naphthylisoquinoline alkaloids," *Toxicol. Appl. Pharmacol.*, vol. 409, p. 115297, Dec. 2020. doi: 10.1016/j.taap.2020.115297.

[150] D. S. P. Cardoso, A. Kincses, M. Nové, G. Spengler, S. Mulhovo *et. al.*, "Alkylated monoterpene indole alkaloid derivatives as potent P-glycoprotein inhibitors in resistant cancer cells," *Eur. J. Med. Chem.*, p. 112985, Nov. 2020. doi: 10.1016/j.ejmech.2020.112985.

[151] R.-M. Liu, P. Xu, Q. Chen, S.-L. Feng, Y. Xie, "A multiple-targets alkaloid nuciferine overcomes paclitaxel-induced drug resistance *in vitro* and *in vivo*," *Phytomedicine*, vol. 79, p. 153342, Dec. 2020. doi: 10.1016/j.phymed.2020.153342.

[152] S.-Z. Han, H.-X. Liu, L.-Q. Yang, L. de Cui, Y. Xu, "Piperine (PP) enhanced mitomycin-C (MMC) therapy of human cervical cancer through suppressing Bcl-2 signaling pathway via inactivating STAT3/NF-κB," *Biomed. Pharmacother.*, vol. 96, pp. 1403-1410, Dec. 2017. doi: 10.1016/j.biopha.2017.11.022.

[153] Y.-J. Chen, C.-C. Kuo, L.-L. Ting, L.-S. Lu, Y.-C. Lu *et. al.*, "Piperlongumine inhibits cancer stem cell properties and regulates multiple malignant phenotypes in oral cancer," *Oncol.*

Lett., vol. 15, no. 2, pp. 1789-1798, Feb. 2018. doi: 10.3892/ol.2017.7486.

[154] S. A. A. Abdelfatah and T. Efferth, "Cytotoxicity of the indole alkaloid reserpine from *Rauwolfia serpentina* against drug-resistant tumor cells," *Phytomedicine*, vol. 22, no. 2, pp. 308-318, Feb. 2015. doi: 10.1016/j.phymed.2015.01.002.

[155] T. Liu, X. Liu, W. Li, "Tetrandrine, a Chinese plant-derived alkaloid, is a potential candidate for cancer chemotherapy," *Oncotarget*, vol. 7, no. 26, pp. 40800-40815, Jun. 2016. doi: 10.18632/oncotarget.8315.

[156] Y.-T. Chang, Y.-C. Lin, L. Sun, W.-C. Liao, C. C. N. Wang *et. al.,* "Wilforine resensitizes multidrug resistant cancer cells via competitive inhibition of P-glycoprotein," *Phytomedicine*, vol. 71, p. 153239, Jun. 2020. doi: 10.1016/j.phymed.2020.153239.

[157] W.-Y. Tong, "Biotransformation of Terpenoids and Steroids," in *Natural Products*, K.G. Ramawat and J. M. Mérillon, Eds. Germany: Springer, 2013, pp. 2733-2759.

[158] M. Biradi and K. Hullatti, "Bioactivity guided isolation of cytotoxic terpenoids and steroids from *Premna serratifolia*," *Pharm. Biol.*, vol. 55, no. 1, pp. 1375-1379, Dec. 2017. doi: 10.1080/13880209.2017.1301491.

[159] N. Gyémánt, M. Tanaka, P. Molnár, J. Deli, L. Mándoky *et. al.,* "Reversal of multidrug resistance of cancer cells *in vitro*: modification of drug resistance by selected carotenoids," *Anticancer Res.*, vol. 26, no. 1A, pp. 367-374, Jan.-Feb. 2006.

[160] S. Y. Eid, M. Z. El-Readi, M. Wink, "Carotenoids reverse multidrug resistance in cancer cells by interfering with ABC-transporters," *Phytomedicine*, vol. 19, no. 11, pp. 977-987, Aug. 2012. doi: 10.1016/j.phymed.2012.05.010.

[161] S. Y. Eid, M. A. lthubiti, M. E. Abdallah, M. Wink, M. Z. El-Readi, "The carotenoid fucoxanthin can sensitize multidrug resistant cancer cells to doxorubicin via induction of apoptosis, inhibition of multidrug resistance proteins and metabolic enzymes," *Phytomedicine*, vol. 77, p. 153280, Oct. 2020. doi: 10.1016/j.phymed.2020.153280.

[162] Y.-N. Teng, M.-J. Sheu, Y.-W. Hsieh, R.-Y. Wang, Y.-C. Chiang *et. al.,* "*β*-carotene reverses multidrug resistant cancer cells by selectively modulating human P-glycoprotein function," *Phytomedicine*, vol. 23, no. 3, pp. 316-323, Mar. 2016. doi: 10.1016/j.phymed.2016.01.008.

[163] S. Mafu and P. Zerbe, "Plant diterpenoid metabolism for manufacturing the biopharmaceuticals of tomorrow: prospects and challenges," *Phytochem. Rev.*, vol. 17, pp. 113-130, May 2017. doi: 10.1007/s11101-017-9513-5.

[164] S. Shaker, J. Sang, X.-L. Yan, R.-Z. Fan, G.-H. Tang *et. al.,* "Diterpenoids from Euphorbia royleana reverse P-glycoprotein-mediated multidrug resistance in cancer cells," *Phytochemistry*, vol. 176, p. 112395, Aug. 2020. doi: 10.1016/j.phytochem.2020.112395.

[165] T. Yang, S. Wang, H. Li, Q. Zhao, S. Yan *et. al.,* "Lathyrane diterpenes from *Euphorbia lathyris* and the potential mechanism to reverse the multi-drug resistance in HepG2/ADR cells," *Biomed. Pharmacother.*, vol. 121, p. 109663, Jan. 2020. doi: 10.1016/j.biopha.2019.109663.

[166] Q. Liu, P. Cai, S. Guo, J. Shi, H. Sun, "Identification of a lathyrane-type diterpenoid EM-E-11-4 as a novel paclitaxel resistance reversing agent with multiple mechanisms of action," *Aging (Albany NY)*, vol. 12, no. 4, pp. 3713-3729, Feb. 2020. doi: 10.18632/aging.102842.

[167] J. Zhu, R. Wang, L. Lou, W. Li, G. Tang *et. al.,* "Jatrophane Diterpenoids as Modulators of P-Glycoprotein-Dependent Multidrug Resistance (MDR): Advances of Structure-Activity Relationships and Discovery of Promising MDR Reversal Agents," *J. Med. Chem.*, vol. 59, no. 13, pp. 6353-6369, Jul. 2016. doi: 10.1021/acs.jmedchem.6b00605.

[168] G. Krstić, M. Jadranin, N. M. Todorović, M. Pešić, T. Stanković *et. al.,* "Jatrophane diterpenoids with multidrug-resistance modulating activity from the latex of *Euphorbia nicaeensis*," *Phytochemistry*, vol. 148, pp. 104-112, Apr. 2018. doi: 10.1016/j.phytochem.2018.01.016.

[169] D. Rédei, N. Kúsz, G. Sátori, A. Kincses, G. Spengler *et. al.,* "Bioactive Segetane, Ingenane, and Jatrophane Diterpenes from *Euphorbia taurinensis*," *Planta Med.*, vol. 84, no. 9-10, pp. 729-735, Jul. 2018. doi: 10.1055/a-0589-0525.

[170] M. A. Reis, A. M. Matos, N. Duarte, O. B. Ahmed, R. J. Ferreira *et. al.,* "Epoxylathyrane Derivatives as MDR-Selective Compounds for Disabling Multidrug Resistance in Cancer," *Front. Pharmacol.*, vol. 8, no. 11, p. 599, May 2020. doi: 10.3389/fphar.2020.00599.

[171] C. Garcia, V. M. S. Isca, F. Pereir, C. M. Monteiro, E. Ntungwe *et. al.,* "Royleanone Derivatives From *Plectranthus* spp. as a Novel Class of P-Glycoprotein Inhibitors," *Front. Pharmacol.*, vol. 11, p. 557789, Nov. 2020. doi: 10.3389/fphar.2020.557789.

[172] A. Ahuja, J. H. Kim, J.-H. Kim, Y.-S. Yi, J. Y. Cho, "Functional role of ginseng-derived compounds in cancer," *J. Ginseng Res.*, vol. 42, no. 3, pp. 248-254, Jul. 2018. doi: 10.1016/j.jgr.2017.04.009.

[173] Y.-J. Kim, J.-N. Jeon, M.-G. Jang, J. Y. Oh, W.-S. Kwon *et. al.,* "Ginsenoside profiles and related gene expression during foliation in Panax ginseng Meyer," *J. Ginseng Res.*, vol. 38, no. 1,

pp. 66-72, Jan. 2014. doi: 10.1016/j.jgr.2013.11.001.

[174] P. Zhang, Z. Cui, S. Wei, Y. Li, Y. Yin *et. al.*, "Diverse limonoids from barks of *Toona ciliata* var. yunnanensis and their biological activities," *Ind. Crops Prod*., vol. 148, p. 112275, Feb. 2020. doi: 10.1016/j.indcrop.2020.112275.

[175] Y. Li, Y.-Z. Xia, S.-M. Hu, L.-Y. Kong, L. Yang, "Tooniliatone A sensitizes multidrug resistant cancer cells by decreasing Bcl-xL via activation of JNK MAPK signaling," *Phytomedicine*, vol. 62, p. 152947, Sept. 2019. doi: 10.1016/j.phymed.2019.152947.

[176] M. Zielińska-Błajet and J. Feder-Kubis, "Monoterpenes and Their Derivatives-Recent Development in Biological and Medical Applications," *Int. J. Mol. Sci.*, vol. 21, no. 19, p. 7078, Sept. 2020. doi: 10.3390/ijms21197078.

[177] J. Ma, X. Hu, J. Li, D. Wu, Q. Lan *et. al.*, "Enhancing conventional chemotherapy drug cisplatin-induced anti-tumor effects on human gastric cancer cells both *in vitro and in vivo* by Thymoquinone targeting PTEN gene," *Oncotarget*, vol. 8, no. 49, pp. 85926-85939, Sept. 2017. doi: 10.18632/oncotarget.20721.

[178] Ç. Şakalar, K. İzgi, B. İskender, S. Sezen, H. Aksu *et. al.*, "The combination of thymoquinone and paclitaxel shows anti-tumor activity through the interplay with apoptosis network in triple-negative breast cancer," *Tumour Biol.*, vol. 37, no. 4, pp. 4467-4477, Apr. 2016. doi: 10.1007/s13277-015-4307-0.

[179] M. Chudzik, I. Korzonek-Szlacheta, W. Król, "Triterpenes as Potentially Cytotoxic Compounds," *Molecules*, vol. 20, pp. 1610-1625, Jan. 2015. doi: 10.3390/molecules20011610.

[180] Y. Cai, Y. Zheng, J. Gu, S. Wang, N. Wang *et. al.*, "Betulinic acid chemosensitizes breast cancer by triggering ER stress-mediated apoptosis by directly targeting GRP78," *Cell Death Dis.*, vol. 9, no. 6, p. 636, May 2018. doi: 10.1038/s41419-018-0669-8.

[181] X.-K. Zhan, J.-L. Li, S. Zhang, P.-Y. Xing, M.-F. Xia, "Betulinic acid exerts potent antitumor effects on paclitaxel-resistant human lung carcinoma cells (H460) via G2/M phase cell cycle arrest and induction of mitochondrial apoptosis," *Oncol. Lett.*, vol. 16, no. 3, pp. 3628-3634, Sept. 2018. doi: 10.3892/ol.2018.9097.

[182] X. Jin, J. Zhou, Z. Zhang, H. Lv, "Doxorubicin combined with betulinic acid or lonidamine in RGD ligand-targeted pH-sensitive micellar system for ovarian cancer treatment," *Int. J. Pharm.*, vol. 571, p. 118751, Nov. 2019. doi: 10.1016/j.ijpharm.2019.118751.

[183] Y. J. Lee, S.-Y. Kim, C. Lee, "Axl is a novel target of celastrol that inhibits cell proliferation and migration, and increases the cytotoxicity of gefitinib in EGFR mutant non-small cell lung cancer cells," *Mol. Med. Rep.*, vol. 19, no. 4, pp. 3230-3236, Apr. 2019. doi: 10.3892/mmr.2019.9957.

[184] Y. Wang, Q. Liu, H. Chen, J. You, B. Peng *et. al.*, "Celastrol improves the therapeutic efficacy of EGFR-TKIs for non-small-cell lung cancer by overcoming EGFR T790M drug resistance," *Anticancer Drugs*, vol. 29, no. 8, pp. 748-755, Sept. 2018. doi: 10.1097/CAD.0000000000000647.

[185] S. H. Kim, J. G. Kang, C. S. Kim, S.-H. Ihm, M. G. Choi *et. al.*, "Cytotoxic effect of celastrol alone or in combination with paclitaxel on anaplastic thyroid carcinoma cells," *Tumour Biol.*, vol. 39, no. 5, p. 1010428317698369, May 2017. doi: 10.1177/1010428317698369.

[186] F.-Z. Lin, S.-C. Wang, Y.-T. Hsi, Y.-S. Lo, C.-C. Lin *et. al.*, "Celastrol induces vincristine multidrug resistance oral cancer cell apoptosis by targeting JNK1/2 signaling pathway," *Phytomedicine*, vol. 54, pp. 1-8, Feb. 2019. doi: 10.1016/j.phymed.2018.09.181.

[187] M. K. Shanmugam, K. S. Ahn, J. H. Lee, R. Kannaiyan, N. Mustafa *et. al.*, "Celastrol Attenuates the Invasion and Migration and Augments the Anticancer Effects of Bortezomib in a Xenograft Mouse Model of Multiple Myeloma," *Front. Pharmacol.*, vol. 9, p. 365, May 2018. doi: 10.3389/fphar.2018.00365.

[188] R. Zhang, Z. Chen, S.-S. Wu, J. Xu, L.-C. Kong *et. al.*, "Celastrol Enhances the Anti-Liver Cancer Activity of Sorafenib," *Med. Sci. Monit.*, vol. 25, pp. 4068-4075, Jun. 2019. doi: 10.12659/MSM.914060.

[189] H. O. Nyaboke, M. Moraa, L. K. Omosa, A. T. Mbaveng, N.-N. Vaderament-Alexe *et. al.*, "Cytotoxicity of Lupeol from the Stem Bark of *Zanthoxylum gilletii* against Multi-factorial Drug Resistant Cancer Cell Lines," *Invest. Med. Chem. Pharmacol.*, vol. 1, no. 1, p. 10, May 2018.

[190] M.-C. Chen, H.-H. Hsu, Y.-Y. Chu, S.-F. Cheng, C.-Y. Shen *et. al.*, "Lupeol alters ER stress-signaling pathway by downregulating *ABCG2* expression to induce Oxaliplatin-resistant LoVo colorectal cancer cell apoptosis," *Environ. Toxicol.*, vol. 33, no. 5, pp. 587-593, May 2018. doi: 10.1002/tox.22544.

[191] C. Gao, X. Li, S. Yu, L. Liang, "Inhibition of cancer cell growth by oleanolic acid in multidrug resistant liver carcinoma is mediated via suppression of cancer cell migration and invasion, mitochondrial apoptosis, G2/M cell cycle arrest and deactivation of JNK/p38 signalling pathway," *J. BUON.*, vol. 24, no. 5, pp. 1964-1969, Sept. 2019.

[192] A. T. Mbaveng, G. F. Chi, I. N. Bonsou, S. Abdelfatah, A. N. Tamfu *et. al.*, "*N*-acetylglycoside of oleanolic acid (aridanin) displays promising cytotoxicity towards human and animal cancer cells, inducing apoptotic, ferroptotic and necroptotic cell death,"

Phytomedicine, vol. 76, p. 153261, Jun. 2020. doi: 10.1016/j.phymed.2020.153261.

[193] L. Zong, G. Cheng, S. Liu, Z. Pi, Z. Liu *et. al.*, "Reversal of multidrug resistance in breast cancer cells by a combination of ursolic acid with doxorubicin," *J. Pharm. Biomed. Anal.*, vol. 165, pp. 268-275, Feb. 2019. doi: 10.1016/j.jpba.2018.11.057.

[194] S. Prasad, V. R. Yadav, B. Sung, S. C. Gupta, A. K. Tyagi *et. al.*, "Ursolic acid inhibits the growth of human pancreatic cancer and enhances the antitumor potential of gemcitabine in an orthotopic mouse model through suppression of the inflammatory microenvironment," *Oncotarget*, vol. 7, no. 11, pp. 13182-13196, Mar. 2016. doi: 10.18632/oncotarget.7537.

[195] C. Ramalhete, S. Mulhovo, H. Lage, M.-J. U Ferreira, "Triterpenoids from *Momordica balsamina* with a Collateral Sensitivity Effect for Tackling Multidrug Resistance in Cancer Cells," *Planta Med.*, vol. 84, no. 18, pp. 1372-1379, Dec. 2018. doi: 10.1055/a-0651-8141.

[196] A. Gupta, B. S. Kumar, A. S. Negi, "Current status on development of steroids as anticancer agents," *J. Steroid Biochem. Mol. Biol.*, vol. 137, pp. 242-270, Sept. 2013. doi: 10.1016/j.jsbmb.2013.05.011.

[197] J. Xiao, M. Gao, B. Fei, G. Huang, Q. Diao, "Nature-derived anticancer steroids outside cardica glycosides," *Fitoterapia.*, vol. 147, p. 104757, Oct. 2020. doi: 10.1016/j.fitote.2020.104757.

[198] J. N. Kong, Q. He, G. Wang, S. Dasgupta, M. B. Dinkins *et. al.*, "Guggulsterone and bexarotene induce secretion of exosome-associated breast cancer resistance protein and reduce doxorubicin resistance in MDA-MB-231 cells," *Int. J. Cancer*, vol. 137, no. 7, pp. 1610-1620, Oct. 2015. doi: 10.1002/ijc.29542.

[199] A. A. Bhat, K. S. Prabhu, S. Kuttikrishnan, R. Krishnankutty, J. Babu *et. al.*, "Potential therapeutic targets of Guggulsterone in cancer," *Nutr. Metab. (Lond)*, vol. 14, p. 23, Feb. 2017. doi: 10.1186/s12986-017-0180-8.

[200] J. M. Ku, S. R. Kim, S. H. Hong, H.-S. Choi, H. S. Seo *et. al.*, "Cucurbitacin D induces cell cycle arrest and apoptosis by inhibiting STAT3 and NF-κB signaling in doxorubicin-resistant human breast carcinoma (MCF7/ADR) cells," *Mol. Cell Biochem.*, vol. 409, no. 1-2, pp. 33-43, Nov. 2015. doi: 10.1007/s11010-015-2509-9.

[201] C. J. Henrich, A. D. Brooks, K. L. Erickson, C. L. Thomas, H. R. Bokesch *et. al.*, "Withanolide E sensitizes renal carcinoma cells to TRAIL-induced apoptosis by increasing cFLIP degradation," *Cell Death Dis.*, vol. 6, no. 2, p. e1666, Feb. 2015. doi: 10.1038/cddis.2015.38.

[202] G. Eksi, S. Kurbanoglu, S. A. Ozkan, "Fortification of Functional and Medicinal Beverages with Botanical Products and Their Analysis," in *Engineering Tools in the Beverage Industry*, A. M. Grumezescu and A. M. Holban, Eds. Netherlands: Elsevier, 2019, pp. 351-404.

[203] F. Yang, F. Wang, Y. Liu, S. Wang, X. Li *et. al.*, "Sulforaphane induces autophagy by inhibition of HDAC6-mediated PTEN activation in triple negative breast cancer cells," *Life Sci.*, vol. 213, pp. 149-157, Nov. 2018. doi: 10.1016/j.lfs.2018.10.034.

[204] A. Pawlik, M. Słomińska-Wojewódzka, A. Herman-Antosiewicz, "Sensitization of estrogen receptor-positive breast cancer cell lines to 4-hydroxytamoxifen by isothiocyanates present in cruciferous plants," *Eur. J. Nutr.*, vol. 55, no. 3, pp. 1165-1180, Apr. 2016. doi: 10.1007/s00394-015-0930-1.

[205] J. Gu, Y. Gui, L. Chen, G. Yuan, H.-Z. Lu *et. al.*, "Use of natural products as chemical library for drug discovery and network pharmacology," *PLoS One*, vol. 8, no. 4, p. e62839, Apr. 2013. doi: 10.1371/journal.pone.0062839.

[206] P. M. Cheuka, G. Mayoka, P. Mutai, K. Chibale, "The Role of Natural Products in Drug Discovery and Development against Neglected Tropical Diseases," *Molecules*, vol. 22, no. 1, p. 58, Dec. 2016. doi: 10.3390/molecules22010058.

[207] J. de Oliveira Viana, M. B. Félix, M. dos Santos Maia, V. de Lima Serafim, L. Scotti, "Drug discovery and computational strategies in the multitarget drugs era," *Braz. J. Pharm. Sci.*, vol. 54, p. e01010, Nov. 2018. doi: 10.1590/s2175-97902018000001010.

[208] Z. Liao, S. W. Wong, H. L. Yeo, Y. Zhao, "Smart nanocarriers for cancer treatment: Clinical impact and safety," *NanoImpact*, vol. 20, p. 100253, Sept. 2020. doi: 10.1016/j.impact.2020.100253.

[209] C. Zhang, M. Yang, A. C. Ericsson, "Antimicrobial Peptides: Potential Application in Liver Cancer," *Front. Microbiol.*, vol. 10, p. 1257, Jun. 2019. doi: 10.3389/fmicb.2019.01257.

[210] X. Luo, Q.-X. Teng, J.-Y. Dong, D.-H. Yang, M. Wang *et. al.*, "Antimicrobial Peptide Reverses *ABCB1*-Mediated Chemotherapeutic Drug Resistance," *Front. Pharmacol.*, vol. 11, p. 1208, Aug. 2020. doi: 10.3389/fphar.2020.01208.

[211] S. E. B. Ambjørner, M. Wiese, S. Christoph Köhler, J. Svindt, X. L. Lund *et. al.*, "The Pyrazolo[3,4-*d*]pyrimidine Derivative, SCO-201, Reverses Multidrug Resistance Mediated by *ABCG2*/BCRP," *Cells*, vol. 9, no. 3, p. 613, Mar. 2020. doi: 10.3390/cells9030613.

[212] R. Punia, K. Raina, R. Agarwal, R. P. Singh, "Acacetin enhances the therapeutic efficacy of doxorubicin in non-small-cell lung carcinoma cells," *PLoS One*, vol. 12, no. 8, p. E0182870, Aug. 2017. doi: 10.1371/journal.pone.0182870.

[213] V. Kuete, A. T. Mbaveng, L. P. Sandjo, M. Zeino, T. Efferth, "Cytotoxicity and mode of action of a naturally occurring naphthoquinone, 2-

acetyl-7-methoxynaphtho[2,3-*b]*furan-4,9-quinone towards multi-factorial drug-resistant cancer cells," *Phytomedicine*, vol. 33, pp. 62-68, Sept. 2017. doi: 10.1016/j.phymed.2017.07.010.

[214] V. Kuete, A. T. Mbaveng, E. C. N. Nono, C. C. Simo, Maen Zeino *et. al.*, "Cytotoxicity of seven naturally occurring phenolic compounds towards multi-factorial drug-resistant cancer cells," *Phytomedicine*, vol. 23, no. 8, pp. 856-863, Jul. 2016. doi: 10.1016/j.phymed.2016.04.007.

[215] J. Li, B. Duan, Y. Guo, R. Zhou, J. Sun *et. al.*, "Baicalein sensitizes hepatocellular carcinoma cells to 5-FU and Epirubicin by activating apoptosis and ameliorating P-glycoprotein activity," *Biomed. Pharmacother.*, vol. 98, pp. 806-812, Feb. 2018. doi: 10.1016/j.biopha.2018.01.002.

[216] Y. Zhang, F.-L. An, S.-S. Huang, L. Yang, Y.-C. Gu *et. al.*, "Diverse tritepenoids from the fruits of Walsura robusta and their reversal of multidrug resistance phenotype in human breast cancer cells," *Phytochemistry*, vol. 136, pp. 108-118, Apr. 2017. doi: 10.1016/j.phytochem.2017.01.008.

[217] S. Darzi, S. A. Mirzaei, F. Elahian, S. Shirian, A. Peymani *et. al.*, "Enhancing the Therapeutic Efficacy of Daunorubicin and Mitoxantrone with Bavachinin, Candidone, and Tephrosin," *Evid. Based Complement. Alternat. Med.*, vol. 2019, p. 3291737, Nov. 2019. doi: 10.1155/2019/3291737.

[218] F. A. Adem, V. Kuete, A. T. Mbaveng, M. Heydenreich, A. Ndakala *et. al.*, "Cytotoxic benzylbenzofuran derivatives from *Dorstenia kameruniana*," *Fitoterapia*, vol. 128, pp. 26-30, Jul. 2018. doi: 10.1016/j.fitote.2018.04.019.

[219] S. K. Jung, M.-H. Lee, D. Y. Lim, S. Y. Lee, C.-H. Jeong *et. al.*, "Butein, a novel dual inhibitor of MET and EGFR, overcomes gefitinib-resistant lung cancer growth," *Mol. Carcinog.*, vol. 54, no. 4, pp. 322-331, Apr. 2015. doi: 10.1002/mc.22191.

[220] G. Hou, X. Yuan, Y. Li, G. Hou, X. Liu, "Cardamonin, a natural chalcone, reduces 5-fluorouracil resistance of gastric cancer cells through targeting Wnt/*β*-catenin signal pathway," *Invest. New Drugs*, vol. 38, no. 2, pp. 329-339, Apr. 2020. doi: 10.1007/s10637-019-00781-9.

[221] E. Heidarian and M. Keloushadi, "Antiproliferative and Anti-invasion Effects of Carvacrol on PC3 Human Prostate Cancer Cells through Reducing pSTAT3, pAKT, and pERK1/2 Signaling Proteins," *Int. J. Prev. Med.*, vol. 10, p. 156, Oct. 2019. doi: 10.4103/ijpvm.IJPVM_292_17.

[222] A. Mari, G. Mani, S. N. Nagabhishek, G. Balaraman, N. Subramanian *et. al.*, "Carvacrol Promotes Cell Cycle Arrest and Apoptosis through PI3K/AKT Signaling Pathway in MCF-7 Breast Cancer Cells," *Chin. J. Integr. Med.*, Jun. 2020. doi: 10.1007/s11655-020-3193-5.

[223] Y.-M. Lin, C.-I. Chen, Y.-P. Hsiang, Y.-C. Hsu, K.-C. Cheng *et. al.*, "Chrysin Attenuates Cell Viability of Human Colorectal Cancer Cells through Autophagy Induction Unlike 5-Fluorouracil/Oxaliplatin," *Int. J. Mol. Sci.*, vol. 19, no. 6, p. 1763, Jun. 2018. doi: 10.3390/ijms19061763.

[224] W. Wei, J. He, H. Ruan, Y. Wang, "*In vitro* and *in vivo* cytotoxic effects of chrysoeriol in human lung carcinoma are facilitated through activation of autophagy, sub-G1/G0 cell cycle arrest, cell migration and invasion inhibition and modulation of MAPK/ERK signalling pathway," *J. BUON.*, vol. 24, no. 3, pp. 936-942, May-Jun. 2019.

[225] S. S. S. Boyanapalli and A.-N. T. Kong, ""Curcumin, the King of Spices": Epigenetic Regulatory Mechanisms in the Prevention of Cancer, Neurological, and Inflammatory Diseases," *Curr. Pharmacol. Rep.*, vol. 1, no. 2, pp. 129-139, Apr. 2015. doi: 10.1007/s40495-015-0018-x.

[226] L. Piao, S. Mukherjee, Q. Chang, X. Xie, H. Li *et. al.*, "TriCurin, a novel formulation of curcumin, epicatechin gallate, and resveratrol, inhibits the tumorigenicity of human papillomavirus-positive head and neck squamous cell carcinoma," *Oncotarget*, vol. 8, no. 36, pp. 60025-60035, Jul. 2016. doi: 10.18632/oncotarget.10620.

[227] K. Mortezaee, M. Najafi, B. Farhood, A. Ahmadi, D. Shabeeb *et. al.*, "NF-κB targeting for overcoming tumor resistance and normal tissues toxicity," *J. Cell Physiol.*, vol. 234, no. 10, pp. 17187-17204, Aug. 2019. doi: 10.1002/jcp.28504.

[228] A. Niedzwiecki, M. W. Roomi, T. Kalinovsky, M. Rath, "Anticancer Efficacy of Polyphenols and Their Combinations," *Nutrients*, vol. 8, no. 9, p. 552, Sept. 2016. doi: 10.3390/nu8090552.

[229] M. Sanaei and F. Kavoosi, "Effect of Curcumin and Trichostatin A on the Expression of DNA Methyltransfrase 1 in Hepatocellular Carcinoma Cell Line Hepa 1-6," *Iran J. Ped. Hematol. Oncol.*, vol. 8, no. 4, pp. 193-201, Oct. 2018.

[230] S. Mapoung, P. Pitchakarn, S. Yodkeeree, C. Ovatlarnporn, N. Sakorn *et. al.*, "Chemosensitizing effects of synthetic curcumin analogs on human multi-drug resistance leukemic cells," *Chem. Biol. Interact.*, vol. 244, pp. 140-148, Jan. 2016. doi: 10.1016/j.cbi.2015.12.001.

[231] D.-S. Popa and M. E. Rusu, "Isoflavones: Vegetable Sources, Biological Activity, and Analytical Methods for Their Assessment," in *Superfood and Functional Food - The Development of Superfoods and Their Roles as Medicine*, N. Shiomi and V. Waisundara, Eds. United Kingdom: IntechOpen, 2017, pp. 133-153.

[232] J. P. Rigalli, P. N. Scholz, G. N. Tocchetti, M. L. Ruiz, J. Weiss, "The phytoestrogens daidzein and equol inhibit the drug transporter BCRP/*ABCG2* in breast cancer cells: potential chemosensitizing effect," *Eur. J. Nutr.*, vol. 58, no. 1, pp. 139-150, Feb. 2019. doi: 10.1007/s00394-017-1578-9.

[233] A. T. Mbaveng, F. Damen, M.-G. F. Guefack, S. B. Tankeo, S. Abdelfatah *et. al.*, "8,8-bis-(Dihydroconiferyl)-diferulate displayed impressive cytotoxicity towards a panel of human and animal cancer cells," *Phytomedicine*, vol. 70, p. 153215, Apr. 2020. doi: 10.1016/j.phymed.2020.

[234] Z. Wang, X. Sun, Y. Feng, Y. Wang, L. Zhang *et. al.*, "Dihydromyricetin reverses MRP2-induced multidrug resistance by preventing NF-κB-Nrf2 signaling in colorectal cancer cell," *Phytomedicine*, p. 153414, Nov. 2020. doi: 10.1016/j.phymed.2020.153414.

[235] M. Wu, M. Jiang, T. Dong, L. X, J. Lv *et. al.*, "Reversal Effect of Dihydromyricetin on Multiple Drug Resistance in SGC7901/5-FU Cells," *Asian Pac. J. Cancer Prev.*, vol. 21, no. 5, pp. 1269-1274, May 2020. doi: 10.31557/APJCP.2020.21.5.1269.

[236] A. Maruszewska and J. Tarasiuk, "Antitumour effects of selected plant polyphenols, gallic acid and ellagic acid, on sensitive and multidrug-resistant leukaemia HL60 cells," *Phytother. Res.*, vol. 33, no. 4, pp. 1208-1221, Apr. 2019. doi: 10.1002/ptr.6317.

[237] H.-N. Jiang, Z.-G. Liu, R. Hu, "[Embelin Reverses the Multi-drug Resistance of K562/D to Daunorubicin Independently of P-gp and MDR1 mRNA]," *Zhongguo Shi Yan Xue Ye Xue Za Zhi*, vol. 25, no. 5, pp. 1342-1349, Oct. 2017. doi: 10.7534/j.issn.1009-2137.2017.05.011.

[238] K. S. Prabhu, K. S. Siveen, S. Kuttikrishnan, A. Iskandarani, M. Tsakou *et. al.*, "Targeting of X-linked inhibitor of apoptosis protein and PI3-kinase/AKT signaling by embelin suppresses growth of leukemic cells," *PLoS One*, vol. 12, no. 7, p. e0180895, Jul. 2017. doi: 10.1371/journal.pone.0180895.

[239] A. K. Siraj, P. Pratheeshkumar, S. K. Parvathareddy, S. P. Divya, F. Al-Dayel *et. al.*, "Overexpression of PARP is an independent prognostic marker for poor survival in Middle Eastern breast cancer and its inhibition can be enhanced with embelin co-treatment," *Oncotarget*, vol. 9, no. 99, pp. 37319-37332, Dec. 2018. doi: 10.18632/oncotarget.26470.

[240] H. Guo, F. Liu, S. Yang, T. Xue, "Emodin alleviates gemcitabine resistance in pancreatic cancer by inhibiting MDR1/P-glycoprotein and MRPs expression," *Oncol. Lett.*, vol. 20, no. 5, p. 167, Nov. 2020. doi: 10.3892/ol.2020.12030.

[241] Wikipedia. "Fisetin". Wikipedia.org. https://en.wikipedia.org/wiki/Fisetin (accessed December 10, 2020).

[242] E. Mukhtar, V. M. Adhami, I. A. Siddiqui, A. K. Verma, H. Mukhtar, "Fisetin Enhances Chemotherapeutic Effect of Cabazitaxel against Human Prostate Cancer Cells," *Mol. Cancer Ther.*, vol. 15, no. 12, pp. 2863-2874, Dec. 2016. doi: 10.1158/1535-7163.MCT-16-0515.

[243] H. C. Pal, A. C. Diamond, L. R. Strickland, J. C. Kappes, S. K. Katiyar *et. al.*, "Fisetin, a dietary flavonoid, augments the anti-invasive and anti-metastatic potential of sorafenib in melanoma," *Oncotarget.*, vol. 7, no. 2, pp. 1227-1241, Jan. 2016. doi: 10.18632/oncotarget.6237.

[244] S. Yu, L.-S. Gong, N.-F. Li, Y.-F. Pan, L. Zhang, "Galangin (GG) combined with cisplatin (DDP) to suppress human lung cancer by inhibition of STAT3-regulated NF-κB and Bcl-2/Bax signaling pathways," *Biomed. Pharmacother.*, vol. 97, pp. 213-224, Jan. 2018. doi: 10.1016/j.biopha.2017.10.059.

[245] Y. Wang, Y. Sui, Y. Tao, "Gambogic acid increases the sensitivity to paclitaxel in drug-resistant triple-negative breast cancer via the SHH signaling pathway," *Mol. Med. Rep.*, vol. 20, no. 5, pp. 4515-4522, Nov. 2019. doi: 10.3892/mmr.2019.10697.

[246] G. Xia, H. Wang, Z. Song, Q. Meng, X. Huang *et. al.*, "Gambogic acid sensitizes gemcitabine efficacy in pancreatic cancer by reducing the expression of ribonucleotide reductase subunit-M2 (RRM2)," J. *Exp. Clin. Cancer Res.*, vol. 36, no. 1, p. 107, Aug. 2017. doi: 10.1186/s13046-017-0579-0.

[247] Wikipedia. "Gambogic acid". Wikipedia.org. https://en.wikipedia.org/wiki/Gambogic_acid (accessed December 10, 2020).

[248] S. Wang, L. Wang, M. Chen, Y. Wang, "Gambogic acid sensitizes resistant breast cancer cells to doxorubicin through inhibiting P-glycoprotein and suppressing survivin expression," *Chem. Biol. Interact.*, vol. 235, pp. 76-84, Jun. 2015. doi: 10.1016/j.cbi.2015.03.017.

[249] W. Kong, X. Ling, Y. Chen, X. Wu, Z. Zhao *et. al.*, "Hesperetin reverses P-glycoprotein-mediated cisplatin resistance in DDP-resistant human lung cancer cells via modulation of the nuclear factor-κB signaling pathway," *Int. J. Mol. Med.*, vol. 45, no. 4, pp. 1213-1224, Apr. 2020. doi: 10.3892/ijmm.2020.4485.

[250] C. T. Scoparo, G. Valdameri, P. R. Worfel, F. A. L. B. Guterres, G. R. Martinez *et. al.*, "Dual properties of hispidulin: antiproliferative effects on HepG2 cancer cells and selective inhibition of *ABCG2* transport activity," *Mol. Cell Biochem.*, vol. 409, no. 1-2, pp. 123-133, Nov. 2015. doi: 10.1007/s11010-015-2518-8.

[251] H. Gao, J. Xie, J. Peng, Y. Han, Q. Jiang *et. al.*, "Hispidulin inhibits proliferation and enhances chemosensitivity of gallbladder cancer cells by targeting HIF-1α," *Exp. Cell Res.*, vol. 332, no. 2, pp. 236-246, Mar. 2015. doi: 10.1016/j.yexcr.2014.11.021.

[252] H. E. Pearson, M. Iida, R. A. Orbuch, N. K McDaniel, K. P. Nickel *et. al.*, "Overcoming Resistance to Cetuximab with Honokiol, A Small-Molecule Polyphenol," *Mol. Cancer Ther.*, vol. 17, no. 1, pp. 204-214, Jan. 2018. doi: 10.1158/1535-7163.MCT-17-0384.

[253] W. Songjang and A. Jiraviriyakul, "Honokiol and Magnolol Inhibit Growth, Metastasis and Induce Apoptosis in Human Cholangiocarcinoma," *Biomed. Pharmacol. J.*, vol. 12, no.2, pp. 759-773, Jun. 2019.

[254] Z.-D. Wang, R.-Z. Wang, Y.-Z. Xia, L.-Y. Kong, L. Yang, "Reversal of multidrug resistance by icaritin in doxorubicin-resistant human osteosarcoma cells," *Chin. J. Nat. Med.*, vol. 16, no. 1, pp. 20-28, Jan. 2018. doi: 10.1016/S1875-5364(18)30026-8.

[255] H. Han, B. Xu, P. Hou, C. Jiang, L. Liu, "Icaritin Sensitizes Human Glioblastoma Cells to TRAIL-Induced Apoptosis," *Cell Biochem. Biophys.*, vol. 72, no. 2, pp. 533-542, Jun. 2015. doi: 10.1007/s12013-014-0499-y.

[256] L.-C. Lin, C.-H. Wu, T.-M. Shieh, H.-Y. Chen, T.-C. Huang *et. al.*, "The licorice dietary component isoliquiritigenin chemosensitizes human uterine sarcoma cells to doxorubicin and inhibits cell growth by inducing apoptosis and autophagy via inhibition of m-TOR signaling," *J. Funct. Foods*, vol. 33, pp. 332-344, Apr. 2017. doi: 10.1016/j.jff.2017.03.061.

[257] B.-Y. Zhang, Y.-M. Wang, H. Gong, H. Zhao, X.-Y. Lv *et. al.*, "Isorhamnetin flavonoid synergistically enhances the anticancer activity and apoptosis induction by cis-platin and carboplatin in non-small cell lung carcinoma (NSCLC)," *Int. J. Clin. Exp. Pathol.*, vol. 8, no. 1, pp. 25-37, Jan. 2015.

[258] J. Bai, S. Zhao, X. Fan, Y. Chen, X. Zou *et. al.*, "Inhibitory effects of flavonoids on P-glycoprotein *in vitro* and *in vivo*: Food/herb-drug interactions and structure-activity relationships," *Toxicol. Appl. Pharmacol.*, vol. 369, pp. 49-59, Apr. 2019. doi: 10.1016/j.taap.2019.02.010.

[259] Q. Liu, D. Zhu, B. Hao, Z. Zhang, Y. Tian, "Luteolin promotes the sensitivity of cisplatin in ovarian cancer by decreasing PRPA1-medicated autophagy," *Cell Mol. Biol. (Noisy-le-grand)*, vol. 64, no. 6, pp. 17-22, May 2018. doi: 10.14715/cmb/2018.64.6.4.

[260] T. Takeda, M. Tsubaki, T. Kino, A. Kawamura, S. Isoyama *et. al.*, "Mangiferin enhances the sensitivity of human multiple myeloma cells to anticancer drugs through suppression of the nuclear factor κB pathway," *Int. J. Oncol.*, vol. 48, no. 6, pp. 2704-2712, Jun. 2016. doi: 10.3892/ijo.2016.3470.

[261] P. Sadhukhan, S. Saha, S. Dutta, P. C. Sil, "Mangiferin Ameliorates Cisplatin Induced Acute Kidney Injury by Upregulating Nrf-2 via the Activation of PI3K and Exhibits Synergistic Anticancer Activity With Cisplatin," *Front. Pharmacol.*, vol. 9, p. 638, Jun. 2018. doi: 10.3389/fphar.2018.00638.

[262] G. Gatouillat, A. A. Magid, E. Bertin, H. El btaouri, H. Morjani *et. al.*, "Medicarpin and millepurpan, two flavonoids isolated from *Medicago sativa*, induce apoptosis and overcome multidrug resistance in leukemia P388 cells," *Phytomedicine*, vol. 22, no. 13, pp. 1186-1194, Dec. 2015. doi: 10.1016/j.phymed.2015.09.005.

[263] Wikipedia. "Myricetin". Wikipedia.org. https://en.wikipedia.org/wiki/Myricetin (accessed December 11, 2020).

[264] A.-W. Zheng, Y.-Q. Chen, L.-Q. Zhao, J.-G. Feng, "Myricetin induces apoptosis and enhances chemosensitivity in ovarian cancer cells," *Oncol. Lett.*, vol. 13, no. 6, pp. 4974-4978, Jun. 2017. doi: 10.3892/ol.2017.6031.

[265] B. B. Chandrika, M. Steephan, T. R. S. Kumar, A. Sabu, M. Haridas, "Hesperetin and Naringenin sensitize HER2 positive cancer cells to death by serving as HER2 Tyrosine Kinase inhibitors," *Life Sci.*, vol. 160, pp. 47-56, Sept. 2016. doi: 10.1016/j.lfs.2016.07.007.

[266] H.-L. Chang, Y.-M. Chang, S.-C. Lai, K.-M. Chen, K.-C. Wang *et. al.*, "Naringenin inhibits migration of lung cancer cells via the inhibition of matrix metalloproteinases-2 and -9," *Exp. Ther. Med.*, vol. 13, no. 2, pp. 739-744, Feb. 2017. doi: 10.3892/etm.2016.3994.

[267] L. Eanes and Y. M. Patel, "Inhibition of the MAPK pathway alone is insufficient to account for all of the cytotoxic effects of naringenin in MCF-7 breast cancer cells," *Biochim. Open*, vol. 3, pp. 64-71, Nov. 2016. doi: 10.1016/j.biopen.2016.09.004.

[268] W. Ma, S. Feng, X. Yao, Z. Yuan, L. Liu *et. al.*, "Nobiletin enhances the efficacy of chemotherapeutic agents in *ABCB1* overexpression cancer cells," *Sci. Rep.*, vol. 5, p. 18789, Dec. 2015. doi: 10.1038/srep18789.

[269] S.-L. Feng, Y. Tian, S. Huo, B. Qu, R.-M. Liu *et. al.*, "Nobiletin potentiates paclitaxel anticancer efficacy in A549/T xenograft model: Pharmacokinetic and pharmacological study," *Phytomedicine*, vol. 67, p. 153141, Feb. 2020. doi: 10.1016/j.phymed.2019.153141.

[270] R. Zhang, Z. Wang, W. You, F. Zhou, Z. Guo Liu *et. al.*, "Suppressive effects of plumbagin on the growth of human bladder cancer cells via PI3K/AKT/mTOR signaling pathways and EMT," *Cancer Cell Int.*, vol. 20, p. 520, Oct. 2020. doi: 10.1186/s12935-020-01607-y.

[271] S. Li, Q. Zhao, B. Wang, S. Yuan, X. Wang *et. al.*, "Quercetin reversed MDR in breast cancer cells through down-regulating P-gp expression and eliminating cancer stem cells mediated by YB-1 nuclear translocation," *Phytother. Res.*, vol. 32, no. 8, pp. 1530-1536, Aug. 2018. doi: 10.1002/ptr.6081.

[272] Z. Zhang, Z. Liu, J. Chen, J. Yi, J. Cheng Wang *et. al.*, "Resveratrol induces autophagic apoptosis via the lysosomal cathepsin D pathway in human drug-resistant K562/ADM leukemia cells," *Exp. Ther. Med.*, vol. 15, no. 3, pp. 3012-3019, Mar. 2018. doi: 10.3892/etm.2018.5742.

[273] C.-H. Chang, C.-Y. Lee, C.-C. Lu, F.-J. Tsai, Y.-M. Hsu *et. al.*, "Resveratrol-induced autophagy and apoptosis in cisplatin-resistant human oral cancer CAR cells: A key role of AMPK and Akt/mTOR signaling," *Int. J. Oncol.*, vol. 50, no. 3, pp. 873-882, Mar. 2017. doi: 10.3892/ijo.2017.3866.

[274] C. Buhrmann, M. Yazdi, B. Popper, P. Shayan, A. Goel *et. al.*, "Resveratrol Chemosensitizes TNF-*β*-Induced Survival of 5-FU-Treated Colorectal Cancer Cells," *Nutrients*, vol. 10, no. 7, p. 888, Jul. 2018. doi: 10.3390/nu10070888.

[275] X.-Z. Liao, Y. Gao, L.-L. Sun, J.-H. Liu, H.-R. Chen *et. al.*, "Rosmarinic acid reverses non-small cell lung cancer cisplatin resistance by activating the MAPK signaling pathway," *Phytother. Res.*, vol. 34, no. 5, pp. 1142-1153, May 2020. doi: 10.1002/ptr.6584.

[276] S. Mohana, M. Ganesan, N. R. Prasad, D. Ananthakrishnan, D. Velmurugan, "Flavonoids modulate multidrug resistance through wnt signaling in P-glycoprotein overexpressing cell lines," *BMC Cancer*, vol. 18, no. 1, p. 1168, Nov. 2018. doi: 10.1186/s12885-018-5103-1.

[277] M. Iriti, R. Kubina, A. Cochis, R. Sorrentino, E. M. Varoni *et. al.*, "Rutin, a Quercetin Glycoside, Restores Chemosensitivity in Human Breast Cancer Cells," *Phytother. Res.*, vol. 31, no. 10, pp. 1529-1538, Oct. 2017. doi: 10.1002/ptr.5878.

[278] C. Gao, Y. Zhou, Z. Jiang, Y. Zhao, D. Zhang *et. al.*, "Cytotoxic and chemosensitization effects of Scutellarin from traditional Chinese herb *Scutellaria altissima* L. in human prostate cancer cells," *Oncol. Rep.*, vol. 38, no. 3, pp. 1491-1499, Sept. 2017. doi: 10.3892/or.2017.5850.

[279] G. He, G. He, R. Zhou, Z. Pi, T. Zhu *et. al.*, "Enhancement of cisplatin-induced colon cancer cells apoptosis by shikonin, a natural inducer of ROS *in vitro* and *in vivo*," *Biochem. Biophys. Res. Commun.*, vol. 469, no. 4, pp. 1075-1082, Jan. 2016. doi: 10.1016/j.bbrc.2015.12.100.

[280] S. Dobiasová, K. Řehořová, D. Kučerová, D. Biedermann, K. Káňová *et. al.*, "Multidrug Resistance Modulation Activity of Silybin Derivatives and Their Anti-inflammatory Potential," *Antioxidants (Basel)*, vol. 9, no. 5, p. 455, May 2020. doi: 10.3390/antiox9050455.

[281] C. Eroğlu, E. Avcı, H. Vural, E. Kurar, "Anticancer mechanism of Sinapic acid in PC-3 and LNCaP human prostate cancer cell lines," *Gene*, vol. 671, pp. 127-134, Sept. 2018. doi: 10.1016/j.gene.2018.05.049.

[282] H.-J. Chen, Y.-L. Chung, C.-Y. Li, Y.-T. Chang, C. C. N. Wang *et. al.*, "Taxifolin Resensitizes Multidrug Resistance Cancer Cells via Uncompetitive Inhibition of P-Glycoprotein Function," *Molecules*, vol. 23, no. 12, p. 3055, Nov. 2018. doi: 10.3390/molecules23123055.

[283] Y.-H. Tseng, S.-S. Chiou, J.-P. Weng, P.-C. Lin, "Curcumin and tetrahydrocurcumin induce cell death in Ara-C-resistant acute myeloid leukemia," *Phytother. Res.*, vol. 33, no. 4, pp. 1199-1207, Apr. 2019. doi: 10.1002/ptr.6316.

[284] Q. Zeng, Y. Che, Y. Zhang, M. Chen, Q. Guo *et. al.*, " Thymol Isolated from *Thymus vulgaris* L. Inhibits Colorectal Cancer Cell Growth and Metastasis by Suppressing the Wnt/β-Catenin Pathway," *Drug Des. Devel. Ther.*, vol. 14, pp. 2535-2547, Jul. 2020. doi: 10.2147/DDDT.S254218.

[285] D. J. Balan, T. Rajavel, M. Das, S. Sathya, M. Jeyakumar *et. al.*, "Thymol induces mitochondrial pathway-mediated apoptosis via ROS generation, macromolecular damage and SOD diminution in A549 cells," *Pharmacol. Rep.*, Oct. 2020. doi: 10.1007/s43440-020-00171-6.

[286] T. Jamali, G. Kavoosi, M. Safavi, S. K. Ardestani, "*In-vitro* evaluation of apoptotic effect of OEO and thymol in 2D and 3D cell cultures and the study of their interaction mode with DNA," *Sci. Rep.*, vol. 8, no. 1, p. 15787, Oct. 2018. doi: 10.1038/s41598-018-34055-w.

[287] Wikipedia. "Tocotrienol". Wikipedia.org. https://en.wikipedia.org/wiki/Tocotrienol (accessed December 12, 2020).

[288] M. Bhardwaj, H. J. Cho, S. Paul, R. Jakhar, I. Khan *et. al.*, "Vitexin induces apoptosis by suppressing autophagy in multi-drug resistant colorectal cancer cells," *Oncotarget*, vol. 9, no. 3, pp. 3278-3291, Dec. 2017. doi: 10.18632/oncotarget.22890.

[289] M. Lv, J.-G. Qiu, W.-J. Zhang, Q.-W. Jiang, W.-M. Qin *et. al.*, "Wallichinine reverses *ABCB1*-mediated cancer multidrug resistance," *Am. J. Transl. Res.*, vol. 8, no. 7, pp. 2969-2980, Jul. 2016.

[290] X. Xu, X. Zhang, Y. Zhang, L. Yang, Y. Liu *et. al.*, "Wogonin reversed resistant human myelogenous leukemia cells via inhibiting Nrf2 signaling by Stat3/NF-κB inactivation," *Sci. Rep.*, vol. 7, p. 39950, Feb. 2017. doi: 10.1038/srep39950.

[291] F. Liu, H. Hoag, C. Wu, H. Liu, H. Yin *et. al.*, "Experimental and Simulation Identification of Xanthohumol as an Inhibitor and Substrate of

ABCB1," *Appl. Sci.*, vol. 8, p. 681, Apr. 2018. doi: 10.3390/app8050681.

[292] Z.-F. Hong, W.-X. Zhao, Z.-Y. Yin, C.-R. Xie, Y.-P. Xu *et. al.*, "Capsaicin Enhances the Drug Sensitivity of Cholangiocarcinoma through the Inhibition of Chemotherapeutic-Induced Autophagy," *PLoS One*, vol. 10, no. 5, p. e0121538, May 2015. doi: 10.1371/journal.pone.0121538.

[293] H. Li, S. Krsti, S. Wang, M. Wink, "Capsaicin and Piperine Can Overcome Multidrug Resistance in Cancer Cells to Doxorubicin," *Molecules*, vol. 23, no. 3, p. 557, Mar. 2018. doi: 10.3390/molecules23030557.

[294] Y. Wang, X. Deng, C. Yu, G. Zhao, J. Zhou *et. al.*, "Synergistic inhibitory effects of capsaicin combined with cisplatin on human osteosarcoma in culture and in xenografts," *J. Exp. Clin. Cancer Res.*, vol. 37, no. 1, p. 251, Oct. 2018. doi: 10.1186/s13046-018-0922-0.

[295] G. Sánchez, A. Bort, P. A. Mateos-Gómez, N. Rodríguez-Henche, I. Díaz-Laviada *et. al.*, "Combination of the natural product capsaicin and docetaxel synergistically kills human prostate cancer cells through the metabolic regulator AMP-activated kinase," *Cancer Cell Int.*, vol. 19, p. 54, Mar. 2019. doi: 10.1186/s12935-019-0769-2.

[296] N. Dai, R. Ye, Q. He, P. Guo, H. Chen *et. al.*, "Capsaicin and sorafenib combination treatment exerts synergistic anti-hepatocellular carcinoma activity by suppressing EGFR and PI3K/Akt/mTOR signaling," *Oncol. Rep.*, vol. 40, no. 6, pp. 3235-3248, Dec. 2018. doi: 10.3892/or.2018.6754.

[297] Z.-H. Tang, W.-X. Cao, X. Guo, X.-Y. Dai, J.-H. Lu *et. al.*, "Identification of a novel autophagic inhibitor cepharanthine to enhance the anti-cancer property of dacomitinib in non-small cell lung cancer," *Cancer Lett.*, vol. 412, pp. 1-9, Jan. 2018. doi: 10.1016/j.canlet.2017.10.001.

[298] S. Lanza-Jacoby and G. Cheng, "3,3'-Diindolylmethane enhances apoptosis in docetaxel-treated breast cancer cells by generation of reactive oxygen species," *Pharm. Biol.*, vol. 56, no. 1, pp. 407-414, Dec. 2018. doi: 10.1080/13880209.2018.

[299] D. C. Hao and L. Yang, "Drug metabolism and disposition diversity of Ranunculales phytometabolites: a systems perspective," *Expert Opin. Drug Metab. Toxicol.*, vol. 12, no. 9, pp. 1047-1065, Sept. 2016. doi: 10.1080/17425255.2016.1201068.

[300] B. Y. K. Law, S. W. F. Mok, W. K. Chan, S. W. Xu, A. G. Wu *et. al.*, "Hernandezine, a novel AMPK activator induces autophagic cell death in drug-resistant cancers," *Oncotarget*, vol. 7, no. 7, pp. 8090-8104, Feb. 2016. doi: 10.18632/oncotarget.6980.

[301] G. Perez-Chacon, C. Martinez-Laperche, N. Rebolleda, B. Somovilla-Crespo, C. Muñoz-Calleja *et. al.*, "Indole-3-Carbinol Synergizes with and Restores Fludarabine Sensitivity in Chronic Lymphocytic Leukemia Cells Irrespective of p53 Activity and Treatment Resistances," *Clin. Cancer Res.*, vol. 22, no. 1, pp. 134-145, Jan. 2016. doi: 10.1158/1078-0432.CCR-15-0736.

[302] M. M. Abdelmageed, R. N. El-Naga, E. El-Demerdash, M. M. Elmazar, "Indole-3- carbinol enhances sorafenib cytotoxicity in hepatocellular carcinoma cells: A mechanistic study," *Sci. Rep.*, vol. 6, p. 32733, Sept. 2016. doi: 10.1038/srep32733.

[303] A. Kundu, J. G. Quirit, M. G. Khouri, G. L. Firestone, "Inhibition of oncogenic BRAF activity by indole-3-carbinol disrupts microphthalmia-associated transcription factor expression and arrests melanoma cell proliferation," *Mol. Carcinog.*, vol. 56, no. 1, pp. 349-361, Jan. 2017. doi: 10.1002/mc.22472.

[304] J. Zhou, G. Li, Y. Zheng, H.-M. Shen, X. Hu *et. al.*, "A novel autophagy/mitophagy inhibitor liensinine sensitizes breast cancer cells to chemotherapy through DNM1L-mediated mitochondrial fission," *Autophagy*, vol. 11, no. 8, pp. 1259-1279, Jun. 2015. doi: 10.1080/15548627.2015.1056970.

[305] O. Kadioglu, B. Y. K. Law, S. W. F. Mok, S.-W. Xu, T. Efferth *et. al.*, "Mode of Action Analyses of Neferine, a Bisbenzylisoquinoline Alkaloid of Lotus (*Nelumbo nucifera*) against Multidrug-Resistant Tumor Cells," *Front. Pharmacol.*, vol. 8, p. 238, May 2017. doi: 10.3389/fphar.2017.00238.

[306] C. Zhang, L.-J. He, Y.-B. Zhu, Q.-Z. Fan, D.-D. Miao *et. al.*, "Piperlongumine Inhibits Akt Phosphorylation to Reverse Resistance to Cisplatin in Human Non-Small Cell Lung Cancer Cells via ROS Regulation," vol. 10, p. 1178, Oct. 2019. doi: 10.3389/fphar.2019.01178.

[307] W. Chen, W. Lian, Y. Yuan, M. Li, "The synergistic effects of oxaliplatin and piperlongumine on colorectal cancer are mediated by oxidative stress," *Cell Death Dis.*, vol. 10, no. 8, p. 600, Aug. 2019. doi: 10.1038/s41419-019-1824-6.

[308] S. Akhtar, I. W. Achkar, K. S. Siveen, S. Kuttikrishnan, K. S. Prabhu *et. al.*, "Sanguinarine Induces Apoptosis Pathway in Multiple Myeloma Cell Lines via Inhibition of the JaK2/STAT3 Signaling," *Front. Oncol.*, vol. 9, p. 285, Apr. 2019. doi: 10.3389/fonc.2019.00285.

[309] R. Sarkhosh-Inanlou, M. Molaparast, A. Mohammadzadeh, V. Shafiei-Irannejad, "Sanguinarine enhances cisplatin sensitivity via glutathione depletion in cisplatin-resistant ovarian cancer (A2780) cells," *Chem. Biol. Drug. Des.*,

vol. 95, no. 2, pp. 215-223, Feb. 2020. doi: 10.1111/cbdd.13621.

[310] M. E. M. Saeed, N. Mahmoud, Y. Sugimoto, T. Efferth, H. Abdel-Aziz, "Molecular Determinants of Sensitivity or Resistance of Cancer Cells Toward Sanguinarine," *Front. Pharmacol.*, vol. 9, p. 136, Feb. 2018. doi: 10.3389/fphar.2018.00136.

[311] Y.-Q. Liu, S.-K. Wang, Q.-Q. Xu, H.-Q. Yuan, Y.-X. Guo *et. al.,* "Acetyl-11-keto-*β*-boswellic acid suppresses docetaxel-resistant prostate cancer cells *in vitro* and *in vivo* by blocking Akt and Stat3 signaling, thus suppressing chemoresistant stem cell-like properties," *Acta Pharmacol. Sin.*, vol. 40, no. 5, pp. 689-698, May 2019. doi: 10.1038/s41401-018-0157-9.

[312] L. Jin, W. Yingchun, S. Zhujun, W. Yinan, W. Dongchen *et. al.,* "3-acetyl-11-keto-beta-boswellic acid decreases the malignancy of taxol resistant human ovarian cancer by inhibiting multidrug resistance (MDR) proteins function," *Biomed. Pharmacother.*, vol. 116, p. 108992, Aug. 2019. doi: 10.1016/j.biopha.2019.108992.

[313] X. Xue, F. Chen, A. Liu, D. Sun, J. Wu *et. al.*, "Reversal of the multidrug resistance of human ileocecal adenocarcinoma cells by acetyl-11-keto-*β*-boswellic acid via downregulation of P-glycoprotein signals," *Biosci. Trends*, vol. 10, no. 5, pp. 392-399, Nov. 2016. doi: 10.5582/bst.2016.01115.

[314] C. Formisano, C. Sirignano, D. Rigano, G. Chianese, G. Zengin *et. al.,* "Antiproliferative activity against leukemia cells of sesquiterpene lactones from the Turkish endemic plant *Centaurea drabifolia* subsp. *Detonsa*," *Fitoterapia*, vol. 120, pp. 98-102, Jul. 2017. doi: 10.1016/j.fitote.2017.05.016.

[315] M. E. M. Saeed, N. Mahmoud, Y. Sugimoto, T. Efferth, H. Abdel-Aziz, "Betulinic Acid Exerts Cytotoxic Activity Against Multidrug-Resistant Tumor Cells via Targeting Autocrine Motility Factor Receptor (AMFR)," *Front. Pharmacol.*, vol. 9, p. 481, May 2018. doi: 10.3389/fphar.2018.00481.

[316] N.-H. Yim, Y. P. Jung, A. Kim, T. Kim, J. Y. Ma, "Induction of apoptotic cell death by betulin in multidrug-resistant human renal carcinoma cells," *Oncol. Rep.*, vol. 34, no. 2, pp. 1058-1064, Aug. 2015. doi: 10.3892/or.2015.4045.

[317] K. S. Snima, R. S. Nair, S. V. Nair, C. R. Kamath, V.-K. Lakshmanan, "Combination of Anti-Diabetic Drug Metformin and Boswellic Acid Nanoparticles: A Novel Strategy for Pancreatic Cancer Therapy," *J. Biomed. Nanotechnol.*, vol. 11, no. 1, pp. 93-104, Jan. 2015. doi: 10.1166/jbn.2015.1877.

[318] S. Toden, Y. Okugawa, C. Buhrmann, D. Nattamai, E. Anguiano *et. al.*, "Novel Evidence for Curcumin and Boswellic Acid-Induced Chemoprevention through Regulation of miR-34a and miR-27a in Colorectal Cancer," *Cancer Prev. Res.*, vol. 8, no. 5, pp. 431-443, May 2015. doi: 10.1158/1940-6207.CAPR-14-0354.

[319] N. Yao, C. Wang, N. Hu, Y. Li, M. Liu *et. al.*, "Inhibition of PINK1/Parkin-dependent mitophagy sensitizes multidrug-resistant cancer cells to B5G1, a new betulinic acid analog," *Cell Death Dis.*, vol. 10, no. 3, p. 232, Mar. 2019. doi: 10.1038/s41419-019-1470-z.

[320] F.-Z. Lin, S.-C. Wang, Y.-T. Hsi, Y.-S. Lo, C.-C. Lin *et. al.*, "Celastrol induces vincristine multidrug resistance oral cancer cell apoptosis by targeting JNK1/2 signaling pathway," *Phytomedicine*, vol. 54, pp. 1-8, Feb. 2019. doi: 10.1016/j.phymed.2018.09.181.

[321] S.-W. Xu, B. Y. K. Law, S. L. Q. Qu, S. Hamdoun, J. Chen *et. al.*, "SERCA and P-glycoprotein inhibition and ATP depletion are necessary for celastrol-induced autophagic cell death and collateral sensitivity in multidrug-resistant tumor cells," *Pharmacol. Res.*, vol. 153, p. 104660, Mar. 2020. doi: 10.1016/j.phrs.2020.104660.

[322] Y.-Y. Yan, H. Bi, W. Zhang, Q. Wen, H. Liu *et. al.*, "Downregulation and subcellular distribution of HER2 involved in MDA-MB-453 breast cancer cell apoptosis induced by lapatinib/celastrol combination," *J. BUON.*, vol. 23, no. 3, pp. 644-651, May-Jun. 2017.

[323] Y. Xiao, J. Liu, M. Guo, H. Zhou, J. Jin *et. al.*, "Synergistic combination chemotherapy using carrier-free celastrol and doxorubicin nanocrystals for overcoming drug resistance," *Nanoscale*, vol. 10, no. 26, pp. 12639-12649, Jul. 2018. doi: 10.1039/c8nr02700e.

[324] F. Cai, L. Zhang, X. Xiao, C. Duan, Q. Huang *et. al.*, "Cucurbitacin B reverses multidrug resistance by targeting CIP2A to reactivate protein phosphatase 2A in MCF-7/adriamycin cells," *Oncol. Rep.*, vol. 36, no. 2, pp. 1180-1186, Aug. 2016. doi: 10.3892/or.2016.4892.

[325] Y.-Z. Liu, C.-M. Yang, J.-Y. Chen, J.-W. Liao, M.-L. Hu, "Alpha-carotene inhibits metastasis in Lewis lung carcinoma *in vitro*, and suppresses lung metastasis and tumor growth in combination with taxol in tumor xenografted C57BL/6 mice," *J. Nutr. Biochem.*, vol. 26, no. 6, pp. 607-615, Jun. 2015. doi: 10.1016/j.jnutbio.2014.12.012.

[326] Y. Zhang, X. Zhu, T. Huang, L. Chen, Y. Liu *et. al.*, "*β*-Carotene synergistically enhances the anti-tumor effect of 5-fluorouracil on esophageal squamous cell carcinoma *in vivo* and *in vitro*," *Toxicol. Lett.*, vol. 261, pp. 49-58, Nov. 2016. doi: 10.1016/j.toxlet.2016.08.010.

[327] S. Mahdizadeh, G. Karimi, J. Behravan, S. Arabzadeh, H. Lage *et. al.*, "Crocin suppresses multidrug resistance in MRP overexpressing ovarian cancer cell line," *Daru*, vol. 24, no. 1, p. 17, Jun. 2016. doi: 10.1186/s40199-016-0155-8.

[328] M. Deng, B. Liu, H. Song, R. Yu, D. Zou *et. al.*, "*β*-Elemene inhibits the metastasis of multidrug-resistant gastric cancer cells through miR-1323/Cbl-b/EGFR pathway," *Phytomedicine*, vol. 69, p. 153184, Apr. 2020. doi: 10.1016/j.phymed.2020.153184.

[329] R. Mazrouei, E. Raeisi, Y. Lemoigne, E. Heidarian, "Activation of p53 Gene Expression and Synergistic Antiproliferative Effects of 5-Fluorouracil and *β*-escin on MCF7 Cells," *J. Med. Signals Sens.*, vol. 9, no. 3, pp. 196-203, Aug. 2019. doi: 10.4103/jmss.JMSS_44_18.

[330] S.-L. Feng, H.-B. Luo, L. Cai, J. Zhang, D. Wang *et. al.*, "Ginsenoside Rg5 overcomes chemotherapeutic multidrug resistance mediated by *ABCB1* transporter: *in vitro* and *in vivo* study," *J. Ginseng Res.*, vol. 44, no. 2, pp. 247-257, Mar. 2020. doi: 10.1016/j.jgr.2018.10.007.

[331] M.-E. F. Hegazy, M. Dawood, N. Mahmoud, M. Elbadawi, Y. Sugimoto *et. al.*, "2*α*-Hydroxyalantolactone from Pulicaria undulata: activity against multidrug-resistant tumor cells and modes of action," *Phytomedicine*, p. 153409, Nov. 2020. doi: 10.1016/j.phymed.2020.153409.

[332] S. Abdelfatah, M. Böckers, M. Asensio, O. Kadioglu, A. Klinger *et. al.*, "Isopetasin and *S*-isopetasin as novel P-glycoprotein inhibitors against multidrug-resistant cancer cells," *Phytomedicine*, p. 153196, Mar. 2020. doi: 10.1016/j.phymed.2020.153196.

[333] Y.-T. Chang, C. C. N. Wang, J.-Y. Wang, T.-E. Lee, Y.-Y. Cheng *et. al.*, "Tenulin and isotenulin inhibit P-glycoprotein function and overcome multidrug resistance in cancer cells," *Phytomedicine*, vol. 53, pp. 252-262, Feb. 2019. doi: 10.1016/j.phymed.2018.09.008.

[334] Y. Liu, T. Bi, W. Dai, G. Wang, L. Qian *et. al.*, "Lupeol enhances inhibitory effect of 5-fluorouracil on human gastric carcinoma cells," *Naunyn Schmiedebergs Arch Pharmacol.*, vol. 389, no. 5, pp. 477-484, May 2016. doi: 10.1007/s00210-016-1221-y.

[335] M. Kayouka, A. Hamade, E. Saliba, F. Najjar, D. Landy *et. al.*, "P-glycoprotein modulates oleanolic acid effects in hepatocytes cancer cells and zebrafish embryos," *Chem. Biol. Interact.*, vol. 315, p. 108892, Jan. 2020. doi: 10.1016/j.cbi.2019.108892.

[336] X. Zhao, M. Liu, D. Li, "Oleanolic acid suppresses the proliferation of lung carcinoma cells by miR-122/Cyclin G1/MEF2D axis," *Mol. Cell Biochem.*, vol. 400, no. 1-2, pp. 1-7, Feb. 2015. doi: 10.1007/s11010-014-2228-7.

[337] R.-P. Ye and Z.-D. Chen, "Saikosaponin A, an active glycoside from Radix bupleuri, reverses P-glycoprotein-mediated multidrug resistance in MCF-7/ADR cells and HepG2/ADM cells," *Xenobiotica*, vol. 47, no. 2, pp. 176-184, Feb. 2017. doi: 10.3109/00498254.2016.1171932.

[338] H. A. Bashmail, A. A. Alamoudi, A. Noorwali, G. A. Hegazy, G. M. Ajabnoor *et. al.*, "Thymoquinone Enhances Paclitaxel Anti-Breast Cancer Activity via Inhibiting Tumor-Associated Stem Cells Despite Apparent Mathematical Antagonism," *Molecules*, vol. 25, no. 2, p. 426, Jan. 2020. doi: 10.3390/molecules25020426.

[339] L. H. Odeh, W. H. Talib, I. A. Basheti, "Synergistic effect of thymoquinone and melatonin against breast cancer implanted in mice," *J. Cancer Res. Ther.*, vol. 14, pp. S324-S330, Jun. 2018. doi: 10.4103/0973-1482.235349.

[340] A. Al-Mutairi, A. Rahman, M. S. Rao, "Low Doses of Thymoquinone and Ferulic Acid in Combination Effectively Inhibit Proliferation of Cultured MDA-MB 231 Breast Adenocarcinoma Cells," *Nutr. Cancer*, pp. 1-8, Mar. 2020. doi: 10.1080/01635581.2020.1743869.

[341] F. Xiang, Y. Fan, Z. Ni, Q. Liu, Z. Zhu *et. al.*, "Ursolic Acid Reverses the Chemoresistance of Breast Cancer Cells to Paclitaxel by Targeting MiRNA-149-5p/MyD88," *Front. Oncol.*, vol. 9, p. 501, Jun. 2019. doi: 10.3389/fonc.2019.00501.

[342] J. Zheng, T. Asakawa, Y. Chen, Z. Zheng, B. Chen *et. al.*, "Synergistic Effect of Baicalin and Adriamycin in Resistant HL-60/ADM Leukaemia Cells," *Cell Physiol. Biochem.*, vol. 43, no. 1, pp. 419-430, Sept. 2017. doi: 10.1159/000480420.

[343] J. H-M. Hsu, P. M-H. Chang, T.-S. Cheng, Y.-L. Kuo, A. T-H. Wu *et. al.*, "Identification of Withaferin A as a Potential Candidate for Anti-Cancer Therapy in Non-Small Cell Lung Cancer," *Cancers (Basel)*, vol. 11, no. 7, p. 1003, Jul. 2019. doi: 10.3390/cancers11071003.

[344] X. Li, F. Zhu, J. Jiang, C. Sun, X. Wang *et. al.*, "Synergistic antitumor activity of withaferin A combined with oxaliplatin triggers reactive oxygen species-mediated inactivation of the PI3K/AKT pathway in human pancreatic cancer cells," *Cancer Lett.*, vol. 357, no. 1, pp. 219-230, Feb. 2015. doi: 10.1016/j.canlet.2014.11.026.

[345] C.-C. Huang, C.-M. Lin, Y.-J. Huang, L. Wei, L.-L. Ting *et. al.*, "Garcinol downregulates Notch1 signaling via modulating miR-200c and suppresses oncogenic properties of PANC-1 cancer stem-like cells," *Biotechnol. Appl. Biochem.*, vol. 64, no. 2, pp. 165-173, Mar. 2017. doi: 10.1002/bab.1446.

[346] M. Farhan, A. Malik, M. F. Ullah, S. Afaq, M. Faisal *et. al.*, "Garcinol Sensitizes NSCLC Cells to Standard Therapies by Regulating EMT-Modulating miRNAs," *Int. J. Mol. Sci.*, vol. 20, no. 4, p. 800, Feb. 2019. doi: 10.3390/ijms20040800.

[347] S.-H. Tu, Y.-S. Chiou, N. Kalyanam, C.-T. Ho, L.-C. Chen *et. al.*, "Garcinol sensitizes breast cancer cells to Taxol through the suppression of caspase-3/iPLA$_2$ and NF-κB/Twist1 signaling pathways in a mouse 4T1 breast tumor model,"

Food Funct., vol. 8, no. 3, pp. 1067-1079, Mar. 2017. doi: 10.1039/c6fo01588c.

[348] Y. Li, Z. Xi, X. Chen, S. Cai, C. Liang *et. al.*, "Natural compound Oblongifolin C confers gemcitabine resistance in pancreatic cancer by downregulating Src/MAPK/ERK pathways," *Cell Death Dis.*, vol. 9, no. 5, p. 538, May 2018. doi: 10.1038/s41419-018-0574-1.

[349] H.-N. Oh, A.-W. Kwak, M.-H. Lee, E. Kim, G. Yoon *et. al.*, "Targeted inhibition of c-MET by podophyllotoxin promotes caspase-dependent apoptosis and suppresses cell growth in gefitinib-resistant non-small cell lung cancer cells," *Phytomedicine*, vol. 80, p. 153355, Jan. 2021. doi: 10.1016/j.phymed.2020.153355.

[350] B. Cao, S. Yang, W. Li, H. Chen, Y. Chen *et. al.*, "GMZ-1 is a podophyllotoxin derivative that suppresses growth and induces apoptosis in adriamycin-resistant K562/A02 cells through modulation of MDR1 expression," *Mol. Med. Rep.*, vol. 17, no. 1, pp. 474-478, Jan. 2018. doi: 10.3892/mmr.2017.7862.