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Review

Plant-Derived Molecules Modulate Multidrug Resistance in Gastrointestinal Cancers: A Comprehensive Review

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Abstract: Multidrug resistance (MDR) development against cytotoxic drugs by tumor cells is one of the main causes of treatment failure in gastrointestinal cancers, a group of cancers of great relevance due to their prevalence and/or mortality. This phenomenon is mediated by diverse mechanisms, including the overexpression of members of the superfamily of membrane transporters of the ATP-binding cassette (ABC). Most of these molecules, including P-glycoprotein (P-gp or MDR1/ABCB), MDR-associated protein 1 (MRP1/ABCC1), MRP2, and breast cancer resistance protein (BCRP/ABCG2), are integrated in the cell membrane, acting as drug efflux pumps. Despite the use of various MDR modulators as adjuvants to improve the chemotherapy response, the results have not been satisfactory. Natural products from plants, such as flavonoids, alkaloids, terpenoids, and coumarins, are capable of modifying drug resistance, suggesting an improvement in the antitumoral effect of the current treatments without generating side effects. This review aims to provide an overview of the most recent studies in relation to plant-derived molecules and extracts that modulate resistance to antitumor drugs and that could be applied in the future in clinical practice to improve the treatment of patients with gastrointestinal cancer.

Keywords: multidrug resistance; gastrointestinal cancer; natural products; biomolecules

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1. Introduction

Currently, cancer is one of the main public health problems worldwide. This disease develops because certain cells escape apoptosis and continue to divide in an uncontrolled manner [1]. In the latest estimates for the year 2020, there were 19.3 million new cases and around 10 million deaths caused by this disease. In addition, these estimates are not going to improve in the coming decades, since up to 30.2 million cases are expected in 2040 [2]. Among the most frequent tumors, and with the highest mortality, we find gastrointestinal tumors [3]. Among gastrointestinal tumors, colon cancer and stomach cancer are in the top five for incidence and mortality, among others. Colon cancer is the third most frequent type of tumor, with an incidence of almost 2 million cases, and has the second highest mortality, with almost 1 million deaths, and stomach cancer is fifth in incidence, with around 1 million cases, and fourth in mortality, with around 800 thousand deaths [2,4].

There are different approaches in the treatment of these tumors, such as surgery, radiotherapy, or chemotherapy, and despite them, neither incidence nor mortality is decreasing. This is largely due to the fact that the tumor cells acquire multidrug resistance (MDR) to treatment, which leads to failure in the treatment and to the survival of the tumor cell [5,6]. Plant-derived natural products have been widely studied for their pharmacological potential to overcome MDR in cancer [7]. These molecules can be classified into several categories, including flavonoids, alkaloids, terpenoids, and coumarins. Flavonoids are known for their antioxidant properties and ability to modulate efflux pumps [8], whereas alkaloids often interfere with microtubule dynamics [9]. Terpenoids have shown promise in inducing apoptosis and reversing drug resistance mechanisms [10], and coumarins exhibit several pharmacological effects, including the modulation of drug-metabolizing enzymes and interference with cancer cell proliferation, contributing to the potential to overcome drug resistance [11].

This review will explore how these and other plant-derived compounds may enhance the efficacy of chemotherapy in gastrointestinal tumors by modulating MDR phenotypes both in vitro and in vivo.

2. Resistance Mechanism

Although multiple advances have been made in the treatment of cancer in the last decade, chemotherapy continues to be the most important option, especially in tumors that present metastases or are in advanced stages. The failure of this treatment is mainly determined by the resistance mechanisms presented by the tumor cells, which can be intrinsic or acquired [12]. Once chemotherapy treatment is started, many tumor cells die, but not all of them present in the tumor do. The cells that survive continue to grow and develop resistance to the treatment. This is why, after a while, to overcome this resistance, different antitumor drugs are used in combination with different mechanisms of action to try to kill all the tumor cells [13]. At this point, the cells that survive have MDR and are, to a greater extent, stem cells [14].

This MDR (Figure 1) can be divided into mechanisms that expel the drug from the cytoplasm to the outside of the cell and mechanisms that prevent the drug from killing the tumor cell [15]. Within the first group, the most common resistance mechanisms are the expressions of P-glycoprotein (P-gp) and MDR-associated protein, representing the MRP family [16,17]. Efflux pumps on the membranes of tumor cells allow the expulsion of the drug from the cells and drive this mechanism.

In the second group, we find all the mechanisms that cells possess to avoid cell death, such as DNA repair, drug degradation or inactivation, or even the use of antioxidants or antiapoptotic proteins. There are many antitumor drugs that induce cellular DNA damage, so tumor cells have developed DNA repair mechanisms to limit this damage and thus survive treatment [18]. Enzymes of the glutathione s-transferase family are involved in drug inactivation, which are responsible for degrading the drug directly or indirectly by inhibiting the RAS–mitogen-activated protein kinase (MAPK) (RAS-MAPK) pathway [19]. For the last type of resistance, the involvement of the BCL2 protein is known as one of the most important antiapoptotic mechanisms since its absence is capable of substantially increasing the cytotoxic effect of antitumor drugs [20].

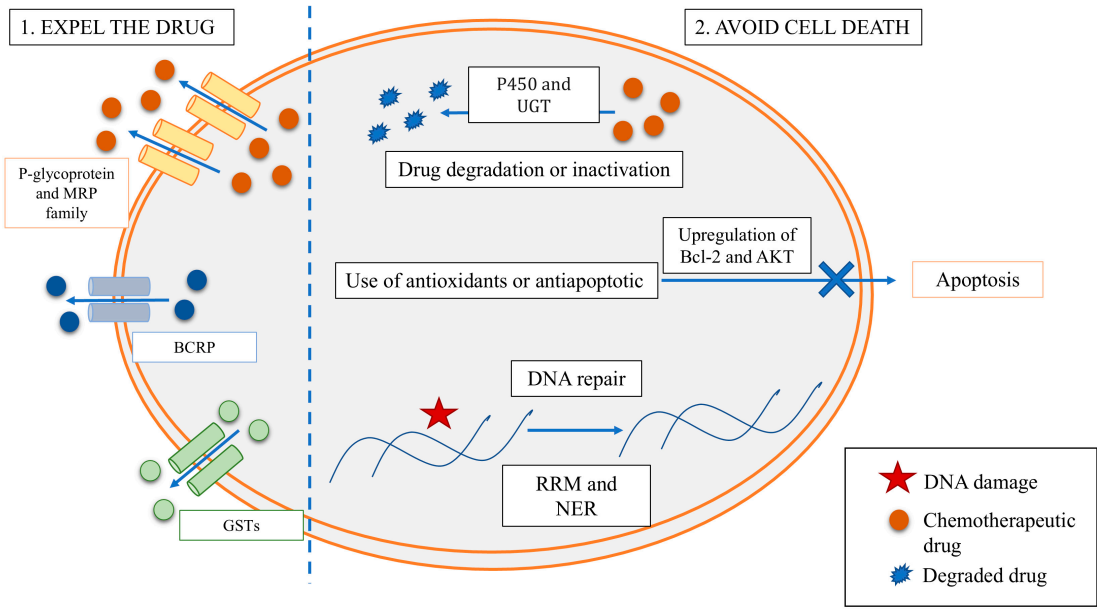

Figure 1. Resistance mechanisms. (**1**) Mechanisms that expel the drug from the cytoplasm to the outside of the cell, like P-gp and the MRP family; (**2**) mechanisms that prevent the drug from killing the tumor cell, like drug degradation or inactivation, the use of antioxidants or antiapoptotic proteins, and DNA repair.

3. Stomach and Esophageal Cancer

Stomach cancer has the fifth highest incidence and fourth highest mortality [2], while esophageal cancer is seventh in incidence and fifth in mortality in men [21]. The emergence of MDR means that the treatment of these tumor types requires a new approach, such as the use of natural products alone or in combination with classical chemotherapy. Stomach cancer presents chemoresistance mediated by P-gp expression, so it is of vital importance to find a mechanism to overcome this resistance. The use of curcumin has been shown to modulate both P-gp expression and function. Huang et al. carried out an in vitro study with the SNU-5 gastric carcinoma cell line and the administration of curcumin together with the drug doxorubicin (DOX). The results showed an increase in the intracellular concentration of the drug derived from the use of curcumin, thus improving the effectiveness of the drug [22]. They studied the regulatory role of curcumin in vitro in the SGC7901/VCR human gastric cancer cell line, a variant resistant to vincristine. Through this, they saw a decrease in the concentration of P-gp expression 24 h after curcumin administration and 77% increased apoptosis when vincristine and curcumin were coadministered [23]. Another joint effect of the administration of DOX together with curcumin was the downregulation of the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), associated with chemoresistance in these tumors, which has been shown to occur in vitro in the SGC-7901 gastric carcinoma cell line [24]. There are some studies that, in addition to testing the effect of curcumin in vitro, also tested it in vivo. Zhou et al. used BGC-823 xenograft tumors, to which they administered a combination of two antitumor drugs, namely 5-fluorouracil (5FU) and oxaliplatin with curcumin, demonstrating powerful inhibition of tumor growth [25]. Another in vivo study that relates the use of curcumin to the inhibition of the transcription factor NF-κB is that of Jiang et al. In this study, the authors generated tumors in BALB/c nude mice by inoculating cells of the tumor line SGC-7901 treated with nanostructured lipid nanoparticles loaded with etoposide and curcumin. The results obtained showed a reduction of up to 90% in tumor size with this treatment compared with the control group [26].

The use of polyphenols is also being studied in stomach cancer, especially those found in green tea. Although there have been cohort studies that did not find any relationship between the consumption of green tea and the risk of stomach cancer [27], it is important to note that the bioavailability of polyphenols is limited when consumed orally [28]. In in vitro studies using the human cell lines MKN-1, MKN-45, MKN-74, and KATO-III, inhibition of proliferation and an increase in apoptosis after treatment were observed with (-)-epigallocatechin gallate (EGCG), a polyphenol found in green tea [29].

Esophageal tumors have a poor prognosis because they spread rapidly and systemically. Standard treatment for these tumors includes chemotherapy agents such as cisplatin or 5FU, as well as paclitaxel, the combination of cisplatin and 5FU being the most commonly used. The most common mechanism of resistance developed by this type of tumor is the expression of ATP synthase (ATP)-binding cassette (ABC) transporter systems, mediated by the ABCG2 protein, recognized as an unfavorable factor in the prognosis of these tumors [30]. Flavonoids such as kaempferol can reverse this resistance, as stated in the in vitro study of To et al., in which they established a cisplatin-resistant cell line derived from the human line HKESC-1 [31]. This flavonoid could act as an antagonist, preventing the overexpression of the ABCG2 protein (a type of ABC protein), thus overcoming resistance and treatment failure.

Another flavonoid used in esophageal cancer is luteolin. Like kaempferol, it is also used in cases of resistance to cisplatin. Liu et al. carried out an in vitro study in six human esophageal squamous carcinoma cell lines, in which they verified that luteolin is capable of attenuating resistance to cisplatin mediated by the overexpression of vaccinia-related kinase (VRK) 1 [32]. Likewise, they carried out in vivo studies inducing subcutaneous tumors in BALB/c nude mice using the Ec9706 tumor line. The results indicated that luteolin could reduce tumor volume on its own, although this reduction is increased when coadministered with cisplatin.

Isoflavones are also used in MDR in this type of tumor. In this case, it is known that after the treatment of tumor cells with radiotherapy, the accumulation of reactive oxygen species (ROS) occurs, which are responsible for inducing cell arrest and the consequent cell apoptosis. To defend themselves against this mechanism of cell death, tumor cells present adaptations to oxidative stress, such as the expression of the nuclear factor erythroid 2-related factor 2 (Nrf2), giving the cell a resistant phenotype [33]. Alpinumisoflavone from the herb Derris eriocarpa could increase the in vitro radiosensitivity of Eca109 and KYSE30 esophageal carcinoma cell lines by inhibiting Nrf2. Although there are studies based on natural products to overcome MDR in these tumor types, they still have a poor prognosis that results in high mortality. This is why more studies are needed to help find other natural products that can reverse resistance and improve patient survival.

4. Colorectal Cancer

Colorectal cancer (CRC) is considered a real public health problem worldwide due to its incidence and the lack of effective treatments in advanced stages [2,34]. CRC is the third most common cancer and the second most common cause of death from cancer, representing between one and two million new cases each year. This mortality has a clear growth trend that has been shown to be related to lifestyle and diet [35].

Despite great advances in recent years, the treatment of CRC has not achieved satisfactory results in terms of a cure or reduction in incidence, especially in advanced stages of the disease in which there is metastatic expansion of the tumor (especially hepatic), drastically influencing patient survival. Surgery (if the tumor is resectable) and chemotherapy are the main treatments for CRC. The chemotherapy currently used is based on different chemotherapies, either as monotherapy or in combination (oxaliplatin, irinotecan, 5FU,

capecitabine, TAS-102, raltitrexed) [36]. In recent years, active biological drugs have been developed for advanced CRC, including the monoclonal antibodies cetuximab, panitumumab, and bevacizumab and a recombinant fusion protein (aflibercept) with very precise indications [37–39]. Despite this, the results are very limited, as clearly indicated by the median survival of these patients (15 to 20.5 months) [40]. The improvement in its prognosis, therefore, requires the development of new strategies that add therapeutic activity to preventive action [41,42]. The development of new therapeutic strategies covers a large number of research fields that range from nanotechnology to the use of systems that activate the immune system or the use of extracts from different origins, among others, that can help improve the response to treatment. In this context, currently, the activity of plant extracts or derivatives in the viability and survival of tumor cells is attracting great interest [43].

One of the main reasons why chemotherapy loses efficacy is the emergence of MDR (Figure 2). This is why compounds of plant origin that act at the level of this resistance mechanism are currently being studied in order to develop effective therapies. Recently, many new potent plant-derived agents for reversing MDR have been discovered, most notably phenolic compounds and terpenoids. For example, triterpenoids isolated by the methanolic extraction of Momordica balsamina have been reported to have an effect on MDR proteins in colon cancer. Of all the compounds that were isolated, four of them (balsaminoside A, karavilagenin C, karavoates A, and karavoates E) acted on the modulation of P-gp in the HT-29 CRC cell line [44].

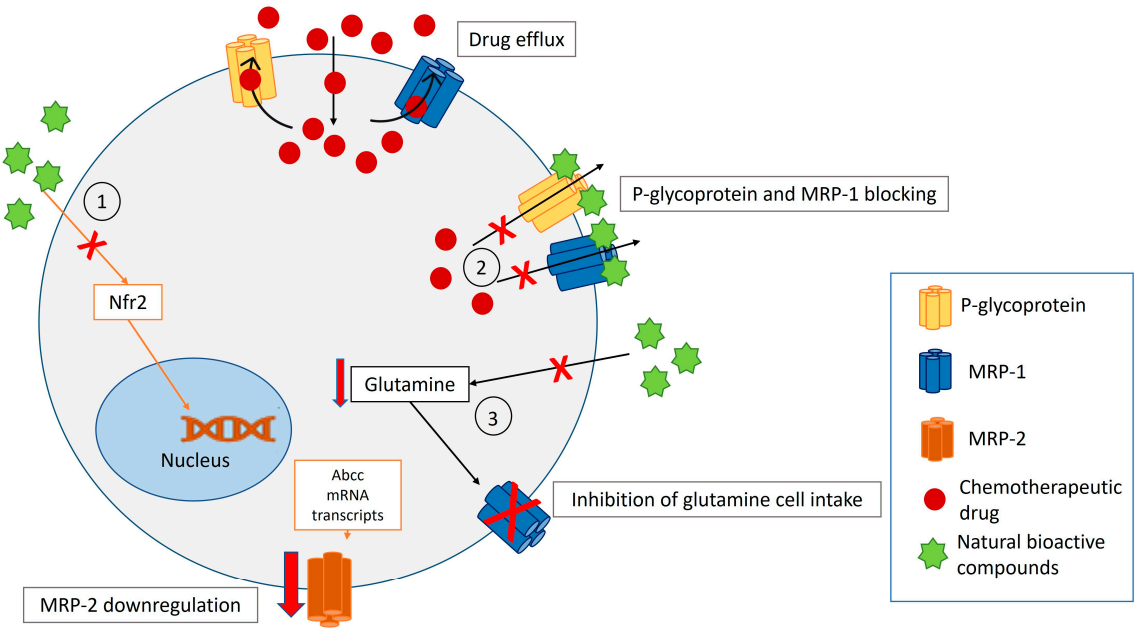

Figure 2. Summary of modulation of MDR mechanism by natural bioactive compounds. (1) Inhibition of Nrf2/MRP2, inducing MRP-2 downregulation. (2) P-gp and MRP-1 blocking by natural bioactive compounds. (3) Natural bioactive compounds inhibit glutamine cell intake and consequently induce MRP-1 dysfunction.

Different diterpenoids and coumarins isolated from various Euphorbia species have also been shown to modulate MDR, more specifically by inhibiting P-gp activity. Of all the isolates, Latilagascene B (isolated from the methanol extract of Euphorbia lagascae aerial parts) proved to be a very effective P-gp inhibitor in LoVo/Dx cells; however, it was not able to restore DOX cytotoxicity in these cells [45].

Other species of Euphorbia are also sources of bioactive compounds that act at this level. From methanolic extracts of the Hungarian Euphorbia species, several diterpenes with skeletons of jatrophan or latirano have been isolated. Of all the compounds isolated,

compound 8 (isolated from the lipophilic phase of methanol extracts of Euphorbia serrulata) was the most potent, interacting synergistically when combined with epirubicin and acting as an effective lead compound for MDR reversal [46].

Besides terpenoid compounds, flavonoid and phenolic compounds also exhibit modulation of MDR [47]. A natural flavonoid compound (Dihydromyricetin) extracted from the leaves of a Chinese medicinal herb known as Vitis heyneana has shown very potent antitumor power by combating chemoresistance by inhibiting Nrf2/MRP2 signaling in CRC cells [48]. Flavones have also been studied as modulators of P-glycoprotein in the LoVo cell line and in the LoVo/DX DOX-resistant line. Specifically, baicalein and luteolin have been shown to induce apoptosis in these cell lines, although it has been found that baicalen could be a substrate of this drug transporter [49].

From Citrus jambhiri Lush and Citrus pyriformis Hassk (Rutaceae), nine naturally occurring compounds were isolated. Of all of them, limonin, deacetylnomilin, hesperidin, neohperidin, stigmasterol, and ß-sitosterol-O-glucoside were the ones that inhibited the efflux of P-glycoprotein, being even more potent than verapamil. An in vitro study carried out on Caco-2 cells showed that these compounds increased the sensitivity to DOX and completely reversed DOX resistance by inhibiting P-gp, limonin being the most potent [50]. Another study has revealed 17 lamellarin compounds isolated from Australian Didemnum species that represent new non-cytotoxic P-gp inhibitor pharmacophores [51].

One of the compounds that has been extensively studied as an antitumor agent in different types of tumors, including CRC, is quercetin. In addition, it has also been shown to be capable of inhibiting P-gp-mediated MDR in various tumor cells. A larger study showed that quercetin increased the cytotoxicity of DOX in the resistant cell line SW620/Ad300 by inhibiting ATP transport that activates P-gp, which in turn increased the intracellular accumulation of DOX. Additionally, this study demonstrated that quercetin could reverse MDR by significantly blocking D-glutamine and D-glutamate metabolism. Specifically, it downregulated the expression of the glutamine transporter solute carrier family 1, member 5 (SLC1A5) in SW620/Ad300 cells [52].

Like quercetin, curcumin has also been extensively studied as an antitumor agent in different types of tumors. Curcumin has been shown to inhibit a series of molecular pathways in the SW620/Ad300 line, which in turn decreased the antioxidative stress ability and P-gp transport activity [53]. Similarly, in the colon tumor cell line HCT-8/5-FU, it has been shown that curcumin acted as a regulator of P-gp, thus reversing the resistance of this cell line to the chemotherapeutic drug 5-Fu [54].

Despite the good results obtained, more studies are needed to reinforce the activity of these bioactive compounds of plant origin and to elucidate new compounds or derivatives thereof that can modulate MDR.

5. Pancreatic Cancer

Pancreatic cancer (PC) is the fourth leading cause of cancer death in Western countries. Its incidence has increased in recent years, but its high mortality rate (greater than 90% at 5 years after diagnosis) has not been reduced. This is due to the late diagnosis of the disease, the absence of serum biomarkers that allow it to be diagnosed prematurely, and high resistance to chemotherapy and radiotherapy [55]. The currently most widespread therapies in patients in advanced stages (generally metastatic) are FOLFIRINOX (a mixture of several drugs) and gemcitabine (GEM). However, PC cells are highly resistant to GEM, so new drugs are needed to reduce this chemoresistance to try to increase the quality of life and survival of patients [56]. Research into the use of natural products to treat PC has spread in recent years. The antitumor mechanisms of these compounds are usually divided into four categories: inhibitors of metastasis and angiogenesis, proapoptotic drugs, and

inhibitors of drug resistance [57]. We are going to focus on studying natural compounds that have been used to try to evade PC cell resistance (Figure 3).

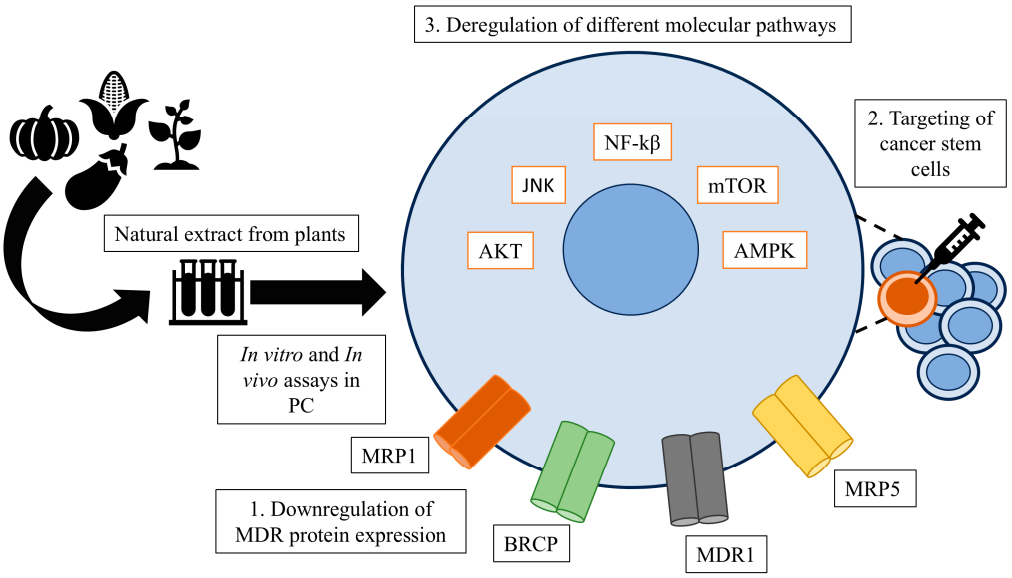

Figure 3. Effects of natural compounds on drug resistance in PC. Natural compounds extracted mainly from vegetables are shown to possibly be effective against drug resistance in PC through three main routes: (1) deregulation of MDR (MDR) proteins, (2) selective treatment against pancreatic tumor stem cells, and (3) deregulation of different molecular pathways that have been related to drug resistance in PC, generally GEM.

One of the natural products that has been most widely used in the literature as a potential antitumor treatment is curcumin. A study determined that curcumin could produce a decrease in the proliferation of several pancreatic tumor lines (BxPC3, PANC-1, MPanc-96, and MIA PaCa-2) and was also capable of synergizing its effect with GEM, reducing resistance to this antitumor drug in pancreatic tumors. This effect was studied both in in vitro and in vivo conditions, determining that curcumin might be capable of suppressing the expression of the nuclear transcription factor (NF-κβ), involved in proliferation, survival, angiogenesis, and chemoresistance [58]. Other studies have shown that the effect of curcumin on drug resistance (specifically 5-FU) might be related to its ability to inhibit the transmembrane resistance protein MRP5. Thus, it was shown that the IC50 of 5-FU decreased significantly in the PANC-1 and Mia PaCa-2 lines after co-treatment with this drug and curcumin [59]. Otherwise, it has been shown that curcumin might carry out this sensitization through the inhibition of EZH2, a catalytic subunit of the polycomb repressive complex 2 (PRC2), present in the PRC2-PVT1-c-Myc axis. This complex is related to the expression of several lncRNAs that modulate the epithelial–mesenchymal transition, a phenomenon associated with drug resistance. The combined treatment of curcumin and GEM in BxPC3 cells resistant to this drug showed that curcumin could possibly sensitize these cells. In addition, it decreased the formation of spheroids and was capable of inhibiting growth in tumors of immunosuppressed mice generated from the BxPC3 GEM-resistant cell line in combination with GEM [60]. Given the suggested efficacy of co-treatment with GEM and curcumin, an attempt was made to encapsulate both drugs in pH-sensitive PEGylated liposomes (poly(ethylene-glycol)-PEG) to try to improve the cytotoxic effect exerted. The results showed that the simultaneous treatment might increase the intracellular accumulation of GEM, and a synergistic cytotoxic effect was observed in the MIA PaCa-2 tumor line, which was especially high when both drugs were encapsulated in the same liposome [61].

Terpenes have also been studied in recent years because of their antitumor activity. One of them is ericalyxin b, an ent-kaurane diterpenoid isolated from Isodon eriocalyx that has shown a synergistic effect in several pancreatic lines together with the drug GEM, decreasing the resistance of SW1990, Capan-1, Panc-1, and Capan-2 to this cytotoxic treatment. This synergy is due to this terpene activating the apoptotic caspase cascade and regulating the PDK1/AKT1/caspase axis and c-Jun N-terminal kinase (JNK) cell signaling, promoting apoptosis and facilitating cell death induced by the drug GEM [62]. Likewise, several jatrophane diterpenes were isolated from alcoholic extracts, and two compounds (apoxywelwitschene and Esolatin M) were shown to be capable of inducing apoptosis by activating caspase 3. Furthermore, they interacted with a transmembrane protein involved in drug resistance, ABCB1, and allowed the sensitization of PC cells against DOX [63]. Other monoterpenes such as terpinen-4-ol have also been tested on PC lines such as MIA PaCa-2, Colo357, and Panc-1, proving that their combination with GEM exerts a significant synergistic effect on tumor lines. Furthermore, this synergistic effect is also seen with oxaliplatin and 5-FU in colorectal tumor lines [64]. On the other hand, 28 triterpenoids extracted from Momordica balsamina were evaluated in the PC cell line EPP85-181 and two drug-resistant variants thereof. In this study, it was observed that two of the extracted compounds (balsaminol F and karavoate A) were quite effective against drug-resistant lines [44]. Finally, a triterpenoid called nimbolide was encapsulated in nanoparticles, and its inhibitory effect against cancer stem cells (CSCs) derived from the MIA PaCa-2 cell line was observed due to its ability to inhibit the AKT and mTOR pathways. This inhibition triggered the mesenchymal–epithelial transition of pancreatic CSCs, losing their MDR and self-renewal properties [65].

Although curcumin and terpenes are the most studied compounds, distinct natural compounds have been shown to be effective in avoiding drug resistance in PC. First, a study found that GEM-resistant cells had increased ATP production, oxygen consumption, and expression of glucose transporters. Against this, the treatment of PANC-1 and MIA-PaCa2 cell lines with bitter melon juice produced a decrease in the phosphorylation of Akt and ERK1/2, proteins that have been found to be overexpressed in resistant cell lines. This dysregulation generated a decrease in their viability, demonstrating that this natural juice was capable of acting as an effective therapy against resistant cells [66]. In addition, an ethanolic extract of oat bran (OBE) showed efficacy in pancreatic tumor cells resistant to GEM. Thus, the toxicity of this extract in MIA PaCa-2 and PANC-1 cells was analyzed, observing that it induced death in PC cells through AMPK activation and JNK downregulation. The ability to sensitize cells to GEM was due to the fact that OBE produces a reduction in the expression of RRM1/2 [67].

Moreover, coix seeds have been used in PC to increase the sensitivity of tumor cells to the drug GEM. Thus, an emulsion prepared from these seeds exerted a synergistic effect with the drug GEM, decreasing its IC50 in the BXPC-3, PANC-1, and AsPC-1 cell lines. Additionally, it was found that simultaneous treatment increased the expression of proapoptotic markers such as Bax and decreased that of antiapoptotic markers (COX-2, survivin, and Bcl-2). An in vivo study carried out on the induction of tumors of the BxPC-3 line showed that co-treatment with GEM and this emulsion significantly decreased the size of the tumors with respect to the treatments applied individually [68]. Meanwhile, extracts of these seeds increased the antitumor effect of the drug GEM, showing that they could decrease the overexpression of the ABCB1 and ABCG2 drug resistance proteins produced by the drug GEM in the PANC-1 and BxPC3 tumor cell lines. This effect was also demonstrated in tumors derived from BxPC3 induced in mice, where it was observed that the combination of GEM and the extract was capable of significantly inhibiting proliferation [69].

Emodin is an anthraquinone isolated from the roots of rheumatic palm leaves currently used as a laxative treatment. This natural compound has been investigated in PC as a possible inhibitor of drug resistance in pancreatic tumor cells. Thus, co-treatment with GEM and emodin was capable of significantly inhibiting the proliferation of tumor cells in two-dimensional cultures of the Bxpc-3 line in a dose dependent-manner with respect to individual treatments, as well as increasing significantly the apoptosis rate of these gemcitabine resistant cells with the combined treatment. This effect was related to the ability of emodin to inhibit the expression and activity of certain membrane protein markers involved in drug resistance and survival and apoptosis signaling proteins, such as NF-kB, involved in upregulation of MDR-1 mRNA expression and ABC transporter protein superfamily, survivin and XIAP (X-linked inhibitor of apoptosis), within an upregulation of the expression of Caspase-3 and 9 observing that co-treatment with this compound and GEM produced the greatest decrease in the expression of these proteins [70].

A different protein that has been implicated in resistance is heat shock protein 27 (HSP27). A study using an enzyme-treated asparagus extract (ETAS) determined that this extract reduced the expression of the HSP27 protein, both in its basal and phosphorylated versions, in a pancreatic tumor line resistant to GEM (KLM1-R). Therefore, the use of this extract could improve the effect of GEM due to the decrease in the expression of molecular pathways that confer resistance to it [71].

A ginsenoside isolated from Panax ginseng (Rg3) has been shown to have antitumor potential in various tumors. Its treatment was characterized in PC, observing how this compound suppressed the growth of two tumor lines resistant to the drug GEM: Panc-1/GEM and SW1990/GEM. Furthermore, it was shown that this antitumor effect was due to this compound being capable of increasing the expression of an lncRNA (CASC2) and the PTEN gene, this PTEN-mediated signaling being involved in the significant suppression of tumor growth that was observed in the cell lines and in an in vivo assay carried out in mice with the Panc-1/GEM line [72]. A distinct natural compound extracted from Garcinia yunnanensis, Oblongifolin C (OC), has been shown to be effective in sensitizing PC cells to GEM. To achieve this, OC triggers proteasome-mediated degradation of the Src protein and negatively regulates the MAPK pathway. This deregulation of Src, a protein related to resistance phenomena, allows GEM to have a greater effect on MIA PaCa-2 and Capan-1 GEM-resistant cell lines. An in vivo assay with tumors generated from the MIA PaCa-2-GEM-resistant line confirmed that the combination of OC and GEM decreased the weight and volume of the tumors generated [73].

On the other hand, a compound isolated from the fungus Chaetomium sp. called chaetospirolactone is capable of sensitizing PC cells to tumor necrosis factor-related ligand (TRAIL) therapy in the PANC-1 and AsPC-1 tumor lines, showing a decrease in the cell proliferation and migration of the lines and an increase in apoptosis. In addition, in vivo tests in mice proved that the combination of the compound and TRAIL therapy decreased the size of the tumors generated [74].

Besides all these natural compounds usually extracted from plants, a medical formula used in China for the treatment of PC called Qingyihuaji (QYHJ) has also been shown to be effective against resistance to GEM. This formulation is generated from five herbs of Chinese origin: Herba Scutellariae barbatae, Herba Hedyotdis, Rhizoma Arisaematis erubescentis, Herba seu Radix Gynostemmatis pentaphylli, and Fructus Amomi Rotundus. This extract was able to inhibit tumor proliferation in a GEM-resistant line (CFPAC-1), producing apoptosis both under in vitro conditions and in tumors of the line induced in immunocompetent mice. Significant differences were observed with respect to the individual treatments of the GEM + QYHJ combination in both tumor volume and weight. Furthermore, this combination reduced the expression of Ki-67 in the removed tumors [75].

A different approach to evade resistance is to focus therapy on killing cancer stem cells. Two plant extracts derived from Pao Pereira and Rauwolfia vomitoria inhibited the proliferation of cancer stem cells in vitro and in vivo, a cell population that is usually related to drug resistance. This effect could be observed when the viability of these stem cells was reduced in in vitro cultures and, subsequently, the tumorigenicity of a PANC-1 stem cell-derived tumor induced in mice was reduced [76,77]. Another compound that has been shown to be effective against cancer stem cells is quercetin, a flavanol present in fruits and vegetables. A study revealed that this compound suppressed the proliferation, invasiveness, and expression of CSC membrane markers through the regulation of β-catenin expression in CSCs derived from the PANC-1 and HPAC lines. Therefore, the combination of quercetin and GEM allowed the inhibition of these cells with "stem" characteristics that are involved in tumor resistance processes [78].

Fucoidan, an extract from the marine brown alga Turbinaria conoides, was employed in the Panc-1, MiaPaCa-2, Panc-3.27, and BxPC-3 pancreatic cell lines, and it achieved a notable increase in the expression of cleaved caspases 3, 8, and 9 and PARP and, through that, inhibition of the NFκB signaling pathway ligated to MDR development, and activation of p53 [79].

Moreover, another natural compound that has shown relevant antitumoral MDR is aronia berry extract (ABE), with a range of natural compounds such as flavonoids, coumarins, resins, saponins, and terpenoids from Aronia Melanocarpa, a species of shrub in the Rosaceae family native to eastern North America. It was employed over GEM-resistant pancreatic ductal adenocarcinoma cell lines BxPC-3 and MIA-PaCa-2 and patient-derived 3D pancreatic tumor organoids. In the Gem-R BxPC-3 cell line, the inhibitory rate improved by 52.8% compared with the GEM-only treatment. Similarly, in the Gem-R MIA-PaCa-2 cell line, under the same ratio, the inhibitory rate improved by 56.5% compared with the GEM-only treatment. The apoptosis rate improved by 18.45% and 9.2% in BxPC-3 and MIA-PaCa-2, respectively, with the combined therapy compared with the individual treatments. It was shown that the combination of ABE and GEM targeted the MYD88/NF-κB signaling pathway associated with GEM resistance through the downregulation of TLR3, MYD88, and p65 in both the Gem-R BxPC-3 and Gem-R MIA-PaCa-2 cell lines by 46.6%, 53%, and 37% and 46%, 30%, and 60%, respectively [80].

A study which employed embelin, a benzoquinone extracted from Embelia ribes, a species of plant in the family Myrsinaceae, should also be highlighted. It was tested in the PC cell lines PANC-1 and MIA PaCa-2, obtaining a reduction in cell viability with half the IC50 value in resistant PANC-1 and MIA PaCa-2 in combination with GEM compared with GEM alone. Embelin induced the upregulation of Bax, γH2AX, p53, ERK1/2, and hENT1 expression and the downregulation of Bcl-2 and RRM1, related to tumoral progression and drug resistance, in comparison with the control in both the cell lines. This led to 53% and 42% decreases in cell migration in Panc1 and MIA PaCa-2, respectively, with respect to the individual treatments [81].

Bae et al. employed Evo312, a derivative of evodiamine, an indoloquinazolidine alkaloid found in the traditional herbal medicine Evodia rutaecarpa, in human PC cells (PANC-1) and a corresponding GEM-resistant cell line to try to evade GEM resistance. With this treatment strategy, PKCβI expression was significantly suppressed, as well as the protein expression levels of glycogen synthase kinase 3β, protein kinase B, signal transducer and activator of transcription 5, ribosomal protein S6 kinase β-1, and proline-rich AKT, in GEM-resistant PANC cells. Evo312 treatment significantly increased G2/M phase cell populations by 21%. Treatment with Evo312 increased total cell death to almost 25% with the highest concentration of GEM-resistant PANC cells. Tumor volume was suppressed by 72.15% [82].

Another study that should be highlighted is the study developed by Denda et al. GEM-resistant AsPC-1 and MIA PaCa-2 cell lines were treated with parthenolide, a sesquiterpene lactone derived from the leaves of the medicinal plant Tanacetum parthenium. With this strategy, reductions of 88% and 99% in the IC50 value with parthenolide in GEM-resistant MiaPaCa-2 and AsPC-1, respectively, were achieved. In AsPC-1 GR cells, p65 activity decreased by 85.9% compared with the control, and in MIA PaCa-2 GR cells, it decreased by 47.9%. In AsPC-1 GR cells, vascular tube formation decreased by 36.6% compared with the control, and in MIA PaCa-2 GR cells, it decreased by 30.5%. In AsPC-1 GR, IL-8 secretion decreased by 39.5% and VEGF secretion by 38.2% compared with the control. In MIA PaCa-2 GR, the IL-8 secretory capacity was reduced by 57.0%, and the VEGF secretory capacity was reduced by 44.6%. Parthenolide also suppressed the expression of the multidrug-resistance-related protein MRP1 and NF-κB [83].

Chrysin, a natural bioflavonoid widely found in propolis, honey, and blue passion flowers (Passiflora caerulea), was used to reverse GEM resistance in PANC-1, Capan-2, BxPC-3, and AsPC-1 cells. In this study, human carbonyl reductase 1 (CBR1) was inhibited, enhancing the sensitivity of PC cells to GEM and potentiating the efficacy of GEM treatment in vivo and in vitro. Cell viability was reduced by 70% with chrysin compared with the control in Panc-1 and AsPC-1. Chrysin induced autophagy through ROS generation in PANC-1 cells through autophagy-related proteins such as Beclin-1, ATG5, and LC3. The ferritin heavy polypeptide 1 (FTH1) protein level was downregulated, while the expression of NCOA4 increased along with LC3-II levels. Tumoral volume was reduced by 69% with respect to the control with the combined treatment [84].

Therefore, as can be seen, most of the therapies derived from natural compounds that have shown an effect in PC are involved in sensitizing tumor cells to GEM or in targeting therapy towards cancer stem cells, responsible in part for the significant resistance to drugs that is described in pancreatic tumors. They are summarized in Table 1.

Among all the molecular effects of these natural products, some of the most targeted mechanisms and markers of compounds with drug resistance evasion mechanisms in PC can be highlighted (Figure 4).

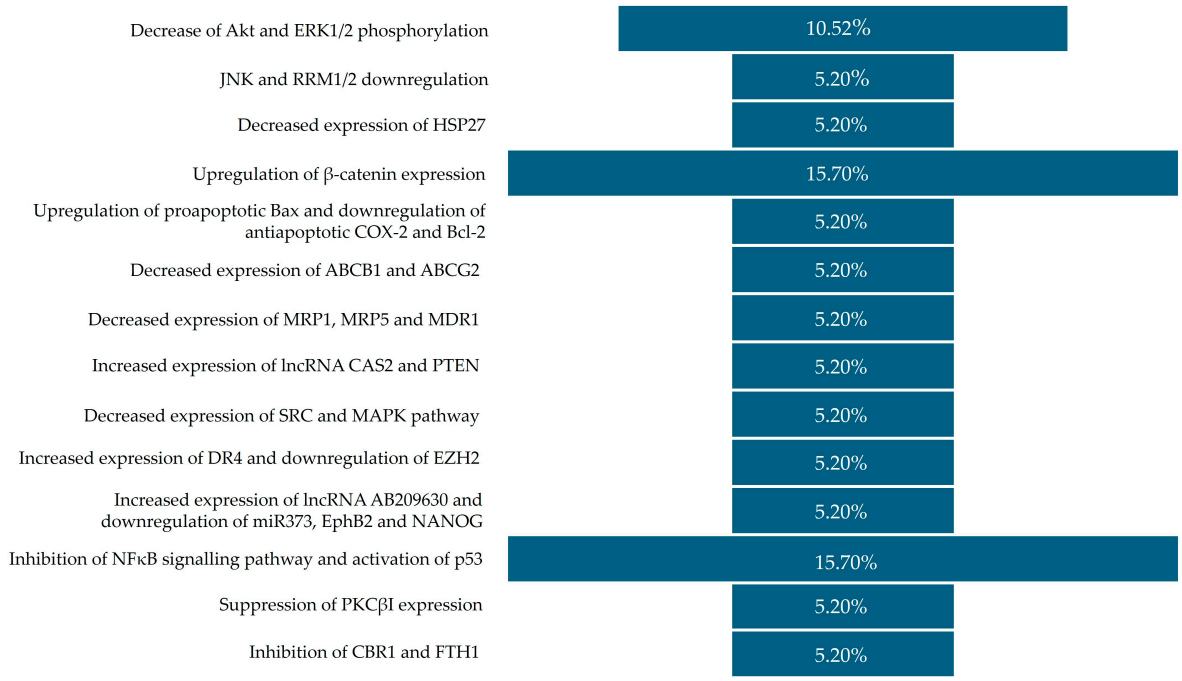

Figure 4. Most targeted mechanisms, markers, and molecular effects of different compounds with drug resistance evasion mechanisms in PC.

Table 1. Classification of compounds with drug resistance evasion mechanisms in PC.

Compound or Extract	Cell Lines Studied	Molecular Effect	In Vivo Study	Reference
Bitter melon juice	PANC-1 and MIA PaCa-2	Decrease in Akt and ERK1/2 phosphorylation. AMPK activation. JNK and RRM1/2 downregulation.	-	[66]
Oat bran ethanolic extract	PANC-1 and MIA PaCa-2			[67]
Enzyme-treated asparagus extract	KLM1-R	Decrease in HSP27 expression.		[71]
Quercetin	PANC-1 and HPAC	Upregulation of β-catenin expression.		[78]
Coix seed emulsion	BXPC-3, PANC-1, and AsPC-1	Upregulation of proapoptotic markers (Bax) and downregulation of antiapoptotic markers (COX-2, survivin, and Bcl-2).	BALB/c mice bearing BXPC-3 tumors	[68]
Coix seed extracts	PANC-1 and BXPC-3	Decrease in ABCB1 and ABCG2 expression.		[69]
Pao Pereira extract	PANC-1, AsPC-1, HPAF-II, BxPC-3, and MIA PaCa-2	Suppression of Wnt/β-catenin signaling pathway.	BALB/c mice bearing PANC-1 tumors	[76]
Rauwolfia vomitoria extract				[77]
Emodin	Bxpc-3	Decrease in NF-kB, survivin and and XIAP expression. Upregulation of Caspase 3 and 9	-	[70]
Rg3 gingenoside	PANC-1/GEM and SW1990/GEM	Increased expression of lncRNA CAS2 and PTEN.	BALB/c mice bearing PANC-1/GEM tumors	[72]
Oblongifolin C	MIA PaCa-2/GEM and PANC-1/GEM	Decrease in SRC expression and MAPK pathway.	BALB/c mice bearing MIA PaCa-2 tumors	[73]
Chaetospirolactone	PANC-1 and AsPC-1	Increased expression of DR4 and downregulation of EZH2.	BALB/c mice bearing AsPC-1 tumors	[74]
Qingyihuaii	CFPAC-1	Increased expression of lncRNA AB209630 and downregulation of miR373, EphB2, and NANOG.	BALB/c mice bearing CFPAC-1 tumors	[75]
Fucoidan	Panc-1, MiaPaCa-2, Panc-3.27, and BxPC-3	Increase in cleaved caspases 3, 8, and 9 and PARP. Inhibition of NFκB signaling pathway and activation of p53.	-	[79]
Aronia berry extracts	Gem-R PDAC cell lines BxPC-3 and MIA-PaCa-2 and patient-derived 3D tumor organoids	Significant reduction in clonogenicity with the combination of GEM and ABE compared with individual treatments, with an apoptosis improvement. Combination of ABE and GEM could target the MYD88/NF-κB signaling pathway associated with GEM resistance in PDAC cells through downregulation of TLR3, MYD88, and p65 by the combined treatment.	-	[80]
Embelin	PC cell lines PANC-1 and MIA PaCa-2	Embelin upregulated Bax, γH2AX, p53, ERK1/2, and hENT1 expression and downregulated Bcl-2 and RRM1. Morphological changes like bulged cells, membrane blebbing, chromatin disintegration, and cytoplasmic vacuole formation were visualized.	-	[81]
Evo312	Human PC cells (PANC-1) and GEM-resistant cell line PANC-GR	PKCβI expression was suppressed, as well as the protein expression levels of glycogen synthase kinase 3β, protein kinase B, signal transducer and activator of transcription 5, ribosomal protein S6 kinase β-1, and proline-rich AKT.	BALB/c-nu, weighing ∼23 g	[82]
Parthenolide	GEM-resistant AsPC-1 (cat. CRL-1682) and MIA PaCa-2	p65 activity was decreased compared with the control, as well as vascular tube formation, IL-8 secretion, and VEGF secretion. Parthenolide also suppressed the expression of the multidrug-resistance-related protein MRP1 and NF-κB.	-	[83]
Chrysin	PANC-1, Capan-2, BxPC-3, and AsPC-1 cells	CBR1 expression was inhibited. Cell viability was reduced by 70% with chrysin compared with control in Panc-1 and AsPC-1. Increased levels of autophagy-related proteins such as Beclin-1, ATG5, and LC3. The FTH1 protein level was downregulated, while the expression of NCOA4 increased along with LC3-II levels.	Male BALB/c nude mice	[84]

6. Biliary Cancers and Gastrointestinal Stromal Tumors

Liver cancer is a neoplasm originating in hepatocytes that is characterized by its intrinsic chemoresistance. It is the most common primary liver neoplasm and the fifth leading cause of death worldwide. Among the risk factors for its appearance are alcoholic cirrhosis, chronic infection by hepatitis B and C, and exposure to aflatoxin. In the early stages, treatment is based on surgery, radiofrequency ablation/thermoablation, or chemo/radioembolization. In the advanced stages, given its intrinsic chemoresistance, treatment is performed using multikinase inhibitors of tumor angiogenesis such as sorafenib and lenvatinib [85].

There are various in vitro studies in which natural bioactive compounds are used in order to reverse drug resistance mechanisms. Quin et al. described compounds derived from Annonaceae (in this case from Uvaria Acuminata) known as acetogenins, which are fat-soluble polyketide compounds. These compounds significantly decreased the expression of MDR1 mRNA (P-gp) in the HepG2 hepatocellular carcinoma line and that of MRP1 in the BEL-7402 line [86]. Another study by Sun et al. (2011) refered to the effect of dioscin, a steroidal saponin, on the sensitization of HepG2 hepatocarcinoma cells to adriamycin when they presented high levels of expression of MDR1 (P-gp) [87].

Cholangiocarcinoma is a tumor originating in the epithelium of the bile ducts. It is associated with pathologies such as ulcerative colitis or sclerosing cholangitis. In the advanced stages, it is characterized by its poor prognosis and its moderate sensitivity to chemotherapy agents such as cisplatin, GEM, and oxaliplatin [85]. In 2014, Hahnvajanawong et al. described two xanthones derived from Garcinia hanburyi called isomorellin and forbesione, which showed decreases of 20% and 30%, respectively, in the expression of MDR1 mRNA in the cholangiocarcinoma cell line KKU-100. When these compounds were combined with DOX, said inhibitions increased up to 70% [88].

In the case of gastrointestinal stromal tumors, no studies have been found that analyze the inhibition of the MDR system by natural compounds. This, together with the fact that there are very few studies in the case of hepatocarcinoma and bile duct cancer, opens up an exciting avenue of research with a view to carrying out new studies.

7. Nanoplatforms, Natural Products, and Resistance

In the case of gastrointestinal cancer, the use of nanocarriers for overcoming MDR phenotypes is a field attracting increasing interest due to nanocarriers' ability to overcome the limitations associated with efflux mechanisms, in addition to improving the solubility, bioavailability, and specificity of many of the conventional drugs used for the treatment of cancer [89]. The use of nanomedicines permits the exploitation of the enhanced permeation and retention effect (EPR) of solid tumors and the establishment of targeted delivery strategies by targeting surface receptors that are overexpressed on tumor cells. Natural products are being studied in detail due to their numerous benefits in the field of drug resistance; however, their hydrophobic character impedes aqueous solubility and decreases absorption. In this context, nanoplatforms can be used as transport/delivery systems for natural compounds by reducing solubility limitations and improving their bioavailability. Furthermore, the use of natural compounds for the synthesis of nanoformulations comprises a promising new strategy in overcoming drug resistance [90] (Figure 5).

The effect of curcumin as a modulator of MDR has been extensively studied in different tumors, demonstrating its ability to regulate the expression of proteins such as Pgp, MRP, and LRP, and therefore its sensitizing activity in tumor cell lines that are resistant to chemotherapy. However, the clinical application of curcumin is limited by its low aqueous solubility [91]. Encapsulation in micelles, polymeric nanoparticles, and lipid nanoformulations, among other nanoplatforms, is an effective strategy for overcoming hydrophobicity

problems and increasing its MDR modulation and anticancer activity (Table 2). In this sense, there are numerous studies on the therapeutic benefits of combining curcumin with antitumor drugs such as DOX in a single nanoformulation to treat resistant tumors [92,93]. In this context, Pramanik et al. synthesized NVA622 polymeric nanoparticles loaded with DOX and curcumin that showed increased nuclear retention of DOX compared with the formulation without curcumin in in vitro and in vivo models of DOX-resistant ovarian, prostate, and multiple myeloma tumors, which all had a high expression of the MDR1 and MRP1 proteins [94]. Similarly, the combination of curcumin and DOX in Poly(lactic-co-glycolic acid) (PLGA) nanoparticles decreased the mRNA expression of MDR1 and BCL-2 by more than 12-fold compared with free DOX treatment and resulted in increased nuclear accumulation of DOX in chronic myeloid leukemia (CML) blasts like K562 cells [95]. Likewise, co-delivery of curcumin and DOX encapsulated in polymeric micelles showed increased cellular entry in a time-dependent manner, significantly enhancing intracellular accumulation and thus the cytotoxic effect of DOX, in addition to reducing the amount of DOX effluxed in a DOX-resistant MCF-7 human breast carcinoma cell line [96]. There are, in addition, studies on the delivery of curcumin and paclitaxel in solid lipid nanoparticles and through a nanoemulsion in resistant breast and ovarian tumor cell lines, respectively [97,98]. According to Baek and Cho's study, polymeric micelles loaded with paclitaxel and curcumin were shown to reduce Pgp protein expression by more than 80% compared with the untreated control [97]. Further, Ganta and Amiji showed that curcumin vehicleized in a nanoemulsion showed its regulatory activity against NFκB factor as well [98].

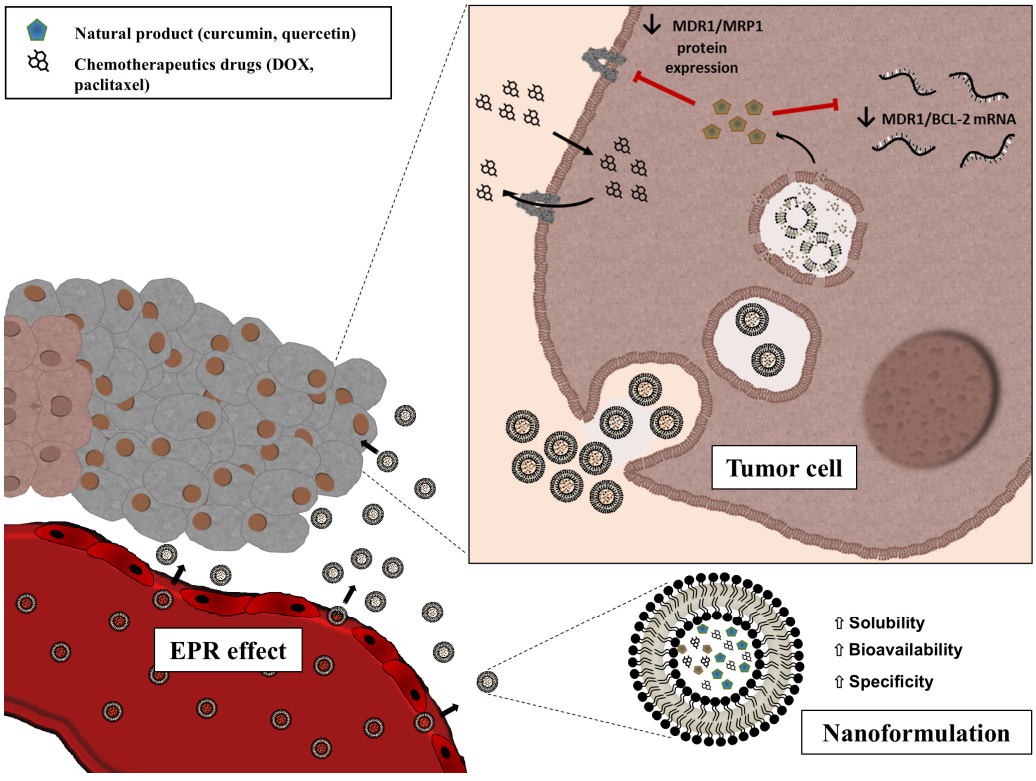

Figure 5. EPR effect and mechanism of action in natural-product-loaded nanoformulations. The use of nanocarriers improves the solubility, bioavailability, and specificity of natural products through the EPR effect, a reduction in hydrophobicity, or drug delivery strategies.

On the other hand, nutlin-3a, an antitumor agent with efficacy in various tumors such as glioblastoma, is limited by acting as a substrate for the resistance proteins MRP-1 and LRP. Das et al. encapsulated curcumin and nutlin-3a in folate-functionalized PLGA nanoparticles and demonstrated dose-dependent inhibition of the gene and protein expres-

sion of MRP-1 and LRP by curcumin in human retinoblastoma cells [99]. Some studies focused on the study of the synergistic antitumor effect of curcumin with other chemotherapeutics in resistant tumor models without testing its MDR modulatory effect. Studies on a paclitaxel-resistant SK-OV-3TR ovarian tumor cell line showed that polymeric micelles loaded with curcumin and paclitaxel exhibited enhanced cytotoxicity in both monolayer cell cultures and tumor spheroids (a 3D multicellular tumor model) and 3-fold greater inhibition of tumor growth in vivo [100,101]. Similar in vitro and in vivo results were obtained in a DOX-resistant A2780 ovarian tumor model with the co-delivery of curcumin and DOX by alginate nanodroplets [92]. There were also studies on nanoformulations of paclitaxel in combination with other natural compounds such as baicalein and resveratrol with promising results for overcoming MDR in breast cancer [102,103]. Furthermore, demethoxycurcumin, another compound containing bioactive curcuminoids, showed better blood solubility than curcumin and could also be used as a mediator of chemoresistance by sensitizing tumor cells to conventional chemotherapeutic agents [104]. In fact, an enhanced synergistic effect between cisplatin and demethoxycurcumin loaded in CD133-targeted chitosan nanoparticles was shown against MDR lung cancer stem-like cells [105].

Also, the use of nimbolide, a triterpene compound that can be isolated from neem, loaded in Poly (D, l-lactide-co-glycolide) nanoparticles should be highlighted, achieving the downregulation of AKT, mTOR, mesenchymal marker N-cadherin, and MDR marker ABCG2 and the upregulation of the epithelial marker E-cadherin [65]. Moreover, Zhang et al. [106] employed polylactic-co-glycolic acid nanoparticles charged with bufalin, a compound secreted by the glands of toads, and 5FU and GEM. With this strategy, the resistance of PC cells to GEM was reversed by inhibiting the expression of ABCB1 and ABCG2 and decreasing the expression of NF-κB and NOD2, also synergistically increasing the anticarcinoma activity of 5FU. Tumor weight was reduced by 60% with the combined therapy compared with the individual treatments.

L-Arg, a nitrogen oxide donor, was charged in gold nanostructures with a biomimetic cell membrane coating with PEG2000 and GEM. A 63% cell viability reduction was achieved with the combination strategy with respect to the control (empty nanostructure with only GEM) in GEM-resistant Panc-1, with an 82% improvement in the apoptosis rate, reversing GEM resistance. A 95% tumor volume reduction was achieved with respect to the control at the end of experiment, with a 100% survival rate improvement 60 days after administration [107]. Piperine, a piperidine alkaloid extracted from black pepper, was used in albumin-bound nanoparticles. Through this strategy, PIP significantly reduced the IC50 value of paclitaxel, and the accumulation of paclitaxel increased after co-incubation with PIP compared with incubation with paclitaxel alone. PIP competed for the drug-binding site of paclitaxel on P-gp at specific concentrations. PIP decreased the P-gp protein level and the expression of the MDR1 gene, blocked tumor cell growth, and increased apoptosis [108].

Table 2. Nanoformulations loaded with natural products to overcome MDR.

Natural Compound	Nanoformulation	Drug	Main Results on MDR Effect	Reference
Curcumin	Alginate nanodroplet	DOX and curcumin	Increased in vitro cytotoxicity and 5-fold tumor inhibition in in vivo DOX-resistant A2780 ovarian tumor model.	[92]
Curcumin	Chitosan/poly (butyl cyanoacrylate) (PBCA) NP	DOX and curcumin	Decreased Pgp expression in DOX-resistant MCF-7 human breast carcinoma cell line.	[93]
Curcumin	NVA622 NP	DOX and curcumin	Increased nuclear accumulation of DOX in DOX-resistant ovarian, prostate, and multiple myeloma tumor cell lines.	[94]
Curcumin	Poly (lactic-co-glycolic acid) (PLGA) NP	DOX and curcumin	12-fold decrease in MDR1 and BCL-2 mRNA expression and increased nuclear retention of DOX in chronic myeloid leukemia (CML) blasts like K562 cells.	[95]

Table 2. *Cont.*

Natural Compound	Nanoformulation	Drug	Main Results on MDR Effect	Reference
Curcumin	PEG2000-DSPE/d-a-tocopheryl poly-ethylene glycol succinate 2000 (TPGS200) mixed micelle	DOX and curcumin	Increased cellular entry in time-dependent manner, enhanced intracellular accumulation, and reduced DOX efflux in DOX-resistant MCF-7 human breast carcinoma cell line.	[96]
Curcumin	Folate-conjugated solid lipid nanoparticle	Paclitaxel and curcumin	Decreased more than 80% Pgp protein expression in DOX-resistant MCF-7 human breast carcinoma cell line.	[97]
Curcumin	Nanoemulsion	Paclitaxel and curcumin	Decreased Pgp and NFκB expression in paclitaxel-resistant SK-OV-3TR human ovarian adenocarcinoma cells.	[98]
Curcumin	Folate-conjugated poly (lactic-co-glycolic acid) (PLGA) NP	Nutlin-3a and curcumin	Decreased gene and protein expression of MRP-1 and LRP by curcumin in dose-dependent manner in Y79 human retinoblastoma cells.	[99]
Curcumin	Poly (ethylene glycol)-phosphatidyl ethanolamine (PEG-PE)/vitamin E micelle	Paclitaxel and curcumin	Increased in vitro cytotoxicity and 3-fold tumor inhibition in in vivo paclitaxel-resistant SK-OV-3TR ovarian tumor model.	[100]
Curcumin	Poly (ethylene glycol)-phosphatidyl ethanolamine (PEG-PE) micelle	Paclitaxel and curcumin	Increased anticancer effect in both spheroids and in vivo paclitaxel-resistant SK-OV-3TR ovarian tumor model.	[101]
Baicalein	Nanoemulsion	Paclitaxel and baicalein	Increased cell entry, in vitro toxicity, and in vivo antitumor effect in Taxol-resistant MCF-7 breast tumor model.	[102]
Resveratrol	PEGylated liposome	Paclitaxel and resveratrol	Increased in vitro cytotoxicity; enhanced tumor retention of drugs and antitumor effect in vivo in DOX-resistant MCF-7 breast tumor model.	[103]
Demethoxycurcumin	CD133 antibody-conjugated chitosan NP	Cisplatin and demethoxycurcumin	Enhanced synergistic effect against MDR A549 lung cancer stem-like cells.	[105]
Quercetin	Hyaluronic acid-based conjugate/d-α-tocopheryl poly (ethylene glycol) 1000 succinate (TPGS1000) mixed micelle	DOX and quercetin	Decreased Pgp expression, and increased DOX intracellular concentration in breast tumor cell line MDA-MB-231/MDR1.	[109]
Quercetin	Biotin-conjugated poly(ethylene glycol)-b-poly(ε-caprolactone) (PEG-PCL) NP	DOX and quercetin	Decreased Pgp activity and expression, decreased DOX efflux, and increased antitumor effect in in vitro and in vivo DOX-resistant MCF-7 breast tumor model.	[110]
EGCG	EGCG-based polyion complex micelle	DOX and EGCG	Increased cell entry and toxicity in DOX-resistant MCF-7 cells.	[111]
Pachymic acid and dehydro-tumulosic acid	Liposome	DOX, pachymic acid, and dehydro-tumulosic acid	Decreased Pgp expression and increased antitumor effect in vivo in DOX-resistant MCF-7 breast tumor model.	[112]
Curcumin	Biotin-conjugated poly (ethylene glycol)(PEG)-poly(curcumin) nanoparticle	Paclitaxel and curcumin	Decreased Pgp expression, 6.6-fold increased intracellular accumulation, and reduced drug efflux in DOX-resistant MCF-7 human breast carcinoma cell line.	[113]
Nimbolide	Poly (D, l-lactide-co-glycolide) nanoparticles	Nimbolide	Downregulation of AKT, mTOR, mesenchymal marker N-cadherin, and MDR marker ABCG2. Upregulation of epithelial marker E-cadherin. Induction of mesenchymal-to-epithelial transition.	[65]
Bufalin	Polylactic-co-glycolic acid nanoparticle	Bufalin and 5-fu and GEM	Inhibition of expression of ABCB1 and ABCG2 and decrease in expression of NF-κB and NOD2. Tumor weight reduced by 60% with combined therapy compared with individual treatments. Increase in anticarcinoma activity of 5FU.	[106]
L-Arg	Gold nanostructures with biomimetic cell membrane coating with PEG2000	L-Arg and GEM	63% cell viability reduction and 82% improvement in apoptosis rate between combined therapy and control; 95% tumor volume reduction with respect to control at end of experiment and 100% survival rate improvement 60 days after administration.	[107]
Piperine	Albumin-bound nanoparticles	Piperine and paclitaxel	Accumulation of paclitaxel increased after co-incubation with piperine compared with paclitaxel alone. P-gp protein decreased as concentration of piperine increased. Piperine downregulated expression of MDR1 gene related to chemoresistance and blocked tumor cell growth, leading to increased apoptosis and decreased cell survival.	[108]

Quercetin is another of the most studied natural compounds for nanomaterial-based delivery, which has been used to reduce MDR and cardiotoxicity associated with anthracy-

cline therapy [114]. In this regard, the study by Liu et al. on mixtures of polymeric micelles transporting DOX and quercetin showed downregulation of Pgp expression, increased intracellular drug concentration, and, therefore, improved cytotoxicity compared with free DOX in the breast tumor cell line MDA-MB-231/MDR1 [109]. The same result was found in an in vitro and in vivo study of biotin-conjugated polymeric nanoparticles in a DOX-resistant MCF-7 breast tumor model [110]. Catechin is another flavonoid compound found in green tea that has been studied for its MDR-modulating role, specifically as an effective modulator of Pgp. Cheng et al. formulated polyion complex micelles loaded with DOX and EGCG that were shown to enhance cell entry and increase toxicity compared with a formulation without ECGC and free DOX in DOX-resistant MCF-7 cells [111]. A study of the triterpenoids pachymic acid and dehydrotumulosic acid purified from an extract of Poria cocos is particularly noteworthy. Their encapsulation in a liposome together with DOX was shown to reduce the protein expression of Pgp and caveolin-1 and resulted in an enhanced antitumor effect in vivo in a DOX-resistant MCF-7 breast tumor model compared with other single-therapy groups [112].

Nanofomulations based on natural products comprise a new field of research in which natural products are used to synthesize nanocarriers with improved results in toxicity, bioavailability, and pharmacological activity, among others [90]. In this context, Hu et al. synthesized biotinylated PEG-poly(curcumin) loaded with paclitaxel that was capable of releasing paclitaxel in a high-GSH-concentration environment, which exhibited suppression of Pgp protein expression, a 6.6-fold increase in intracellular accumulation, and a reduction in drug efflux, resulting in an enhanced anticancer effect compared with free paclitaxel and curcumin in a DOX-resistant MCF-7 cell line [113]. Each natural product employed was integrated into different compositions of nanoparticles, with different proportions (Figure 6).

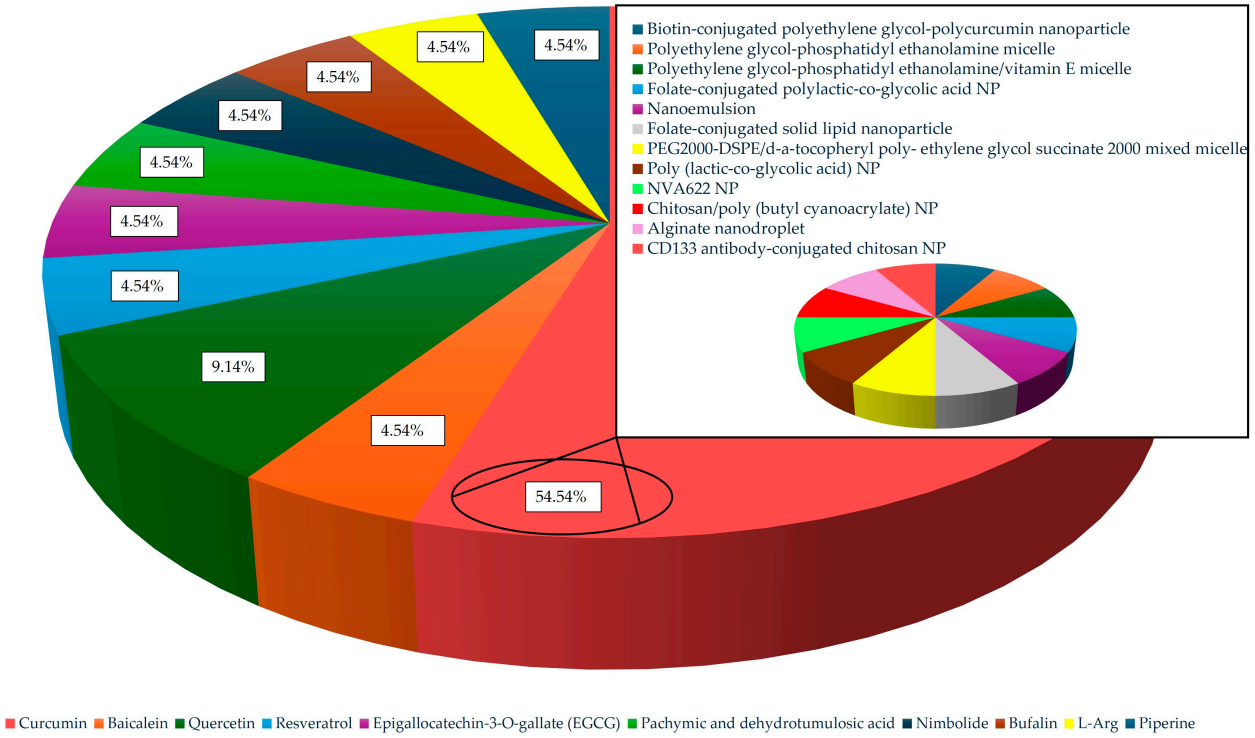

Figure 6. Proportional representation of natural products used and nanoparticle spectrum employed, with curcumin as the most used natural product.

Although the combination of natural compounds and chemotherapeutics in the same nanocarrier appears to be a promising strategy for overcoming MDR, with benefits in

the antitumor activity of conventional drugs, future studies are needed to validate these advantages over current therapies and demonstrate the safety of these nanoformulations through further in vivo biocompatibility testing.

8. Clinical Trials and Patents

The wide chemical diversity of natural compounds has led them to be considered the fourth generation of ABC transporter inhibitors. As we have shown, natural products have demonstrated great potential to overcome MDR both in vitro and in vivo, but most of them need to be tested in clinical trials. Several clinical studies have been carried out involving the treatment of advanced cancer patients with natural products, such as curcumin [114], resveratrol [25], tetrandrine [22], and flavonoids [18]. Although they did not focus specifically on the effect on MDR, previous in vitro and in vivo evidence supports their results in terms of combating tumor resistance. However, studies of multidrug tumor resistance in patients undergoing such clinical trials are needed to test the ability of natural products to reverse it.

On the other hand, although much remains to be done in terms of the clinical translation of natural compounds to overcome MDR, the development of these products is continuously expanding, as evidenced by the publication of a large number of related patents in recent years. In this sense, although products obtained directly from nature are not patentable, they can be patented when, in order to be used as medicine or food, these natural products require a specific manipulation or treatment, or when a new activity or utility can be associated with them.

In the last ten years, numerous patents related to natural products and their activity in reversing MDR have been developed (Table 3). Most of the currently active patents are of Chinese origin, and they are related to natural compounds and plants of traditional Chinese medicine, as described by the inventors Yu and Ronghua (CN102908405A) [115]. Some of the patents on the list focus on protecting the extraction method used to obtain a functional extract. For example, Seong-gyu et al. are the inventors of multiple patents where extracts derived from diverse plants (*Trichosanthes kirilowii* Maxim, *Dictamnus dasycarpus* Turcz., and *Morus alba* L.) are described as MDR inhibitors (KR20120124151A; KR20120124142A; KR101283562B1; WO2021187905A1) [116–119]. Other reasons for the development of these patents are, on the one hand, to provide a new use for natural products, as in the case of salvianolic acid A (CN103690519A) [120] and ergotamine (CN110327337A) [121], and, on the other hand, to facilitate compound isolation and preparation, as in the examples of dicoumarol (CN112121043A) [122], 5alpha-epoxylantolactone from Compositae methanol extract (CN110051663A) [123], the new skeleton cyclic lipopeptide from the neem plant family (CN111689923A) [124], and terpenoids isolated from kansui tuber (CN112479889A) [125], from *Hypericum monogynum* L. (CN113149820A) [126], and from *Euphorbia soria* (CN107827752A) [125]. Derivatives of another *Euphorbia* species have also been patented for the preparation of antitumor drugs (CN107164421A) [127].

Table 3. Patents published in the last 10 years related to the use of natural products in overcoming MDR.

Patent No.	Inventors	Title	Natural Compound, Extract, or Preparation	Year	Reference
CN102908405A	C. Yu and Z. Ronghua	Traditional Chinese medicine composition of reversing tumor multi-drug resistance (MDR) and preparation method thereof	Traditional Chinese medicine composition	2013	[115]
KR20120124151A	G. Seong-gyu et al.	Composition for inhibition of MDR containing an extract of *Morus alba* L.	Extract of *Morus alba* L.	2012	[116]
KR20120124142A	G. Seong-gyu et al.	Composition for inhibition of MDR containing an extract of *Dictamnus dasycarpus* Turcz.	Extract of *Dictamnus dasycarpus* Turcz.	2012	[117]

Table 3. *Cont.*

Patent No.	Inventors	Title	Natural Compound, Extract, or Preparation	Year	Reference
WO2021187905A1	G. Seong-gyu	Pharmaceutical composition for cancer and resistant cancer comprising *Trichosanthes kirilowii* maxim, *Dictamnus dasycarpus* Turcz and *Morus alba* L.	Extract of *Trichosanthes kirilowii* Maxim, *Dictamnus dasycarpus* Turcz., and *Morus alba* L.	2021	[118]
KR101283562B1	G. Seong-gyu et al.	Composition for inhibition of MDR containing an extract of *Trichosanthes kirilowii* maxim	Extract of *Trichosanthes kirilowii* maxim	2013	[119]
CN103690519A	X. Wang et al.	Application of salvianolic acid A in preparation of medicine for treating tumor multi-drug resistance	Salvianolic acid A	2014	[120]
CN110327337A	Y. Ma et al.	Application of ergotamine as a tumor multiple drug resistance reversal agent	Ergotamine	2019	[121]
CN112121043A	X. Chen et al.	Application of dicoumarol in tumor resistance	Dicoumarol	2020	[122]
CN110051663A	Y. Ma et al.	Application of 5alpha-epoxyalantolactone in resisting multidrug resistant tumors	5alpha-epoxyalantolactone isolated and purified from methanol extract of Compositae	2019	[123]
CN111689923A	Y. Jianmin et al.	Novel skeleton cyclic lipopeptide compound with activity of reversing MDR of tumor as well as preparation method and application of same	A new skeleton cyclic lipopeptide from a plant of the neem family	2020	[124]
CN107827752A	A. Aisa and H. Rui	Macrocyclic diterpene compounds in fruit of *Euphorbia sororia* A. schrenk as well as preparation method of macrocyclic diterpene compounds and use of macrocyclic diterpene compounds in reversion of MDR	Three macrocyclic diterpenoids isolated from the fruit of *Euphorbia sororia*	2018	[125]
CN113149820A	Y. Li et al.	Monocyclic meroterpenoid structure compound and preparation method and application thereof	Monocyclic meroterpenoid from *Hypericum monogynum* L.	2021	[126]
CN107164421A	Z. Chen and Y. Wu	The method for transformation and its purposes in antineoplastic is prepared of the terpane type derivative of hydroxylating *Euphorbia lathyris* two	Hydroxylated lathyrane derivatives from *Euphorbia lathyris* L.	2017	[127]
CN102697795A	Y. Sun et al.	Anti-tumor combined medicament	Nanoformulation loaded with epirubicin and quercetin	2012	[128]
WO2012078831A3	A. Maitra and D. Pramanik	Smart polymeric nanoparticles which overcome MDR to cancer therapeutics and treatment-related systemic toxicity	Nanoformulation loaded with curcumin	2012	[129]
CN103142481A	X. Yang et al.	Drug-loaded liposome overcoming tumor drug resistance, preparation method and application thereof	Nanoformulation loaded with paclitaxel and resveratrol	2013	[130]
CN111568882A	J. Ren et al.	Compound curcumin nanoparticle, and preparation method and application thereof	Nanoformulation loaded with curcumin	2020	[131]
CN112479889A	Q. Huang et al.	Canarium album alkane diterpenoids and extraction method and application thereof	Pseudolephane diterpenoids extracted from kansui tuber	2021	[132]

In addition, the good experimental results have made the application of nanoformulations loaded with natural products against MDR also patentable. These patents include diverse natural compounds such as curcumin, quercetin, ceramide, and resveratrol loaded in nanocarriers to improve the modulation of MDR. Both the WO2012078831A3 and CN111568882A patents [129,131] focused on developing the MDR inhibitory activity of curcumin mediated by nanoformulations. Meanwhile, CN111568882A prepared a compound curcumin nanoparticle, which decreased curcumin metabolization through piperine and used P-gp inhibitors as auxiliary materials, resulting in an enhanced antitumor efficacy of curcumin and MDR reversion; WO2012078831A3 described polymeric nanoparticles encapsulated with curcumin and one or more chemotherapeutic agents. In the same way, the patent CN102697795A [128] described how epirubicin and quercetin encapsulated in

the same nanoparticles can reverse leukemia drug-resistant K562/A02 cells. Similarly, the CN103142481A patent [130] presented a liposome containing paclitaxel and resveratrol, capable of inhibiting MDR in chemoresistant cells. Finally, among the patents relative to nanoencapsulation, WO2014144421A1 presented a novel mechanism for dealing with MDR based on ceramide-loaded nanoliposomes that induces rapid translocation of a chemotherapeutic drug, daunorubicin, from the cytoplasm to the nucleus. It is necessary to continue research in this field and advance the clinical applications of natural products that have already been patented.

9. Conclusions

Gastrointestinal cancers are among the most prevalent and lethal malignancies worldwide, for which treatment is often compromised by the development of MDR. MDR is a complex phenomenon where cancer cells become resistant to a broad spectrum of chemotherapeutic agents, primarily due to the overexpression of ABC transporter proteins. These proteins, such as P-gp, MRP1/ABCC1, MRP2, and breast cancer resistance protein (BCRP/ABCG2), can act as efflux membrane pumps, expelling chemotherapeutic drugs from cancer cells and reducing their cytotoxic efficacy and antitumoral capacity. Although there have been decades of research and the development of MDR modulators, they still have limited efficacy, off-target effects, and toxicity. This issue requires an improvement in therapeutic responses with the development of new strategies.

Plant-derived molecules offer a promising and versatile solution. Different compounds such as flavonoids, alkaloids, terpenoids, and coumarins have shown significant potential in modulating MDR mechanisms. These natural products can inhibit the activity of ABC transporters, downregulate their expression, and disrupt the signaling pathways ligated to them. For instance, flavonoids such as quercetin and kaempferol competitively bind to ABC transporter binding sites, reducing drug efflux and enhancing intracellular drug retention. Similarly, para-benzoquinones like embelin have shown the capacity to reverse MDR by targeting both transporter activity and cancer cell survival pathways. This natural strategy potentiates the effectiveness of standard chemotherapeutic therapies while minimizing toxicity to normal cells.

Nanoplatforms, including liposomes, dendrimers, polymeric nanoparticles, and micelles, offer advanced drug delivery systems designed to overcome the limitations of traditional therapies. These nanocarriers provide several benefits, such as enhanced solubility of hydrophobic drugs, improved drug stability, controlled release, and selective tumor targeting. When used in combination with plant-derived molecules, nanoplatforms can co-deliver chemotherapeutic agents and MDR modulators directly to tumor cells, circumventing the efflux mechanisms of ABC transporters. Moreover, nanocarriers can be functionalized with ligands specific to tumor-associated markers, ensuring precision delivery while sparing healthy tissues. This targeted approach not only improves the therapeutic efficiency of anticancer drugs but also reduces systemic toxicity and off-target effects. For example, nanoparticles loaded with both 5FU and GEM and a cardiotonic steroid, such as bufalin, as an MDR modulator have shown synergistic effects, significantly increasing drug accumulation within cancer cells and promoting apoptosis.

The integration of plant-derived molecules with innovative strategies based on nanotechnology represents a paradigm shift in the management of gastrointestinal cancers. While preclinical studies are encouraging, challenges remain, including large-scale production, regulatory approval, and validation in clinical trials. Addressing these hurdles will be critical to translating these promising strategies into routine clinical practice.

In conclusion, the combination of plant-derived compounds, such as quercetin, kaempferol, and embelin, with nanoplatforms, mainly polymeric nanoparticles, liposomes,

and dendrimers, offers a synergistic approach to overcoming MDR in gastrointestinal cancers. By targeting the underlying mechanisms of drug resistance and enhancing drug delivery, this strategy has the potential to improve treatment efficacy, reduce toxicity, and ultimately enhance patient outcomes. Continued research and innovation in this field could lead to significant advancements in cancer therapeutics, offering hope to millions affected by these challenging malignancies.

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