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*Review*

# Vegetal-Derived Bioactive Compounds as Multidrug Resistance Modulators in Colorectal Cancer

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**Abstract:** Colorectal cancer is one of the leading causes of morbidity and mortality today. Knowledge of its pathogenesis has made it possible to advance the development of different therapeutic strategies. However, the appearance of drug resistance constitutes one of the main causes of treatment failure. Bioactive compounds of vegetable origin are being studied as a new strategy to improve antitumor treatment, due to their ability to regulate the pathways involved in the development of carcinogenesis or processes that are decisive in its evolution, including multidrug resistance. In vitro and in vivo studies of these substances in combination with cytotoxic drugs have shown that they reduce resistance and increase therapeutic efficacy. The objective of this review is to summarize the knowledge that is described in the scientific literature on the antitumor and chemo-sensitizing capacity of vegetable-derived biomolecules such as polyphenols, flavonoids, and terpenes. These compounds may hold a promising future in improving the treatment of colorectal cancer.

**Keywords:** colorectal cancer; vegetables; multidrug resistance; biomolecules; resistance mechanisms



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## 1. Introduction

Colorectal cancer (CRC) accounted for 9.39% of deaths by cancers in 2020 and is the third most commonly diagnosed cancer in the word. CRC incidence could double by 2035 due to an increase in the number of cases and their early diagnosis [1]. Current treatment is based on resection combined with chemotherapy and adjuvant radiotherapy in the early stages and larger resections that are associated with chemotherapy (oxaliplatin, irinotecan, 5-fluorouracil (5-FU) and capecitabine, among others) in metastatic stages [2]. However, despite the use of different therapeutic options, the average survival in metastatic patients is low (3 years) although the 5-year survival rates of patients that are diagnosed with localized tumors or with regional dissemination are 90% and 69%, respectively [3,4]. Acquired or intrinsic drug resistance in CRC is one the main causes of treatment failure. A clinical assay that was performed with patients from 13 European countries, Israel, and South Africa showed that more than 50% of CRC patients had resistance to the drug 5-FU [5,6]. In addition, the mechanisms that generate resistance to one drug produce resistance to others (multidrug resistance or MDR). The mechanism that is mediated by the ATP-dependent transporter family (ATP-binding cassette family, ABC) is prominent in CRC, including the p-glycoprotein (p-GP; ABCB1), a drug efflux pump which prevents cellular uptake of many structurally and functionally cytotoxic compounds [7,8]. Understanding resistance phenomena is essential for improving CRC patient prognosis.

In this context, it has been shown that some plant-derived natural products or their association with the classic cytotoxic drugs used in cancer treatment were capable of overcoming multidrug resistance and/or reducing the effective antitumor drug dose [9].

Despite the low proportion of plant species that have been explored for their antitumor activity [10], plant-derived natural products have played an important role in the treatment and prevention of cancer. Most of the compounds from vegetables and fruits with significant antitumor activity also showed clear advantages in relation to modern drugs that are used in chemotherapy [11]. Furthermore, this therapeutic strategy based on the use of natural compounds showed minimal side effects and lower cost than synthesized antitumor drugs [12]. However, biodistribution, biotransformation, and transport limitations of natural products may hinder their application in cancer patients. Furthermore, their effect on the immune system is not fully analyzed [13–15]. Concretely in CRC, the therapeutic potential of some natural compounds has been clearly demonstrated [16]. In addition, their combination with other conventional chemotherapeutic drugs has demonstrated a significant synergistic effect [17]. In fact, curcumin, resveratrol, and (-)-Epigallocatechin Gallate (EGCG) and terpenoids, secondary plant metabolites that are composed of isoprene units, enhanced the effect of cytotoxic drugs [18–20]. The antitumor effect exerted by these compounds is carried out through several pathways including cell cycle arrest and cell death by apoptosis [21]. On the other hand, polyphenols from plants also prevent multidrug resistance in several types of solid tumors, including CRC. In addition, these compounds inhibit cell proliferation, angiogenesis, and metastasis, as well as regulating the proinflammatory response [22]. Finally, quercetin, a flavonoid, not only modulates the drug resistance phenomena but is capable of increasing sensitivity to doxorubicin in CRC through the inhibition of a glutamine transporter (SLC1A5) [23,24].

The objective of this review is to study the different families of plant-derived compounds that modulate drug resistance in CRC, observing their ability to be used as a future therapy against this type of cancer.

## 2. Colorectal Cancer: Resistant Mechanisms

Despite the discovery of new drugs against CRC, the emergence of resistance to these agents is inevitable. Drug resistance can be innate (dysregulations of tumor cells before treatment) or acquired (resistance after treatment cycles) [25,26]. Drug efflux mediated by transmembrane transporters, specifically those of the ATP binding cassette superfamily (ABC), is one of most relevant mechanisms in CRC. These proteins are capable of expelling toxic substances from the inside of cells including different anticancer agents [27]. Specifically, p-GP, encoded by the ABCB1 gene, was overexpressed in different CRC cell lines, conferring resistance to treatment. In addition, resistant CRC cells overexpressed CD133, a protein that regulates p-GP expression through the AKT/NF-κB/MDR1 axis [28,29]. Other members of the ABC family, such as MRP1 and BCRP, are also overexpressed in some CRC cell lines, leading to multiple resistance to chemotherapeutic drugs as 5-FU, doxorubicin, irinotecan, vincristine, among others [30,31], while MRP2-mediated resistance to oxaliplatin and vincristine in CRC, being Nrf2, signaling is critical for its expression (Figure 1) [32]. Drug resistance in CRC can also arise when there are alterations in antitumor drug targets, such as mutations or changes in expression due to epigenetic variations [33]. Finally, an increase in the expression of repair protein-DNA, such as MGMT, was detected in some 5-FU-resistant CRC lines [34].

Apoptosis evasion promotes carcinogenesis and tumor progression, leading to the appearance of pharmacological resistance, especially to drugs that induce this pathway such as doxorubicin and cisplatin. Several apoptosis-resistant tumors were associated with the increased or decreased expression of antiapoptotic (BCL-2, MCL-1, and BCL-XL) and proapoptotic (p53, BAX, and BIM) genes, respectively [35]. In addition, modulation of DNA methylation, histones and chromatin remodeling can alter the expression of genes that are involved in the metabolism and activity of chemotherapeutic drugs, inducing resistance [33]. Moreover, tumor heterogeneity also plays a role in this phenomenon, as it makes treatment more difficult because of the presence of cancer stem cells which are more resistant to drugs. These cells have a self-healing and differentiation capacity and are associated with greater tumorigenicity. These cells are also capable of acquiring mesenchymal characteristics,

which is related to the cell migration process and metastasis and a worse prognosis in patients [36,37]. On the other hand, it is known that the most resistant cells within the tumor sinus can transfer small miRNAs to their environment, inducing resistance in neighboring cells [38]. Finally, another important factor to highlight is the tumor microenvironment, including the extracellular matrix, blood vessels, fibroblast, and immune system cells. This microenvironment will be an additional layer of protection against drugs, making the entry of chemotherapeutics into the tumor sinus more limited [39].

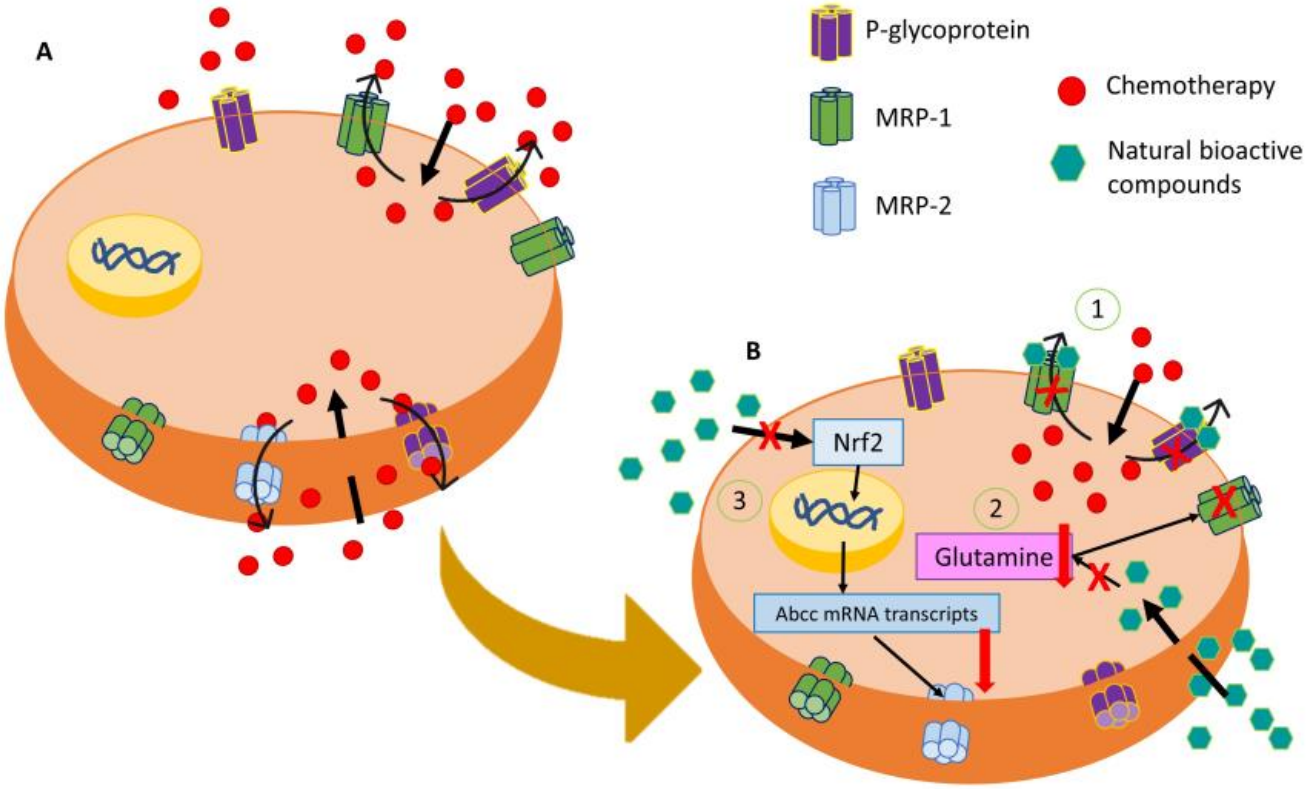


**Figure 1.** Representative image of modulation of the MDR mechanism of resistance by natural bioactive compounds. (**A**) Main membrane transporters that are involved in chemoresistance by expelling them into the extracellular medium. (**B**) Action of natural bioactive compounds in the regulation of MDR by (1) MRP-2 downregulation through the inhibition of the Nrf2/MRP2 pathway, (2) P-glycoprotein and MRP-1 blocking by natural bioactive compounds, and (3) inhibition of glutamine cell intake producing an MRP-1 disfunction.

## 3. Natural Products: A New Source of Molecules with Antitumor Activity

Many plant compounds are substances with known bioactive activity that can be used as chemotherapeutic agents in cancer. One of the best known, taxol, is a potent diterpene with antitumor activity that is derived from the bark of the yew tree (*Taxus brevifolia*). These compounds show advantages over traditional drugs, such as greater bioavailability, accessibility, cost-effectiveness, and lower systemic toxicity [40]. This last point is highly relevant since conventional drugs show many side effects [20]. In addition, these compounds show a synergy with conventional therapies and a benefit for the treatment of CRC by avoiding drug resistance [41–43]. Therefore, plant-derived natural compounds allow us to have more cancer treatment options. Polyphenols, flavonoids, and terpenes have been described as the main molecules that are able to modulate chemoresistance phenomena in CRC (Figure 2).

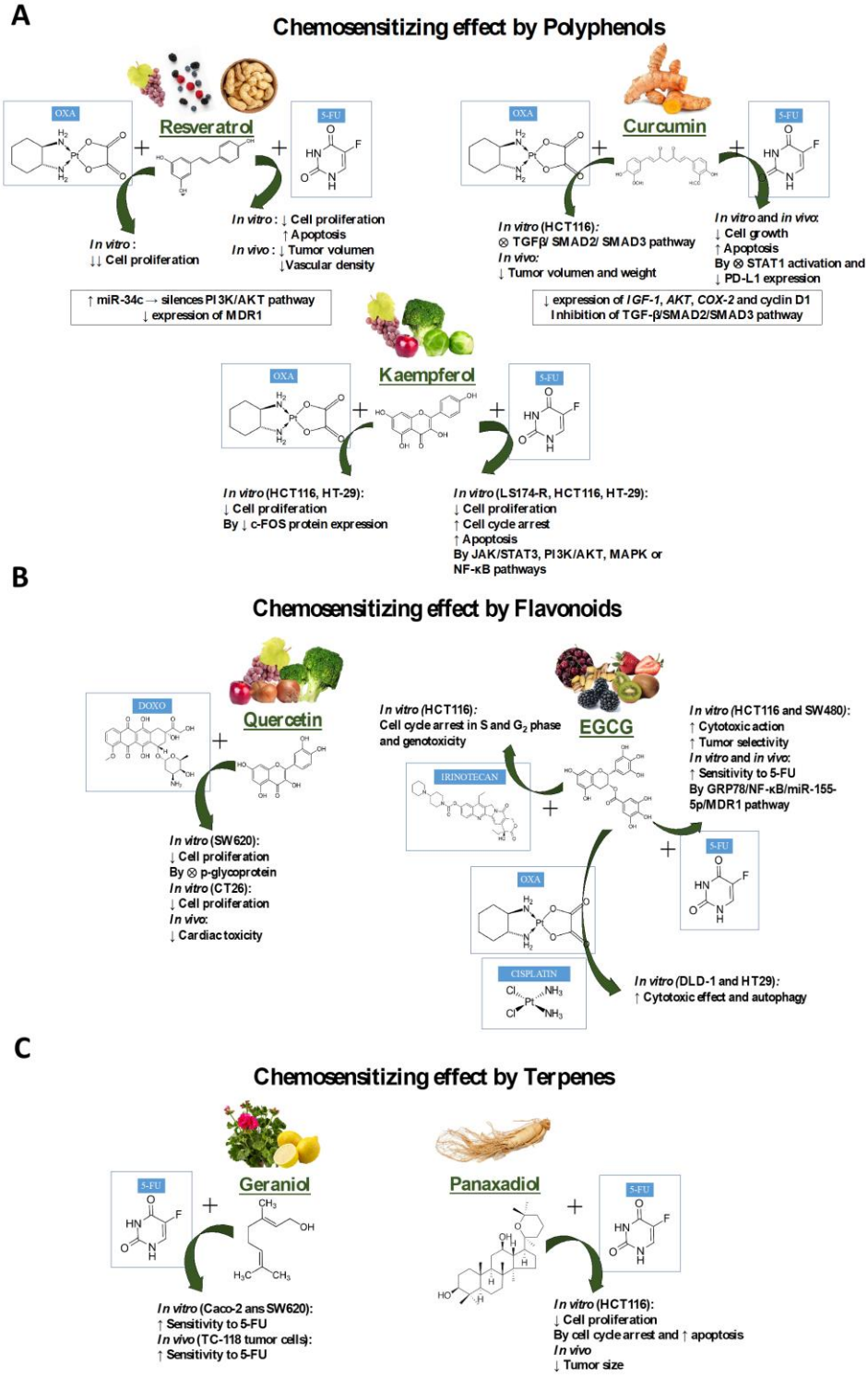


**Figure 2.** Sensitizing effect on chemotherapeutic drugs that are frequently used in CRC exerted by natural compounds of the following families (**A**) polyphenols, (**B**) flavonoids, and (**C**) terpenes, analyzed in this review. DOXO (doxorubicin); 5-FU (5-fluorouracil); OXA (oxaliplatin).

### *3.1. Polyphenols*

Polyphenols (Figure 2A) comprise a heterogeneous group of phytochemicals that contain one or more phenolic rings in their chemical structure. They are divided into different groups, including stilbenes, phenolic acids, lignans, xanthones, tannins, and flavonoids [44]. These compounds are synthesized by different plants to carry out different

functions, including protection against UV radiation and infection by microorganisms, as well as regulation of cell growth [45,46]. The three most studied polyphenols in CRC are resveratrol, curcumin, and kaempferol.

#### 3.1.1. Resveratrol

Resveratrol is a polyphenol belonging to the stilbenes group. It is found in grapes, blueberries, and peanuts, intervening in the response to infection by microorganisms [47]. From its study it has been determined that it has antioxidant, anti-inflammatory, antitumor, cardioprotective, and neuroprotective properties. These effects are mainly based on its ability to suppress inflammation, regulate various enzymatic processes that are involved in the metabolism of numerous substances, eliminate reactive oxygen species, and inhibit cell proliferation through its action as a phytoestrogen. The therapeutic action of resveratrol comprises different mechanisms such as the induction of cell death through apoptosis and autophagy, the capacity to suppress tumor proliferation, or the inhibition of angiogenesis and metastasis [48]. The preventive and therapeutic effect has also been observed for CRC. In vitro studies that were carried out in different colon cancer cell lines have demonstrated the ability of this compound to inhibit cell growth and proliferation, promoting cell cycle stop and derived apoptosis activating apoptotic markers such as caspases 3 and 8. In the CRC line HT-29, this compound had an $IC_{50}$ of 10 mg/mL after 72 h of treatment [49]. Particularly, in HCT116 and CaCo-2 cell lines, it has been observed that resveratrol inhibits cell cycle initiation by the downregulation of the CCND1/CDK4 complex. In addition, resveratrol treatment decreases the synthesis of proangiogenic factors such as VEGF in CRC [50]. Furthermore, it has been observed that it is able to reverse the Warburg effect in tumor cells through modulation of the pyruvate dehydrogenase complex, influencing the process of glycolysis [51]. Its in vivo antitumor capacity has also been shown. Thus, in murine models of rats and mice that had the KRAS proto-oncogene overexpressed, dietary administration of 150 or 300 ppm resveratrol for 4 weeks was shown to prevent tumor growth through the deregulation of KRAS via miR-96 [52]. On the other hand, a model of colonic tumorigenesis in situ showed that resveratrol prevented the formation of precursor lesions (dysplasia or adenomas), in addition to reducing the volume of tumors if they had been generated. The downregulation of the pro-apoptotic gene BAX was observed in the treated tumor mucosa, as well as a reduction of COX-2 and NF-κB [47,53]. Human clinical trials showed that resveratrol intake was safe and well tolerated systemically, with side effects such as diarrhea, abdominal pain, and nausea being observed in patients that were treated with more than 1 g per day. Despite this, the bioavailability of resveratrol in the body is limited with 71–98% recovery of the compound or its derivatives in urine and feces after oral administration [47,54,55].

Another possibility that was studied was the combination of resveratrol together with traditional chemotherapy drugs, showing the sensitization of tumor cells to conventional drugs and the reduction of existing resistance to these drugs. Thus, its combination with 5-FU produced a decrease in cell proliferation and an increase in apoptosis in vitro, accompanied by a reduction in tumor volume and vascular density in vivo [56–58]. Synergistic effects have also been shown with oxaliplatin, observing that their combination produces a greater inhibition of cell proliferation compared to the chemotherapy alone. The effect of resveratrol is found to be exerted through increased expression of miR-34c, which silences the PI3K/AKT pathway and triggers reduced expression of the resistance gene MDR1 [59]. The death that is produced by this combination is through necrotic and apoptotic pathways [60].

Due to the low bioavailability of resveratrol, formulations have been designed to allow improved transport into the cell. Khayat et al. designed zein nanoformulations that had a high encapsulation of the plant compound and were more effective in inducing apoptosis and oxidative stress in cells compared to the free drug in HCT116, Caco-2, and HT-29 cell lines [61]. Another study designed gels that were capable of encapsulating resveratrol with high efficacy for efficient oral administration. These formulations were tested in

HCT116 cells, obtaining greater efficacy in cytotoxicity assays and significantly increasing the expression of pro-apoptotic genes such as Bcl-2 compared to free resveratrol [62]. Feng et al. synthesized lipid nanocapsules encapsulating resveratrol and showed 70% drug release at 48 h, increasing the cytotoxic effect of the free drug and significantly increasing the induced apoptosis in the HT-29 cell line [63]. Finally, other formulations encapsulating resveratrol in mesoporous silica nanoparticles and liposomes were developed. The former showed high drug loading capacity and improved efficacy against free drug in HT-29 and LS147T lines [64]. Meanwhile, liposomes showed a high drug release after 24 h and increased the cytotoxic effect of the free drug in the HT-29 line, increasing the delivery of this hydrophobic agent [65].

#### 3.1.2. Curcumin

On the other hand, curcumin is one of the most studied bioactive compounds as an adjuvant in CRC. This phytochemical is derived from turmeric (*Curcuma longa*) and is used as a dietary supplement or food flavoring [66]. The mechanisms by which it influences CRC have been extensively studied. It is known to regulate the microbiome, protect the intestinal barrier and promote anti-inflammatory activity in the intestine through inactivation of the proinflammatory factor NF-κB and by increasing the expansion of CD4+ FOXP3+ regulatory T lymphocytes in the mucosa. In addition, it modulates tumor cell death via the autophagy mechanism by suppressing the PI3K/AKT/mTOR signaling pathway and it is able to trigger epigenetic modifications that increase its chemosensitizing power together with other drugs [67]. Pharmacokinetic and toxicity studies showed that its administration in humans is safe, although its absorption is low and it is a compound that is rapidly eliminated by the body, problems that currently prevent it from being tested as a therapeutic agent [68].

The chemopreventive action of curcumin in CRC has been demonstrated in numerous in vitro studies. In the HT116 cell line, it inhibits proliferation by blocking the WNT/β-catenin pathway that is mediated by c-MYC, producing cell cycle arrest in G2/M phase, and inducing apoptosis. In the HT-29 cell line, curcumin is also able to stop the cycle in the G1 phase and induce apoptosis by acting on the pAKT-AMPK-COX-2 signaling pathway at a dose of 20 μM [69]. In addition, curcumin has been shown to inhibit the migration and invasion of HT116 and LoVo cell lines [70]. In vivo studies that were conducted in murine models have shown that a dose of 300 mg/kg prevents progression to cancer from precancerous lesions, reducing the number of adenomas and tumor size [71,72]. Clinical studies that were conducted in humans observed that oral consumption of curcumin in CRC patients reduced serum TNF-α levels and increased apoptosis in the tumor tissue tested [73].

Curcumin has also been studied as an adjuvant and chemosensitizer in combination with drugs that were traditionally used in the treatment of CRC. Several in vitro and in vivo studies have demonstrated the ability of curcumin to decrease tumor cell resistance to drugs such as 5-FU and oxaliplatin. Particularly, in vitro studies indicate that this compound decreases the expression of several genes (IGF-1, AKT, COX-2, and cyclin D1) that are involved in resistance to these two drugs [73]. It has also been shown, in oxaliplatin-resistant HCT116 cell lines that were cultured with this chemotherapeutic and curcumin, that resistance is reversed through inhibition of the TGF-β/SMAD2/SMAD3 pathway. In mice that were transplanted with oxaliplatin-resistant HCT116 cells, the administration of curcumin together with oxaliplatin has also been observed to significantly reduce tumor volume and weight [74]. The combination of a slightly cytotoxic dose of curcumin (10 μM) with 5-FU (5 μM) produced a synergistic antitumor response, reducing cell growth, and inducing apoptosis as observed in in vitro and in vivo studies. This chemo-sensitizing effect is carried out by inhibiting STAT1 activation, which reduces PD-L1 expression [75]. Furthermore, this synergism could also lead to a decrease in CRC progression and metastasis, thanks to the ability of curcumin to decrease the expression of IGF-1 and the myc oncogene [76].

As curcumin is one of the most studied natural compounds, studies have attempted to encapsulate it to increase its bioavailability and absorption. Han et al. designed a nanoformulation based on fusion proteins that were capable of being efficiently introduced into cells with high expression of epidermal growth factor receptor (EGFR), being more effective in the HCT116 line (EGFR-positive) versus SW620 (EGFR-negative) [77]. Wang et al. encapsulated the compound in micelles and increased its bioavailability and cytotoxic activity in CRC cell lines. Moreover, after simulated in vitro digestions, 40% of the formulation was still effective against tumor cell lines, thus possessing potential for the prevention and treatment of this type of cancer [78]. Although this drug was encapsulated in other types of nanoformulations such as PLGA (poly lactic co-glycolic acid)-coated nanoparticles [79] or in β- cyclodextrins [80] showing efficacy, an interesting study that was carried out by Gupta et al. used poly(allylamine)/eudragit nanoparticles that were capable of encapsulating doxorubicin and curcumin with high efficiency. The combination of both drugs in the nanoformulation showed high cytotoxicity in CRC HCT116 cells and in Balb/C murine models, with retention of these nanoformulations in the colon region 24 h after treatment [81].

Therefore, the findings that were observed in the multiple studies employing the use of curcumin and resveratrol in CRC demonstrate their great capacity as chemopreventive and sensitizing agents in combination with other cytotoxic drugs. However, it is still essential to continue studying these compounds to be able to introduce them into clinical practice in the future.

#### 3.1.3. Kaempferol

Kaempferol is a flavanol that is present in vegetables and plants such as broccoli, grapes, apples, brussels sprouts, or black tea. This bioactive compound possesses cardioprotective, neuroprotective, anti-inflammatory, antidiabetic, antioxidant, and antitumor properties [82]. The mechanisms of action underlying the anticancer effect of kaempferol are based on inhibition of the cell cycle in the G2/M phase to prevent tumor growth and proliferation, as well as induction of apoptosis by acting on different cell signaling pathways. Several in vitro studies have also observed its anti-angiogenic effect and anti-metastatic, inhibiting VEGF production and decreasing the expression of markers that are involved in epithelial-mesenchymal transition (EMT) at a dose of 0.1 μM in MDA cell lines [83,84]. Pharmacokinetic studies that were performed in rats determined that the bioavailable fraction of this compound after oral doses was 2% of the total administered [85]. To overcome this obstacle, the combination with quercetin has been tested, resulting in an increase in its bioavailability, in addition to improving efficacy [82]. In this way, this bioactive compound would act selectively on tumor cells, without affecting healthy ones. This compound exhibits cytotoxic effects on various CRC cell lines, such as HCT116, HT-29, HCT-15, LS174-R, and SW480, both when used alone and in combination with other chemotherapeutic agents. In HT-29 cell lines, the ability of this compound to inhibit the cell cycle has been studied, resulting in cell cycle arrest in G1 and G2/M phases through inhibition of CDK2, CDK4, and Cdc2 activity [86].

In vitro studies in the 5-FU-resistant LS174-R cell line and in other CRC lines such as HCT116 and HT-29 have shown that the antiproliferative activity that is exerted by the combination of kaempferol with this chemotherapeutic agent is through cell cycle arrest and induction of apoptosis, acting on signaling pathways such as JAK/STAT3, PI3K/AKT, MAPK, or NF-κB [87,88]. Other studies that were carried out in oxaliplatin-resistant HCT116, and HT-29 cell lines have shown that the combination of kaempferol with this drug generates a greater cytotoxic response, decreasing cell proliferation. The chemosensitization of these cells is mediated by the suppression of c-FOS protein expression [89].

Although not many nanoformulations have been synthesized to improve the bioavailability of kaemferol in the treatment of CRC, Meena et al. designed PEGylated gold nanoparticles that efficiently co-encapsulated DOX and the natural compound, improving the cytotoxic effect of both drugs separately and inducing apoptosis in the HT-29 line,

without having high toxicity in the HTB-38 non-tumorous colorectal line. Finally, an in vivo experiment that was performed on mice showed a significant reduction in tumor volume without observing side effects [90].

Data on the use of kaempferol in vivo are still scarce, so it is imperative to continue its research to better understand its anticancer potential.

### 3.2. Flavonoids

Flavonoids represent a broad group of bioactive compounds from vegetables and plants. Although they have been catalogued as a subtype of polyphenols, as they are made up of a great variety of compounds, they are studied separately. The chemical structure of these substances is made up of a carbon skeleton with two aromatic rings joined by three carbons, with different modifications depending on the compound [43]. The subgroups that make up this family are chalcones, flavanols, flavones, flavanones, flavanols, isoflavones, and anthocyanins. Plants synthesize these extracts to provide color and aroma, for their protective properties against radiation or microbial infections, and their high detoxifying power [66]. There are numerous benefits of these compounds against various diseases, acting as antioxidants, anti-inflammatory, antibacterial, or antiviral agents, improving cognitive functions or preventing the onset of cancer and cardiovascular diseases [91]. Quercetin and EGCG (epigallocatechin gallate) are some of the most representative molecules of this group of compounds (Figure 2B).

#### 3.2.1. Quercetin

Quercetin is the most representative bioactive compound of the flavanols group, and the one with the greatest presence in foods consumed daily. It can be found in onions, apples, grapes, broccoli, or tea [66]. This compound has been shown to be an excellent antioxidant and anti-inflammatory in vitro, also presenting an antitumor and antimicrobial effect [92]. Numerous in vivo and in vitro studies have analyzed the mechanisms of action by which quercetin exerts its antitumor effect. It mainly acts by regulating the cell cycle, inhibiting cell proliferation and growth through the modulation of different molecular pathways such as PI3K/AKT/mTOR and MAPK/ERK1/2. The cytotoxic effect of this compound has been shown in CRC lines HCT-15 and RKO at doses up to 300 μM [93] and with $IC_{50}$ of 50, 100, and 50 μM in CRC lines CT26, MC38, and HT29 after 24 h of treatment, respectively [94]. The combination of quercetin with other bioactive compounds, such as curcumin, has also been shown to enhance the antiproliferative effect in different types of cancer by modulating the Wnt/β-catenin signaling pathway as observed in in vitro studies [95]. This compound also induces cell death through autophagy and apoptosis of tumor cells by increasing the expression of pro-apoptotic proteins and reducing the expression of anti-apoptotic proteins. In addition, it possesses anti-angiogenic and anti-metastatic activity, inhibiting VEGF protein expression and the EMT process increasing E-cadherin and decreasing mesenchymal markers such as N-cadherin, vimentin, and Snail. Lastly, in CRC quercetin inhibits tumor invasion and migration by regulating the expression of matrix metalloproteinases (MMPs) [92]. In in vivo studies, it is involved in reducing tumor size, reducing the number of precancerous lesions, suppressing metastasis, and reducing resistance to chemotherapy drugs [96].

This compound has also been shown to synergize with doxorubicin. Thus, a study that was carried out in the SW620 cell line observed that quercetin improves the cytotoxic activity of doxorubicin acting at the p-GP level [24]. On the other hand, encapsulation of the compound and its use together with doxorubicin increases cell growth inhibition in the CT26 cell line, reducing cardiac toxicity in murine models [97].

Although quercetin has not been generally encased in formulations, Wen et al. encapsulated this compound in a film containing chitosan nanoparticles and showed it to be an effective delivery system in CRC. It produced an effective cytotoxic effect on the Caco-2 line, exerting its effect through cell cycle arrest in G0/G1 phase and inducing apoptosis [98].

#### 3.2.2. Epigallocatechin Gallate

Epigallocatechin gallate (EGCG) belongs to the flavanol group and is the most studied compound of this group in CRC. It is found mainly in green tea but is also found in other foods such as pistachios, strawberries, kiwis, hazelnuts, blackberries, and cherries. This compound is characterized by its antitumoral properties, acting as a chemopreventive agent through the inhibition of carcinogenesis in numerous types of cancer. The mechanisms that are used by this catechin to carry out its antitumor effect are based on the regulation of various signaling pathways that are involved in proliferation, apoptosis, angiogenesis, and metastasis. Among them, EGCG inhibits colonic tumor cell proliferation and migration inducing apoptosis through the activation of caspase-3 and PARP, in addition to produce the downregulation of STAT3. This compound was tested on CRC lines SW480, SW620, and LS411N and $IC_{50}$ values of 74.6, 99.4, and 112.1 µg/mL were obtained after 24 h of treatment, respectively [99,100].

Its chemo-sensitizing activity has been studied in CRC cells that are resistant to chemotherapeutics. The combination of EGCG with 5-FU increases the efficacy of the latter, as well as its cytotoxic action, acting on tumor target cells. This effect has been observed in HCT116 and SW480 cell lines [101,102]. One of the mechanisms that is used by EGCG to enhance sensitivity to 5-FU is the inhibition of the GRP78/NF-κB/miR-155-5p/MDR1 pathway, having been demonstrated in in vitro and in vivo studies [103]. Furthermore, in vivo experiments demonstrated that administration of 30 mg/kg EGCG for two weeks decreased the number of hepatic metastatic lesions, reduced tumor growth, and increased apoptosis in tissues. In addition, less vascularization was found in treated tumors versus controls [104].

EGCG also has synergistic effects in combination with irinotecan in HCT116 cell lines. It has been observed that this drug produces S- and G2-phase arrest, inducing genotoxicity, an effect that was not observed in cells that were treated with EGCG alone [18]. Cisplatin and oxaliplatin are two chemotherapeutics that are used in the treatment of CRC. The combination of EGCG with these two agents in DLD-1 and HT-29 cell lines has shown an increased cytotoxic effect, causing cell proliferation inhibition and inducing autophagy [105]. These studies suggest that the combination of EGCG with different chemotherapeutics in CRC produce a synergism that increases antitumor activity.

To improve the bioavailability of this compound, Wang et al. synthesized gelatin and chitosan nanoparticles encapsulating 5-FU and ECGC, the latter compound inhibited tumor growth through its anti-angiogenic action and its ability to induce apoptosis. Encapsulation in this formulation allowed both compounds to increase blood circulation time in in vivo experiments, making them effective formulations against CRC [106].

A clinical trial was carried out with green tea extract, whose main bioactive compound was EGCG, trying to show whether the administration of 150 mg twice a day was able to reduce the risk of CRC, with no significant differences between the treatment group and the placebo [107]. Moreover, the chemo-sensitizing effect of EGCG is a breakthrough in overcoming tumor resistance. However, more evidence is needed to translate these results to clinical assays.

#### 3.2.3. Other Flavonoids of Interest

In addition to the flavonoids that were analyzed above, which are the most studied as phytochemicals in CRC, there are other compounds that are derived from citrus fruits that show interest as active compounds against cancer. Among them, narangenin is a compound that is extracted from thyme (*Thymus vulgaris* L.), a shrub that grows in regions all over the world, especially in Mediterranean regions. Efficacy of this compound has been shown in CRC lines such as SW1116 and SW837, showing $IC_{50}$ at 24 h of 1 and 1.55 mM, respectively, while in the non-tumor line CRL1554 it did not reach an $IC_{50}$ dose at the 4 mM dose [108]. Another study showed that naringenin exerted its anti-tumor effect by deregulating cyclin D1 expression, leading to cell cycle arrest in HCT116 and SW480 lines [109]. This compound also showed an in vivo chemopreventive effect against

the induction of precancerous lesions, reducing processes such as lipid peroxidation, ROS formation, and the activation of proinflammatory pathways in Wistar rat models [110]. Despite its interesting effects, this compound has low water solubility, cell permeability, and bioavailability. Therefore, Shabad et al. developed nanogels that were capable of increasing its dissolution capacity, obtaining a higher toxicity in in vitro models [111]. Another studied flavonoid is aromadendrin, derived from mandarin molasses. A study in the LoVo cell line and a DOX-resistant derivative (LoVo/Dx) showed that its effect is very limited in this type of cancer, producing a low cytotoxic effect [112]. Finally, another citrus-derived compound (tangeretin, present in the peel of several citrus fruits) showed synergistic activity with the chemotherapeutic drug 5-FU through early induction of oxidative stress and apoptosis in the HCT116 cell line. Bai et al. demonstrated that this synergistic effect occurs due to the natural compound that is able to decrease the expression of miR-21, whose expression increases after treatment with 5-FU, rescuing PTEN expression and inducing cellular autophagy [113].

### *3.3. Terpenes*

Terpenes (Figure 2C) are another large group of bioactive compounds, many of which have CRC effects. These substances are part of the leaves, fruits, flowers, or roots of many plants, giving them a characteristic odor. When these compounds are oxidized, they become terpenoids, some of them being limonene, vitamin A, or β-carotene [42]. The study of these compounds as resistance modulators in CRC is not so recent or extensive, however, some evidence of the potential antitumor effect has been found in some of them.

#### 3.3.1. Geraniol

Geraniol is a monoterpene that is found mainly in essential oils of aromatic plants and used in perfumes. It has been used as an active ingredient in many drugs since it exhibits analgesic and anti-inflammatory activity [114]. This compound presents preventive and therapeutic activity in many types of cancer, carrying out its effects by acting on the regulation of different signaling pathways such as PI3K/AKT/mTOR, MAPK/ERK1/2, or NF-κB, and modulating the expression of different molecules such as cyclins, CDKs, interleukins, and different growth factors [115].

In the Caco-2 cell line, it has been observed that this compound triggers the inhibition of cell proliferation by inducing an S-phase cycle arrest ($IC_{30}$ = 200 μM after 7 days). In addition, it was shown that it is able to induce apoptosis in in vivo models, showing a decrease in the expression of the anti-apoptotic protein BCL-2 in tumor tissue after treating mice with a dose of 250 mg/kg for 4 weeks. Its oral administration in in vivo models prevents the development of CRC, reducing the number and size of precursor lesions [116].

Furthermore, its chemosensitizing effect was observed in Caco-2 and SW620 cell lines, and in murine models originated with 5-FU-resistant TC-118 tumor cells, having shown that co-treatment sensitizes tumor cells to 5-FU [117,118]. However, these studies are scarce, which requires further analysis to understand the effects of geraniol on resistance phenomena.

#### 3.3.2. Ginsenosides

Ginsenosides are a subgroup of bioactive chemical compounds that are found in the root of ginseng, an Asian plant. These substances are used in teas, in the preparation of creams, or capsules. Of all the compounds that make up this subgroup, panaxadiol is one of the most notable for its antitumor action in many types of cancer. In the CRC cell line HCT116, this terpene inhibits cell proliferation ($IC_{50}$ lower than 10 μM after 72 h of treatment) by suppressing PD-L1 expression; modulating different cellular pathways such as mTOR, MAPK/ERK, or JAK-STAT; and molecules such as HIF-1α. It has also been observed to decrease VEGF levels to exert antiangiogenic action. This has also been shown in studies that were performed on murine models treating mice at a dose of 30 mg/kg every 2 days for 3 weeks [119,120].

Another of the best known ginsenosides is Rg3. A study demonstrated that Rg3 was able to inhibit cell proliferation ($IC_{50}$ between 100–200 μM after 48 h of treatment) and promote apoptosis in the HT-29 tumor line, decreasing its pluripotency and decreasing its angiogenesis through deregulation of the AMPK molecular pathway [121]. Analysis of its in vivo activity showed that its treatment with 25 mg/kg of Rg3 for 12 consecutive days reduced tumor vascularization and increased the toxicity that was produced by the chemotherapeutics 5-FU and oxaliplatin, allowing evasion of chemoresistance to both drugs [122].

The study of panaxadiol in the HCT116 cell line resistant to 5-FU has demonstrated the ability to inhibit proliferation producing synergy in combination with this chemotherapeutic compound, stopping the cell cycle and inducing apoptosis. Its sensitizing effect has also been analyzed in mouse models combining 30 mg/kg of 5-FU and 15/30 mg/kg of panaxadiol, confirming the results that were obtained in vitro, where a significant reduction in tumor size has been observed [123]. Another in vitro study demonstrated that panaxadiol was synergistic with irinotecan in HCT116 and SW480 tumor lines [124]. On the other hand, Rg3 showed synergy with 5-FU both in vitro and in vivo in SW620 and LOVO lines, having shown suppression of proliferation and tumor development and metastasis generation through PI3K/Akt activation [125].

Among all the terpenes that were studied, Rg3 has been the most encapsulated in formulations to increase its biological availability. Qiu et al. synthesized nanoformulations of Rg3 encapsulated in pH-sensitive poly (ethylene glycol) that increased the blood circulation of the compound showing rapid release and enhanced cytotoxicity against free drug in SW480, SW620, and CL40 tumor cells. Meanwhile, these formulations did not possess toxicity in the non-tumor line CCD-18Co at the concentrations that were tested. Meanwhile, in vivo experiments showed a greater reduction of tumor volume versus the free compound, increasing apoptosis in the tumor sinus [126]. Finally, Sun et al. synthesized folato-targeted polyethylene glycol nanoparticles based on cyclodextrins that co-encapsulated Rg3 and quercetin. The microtumor environment modulating effect that was demonstrated by Rg3 together with the oxidative stress inducing ability of quercetin exhibited a high cytotoxic effect on CRC lines CT26 and HCT116. The in vitro effect was reflected in in vivo experiments, where increased survival of mice was shown in combination with an anti-PD-L1 drug [127].

Rg3 was tested in clinical trials as a possible hepatocellular carcinoma treatment (NCT02724358 and NCT01717066), although it was not tested for CRC therapy as there is no sufficient knowledge of this compound in this type of carcinoma.

## 4. Discussion

Chemotherapeutic treatment of colon cancer has been compromised mainly by the appearance of resistance, which reduces therapeutic efficacy and leads to a lower cure rate and worse prognosis. These can be produced by the existence of previous mutations in genes that are involved in resistance, by the activation of cellular pathways that are involved in cellular detoxification, and the existence of transmembrane transporters that expel the drugs to the exterior (such as p-glycoprotein) [128]. In addition to this protein, other members of the transmembrane protein family such as MRP1 and BCRP are also overexpressed in CRC, and a relationship has been observed between their expression and resistance phenomena against drugs that are frequently used in this type of tumor, such as 5-FU and doxorubicin [30,31]. It has long been shown that plant compounds can be used as a therapy for different types of cancer. Thus, a plant-derived compound such as taxol has been used for years as a chemotherapeutic agent and is currently used as a therapy in non-small cell lung cancer (NSCLC), breast, pancreatic, and cervical cancer [129]. These types of compounds can exert their actions at the molecular level through processes such as the regulation of oxidative stress or epigenetic modification in cells [130] (Figure 3).

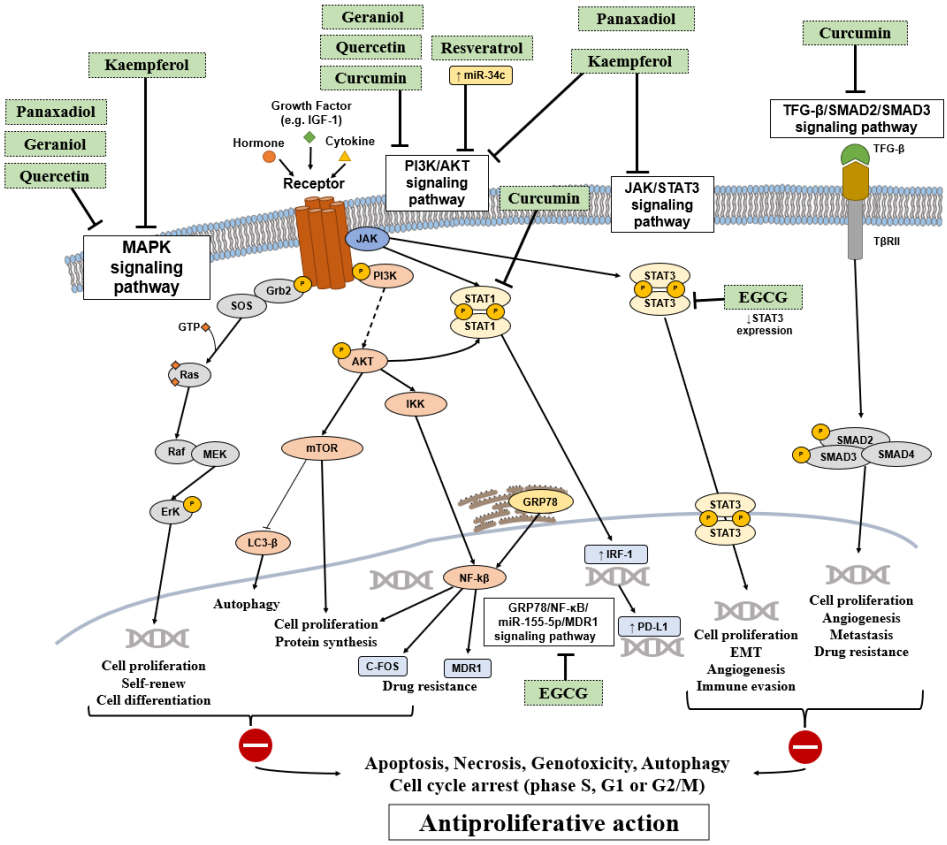


**Figure 3.** Main signaling pathways that were altered after treatment with several of the natural compounds that were analyzed in this review. Most pathways are linked to multidrug resistance processes and their inhibition leads to cell death processes that are induced by apoptosis, necrosis, autophagy, or mediated by genotoxicity.

It has been shown that the most studied compounds of plant origin in CRC are polyphenols, specifically resveratrol and curcumin (Table 1). Resveratrol belongs to the stilbenes group and has been shown to possess high antioxidant and antitumor activity, causing cell death through the induction of apoptosis and autophagy. Similar to resveratrol, the other polyphenols that were studied induce death through these pathways [48,67,73,83].

Polyphenols have been classified as chemopreventives and chemotherapeutics, although their sensitizing effect has also been observed in in vitro and in vivo models. These compounds can modulate drug resistance by increasing drug internalization into the cell, decreasing enzymes that are responsible for drug degradation (such as glutathione-S-transferases and cytochromes) and reducing the expression of transmembrane detoxifying proteins in the cell. In addition, they can induce apoptosis, oxidative stress damage, and inhibit metastasis-triggering processes such as EMT [131]. The alteration of all these resistance mechanisms implies that these polyphenols have been shown to be effective in combination with traditional drugs such as 5-FU or oxaliplatin [56,73,75,87–89]. This effect is also observed in foods with high polyphenol contents such as the strawberry tree honey, that chemosensitizes the drug 5-FU in colon cancer lines such as HCT116 and LoVo [132]. In addition to this, it has been observed that curcumin and resveratrol had the capacity to inhibit tumor proliferation in in vivo models and prevented the formation of tumor precursor lesions, with an increase in apoptosis of induced tumor tissues [47,53,76]. Pharmacokinetic studies have been carried out in humans, where low bioavailability has been observed [47,52,54,71,75]. Given the low bioavailability of these compounds, the use of nanotechnology for their encapsulation could help stabilize the compound and prevent its degradation in blood. In addition, the use of nanotechnology allows specific targeting of tumor cells through their functionalization with antibodies or peptides [14,15].

**Table 1.** Summary of the in vitro and in vivo effects that were exerted by the bioactive natural compounds that were analyzed.

| Fam. | Comp. | Sinergy | In Vitro | In Vivo | Clinical Trials | Refs. |
|---|---|---|---|---|---|---|
| Polyphenols | Resveratrol | 5-FU, OXA | Apoptosis and decreased AC (VEGF inhibition). $IC_{50}$ of 10 mg/mL in HT-29 (72 h). | 150 or 300 ppm doses prevented cancerous lesions and induced apoptosis via BAX | Safe intake up to a 1g/day dose. Limited BAV (2–29%). | [20,47,49,50,52,54,55,57,58] |
| | Curcumin | 5-FU, OXA DOX, 5-FU, OXA | G1-CCA and apoptosis at 20 µM. Reduced cell migration and invasion. | 300 mg/kg dose prevented precancerous lesions and decreased tumor size. | Low absorption and BAV. Increased tumor apoptosis. | [69–76,81] |
| | Kaempferol | DOX, 5-FU, OXA | G1 and G2/M-CCA and apoptosis induction. Decreased AC at 0.1 µM in MDA cell line. | Decreased AC and MC. | Low toxicity and BAV (2%). | [82–90] |
| Flavonoids | Quercetin | DOX | CCA, apoptosis and decreased AC and MC. CYT in up to 300 µM doses in HCT-15, RKO, CT26, MC38, and HT29 cells | 10 and 50 mg/kg reduced precancerous lesions and tumor size. Decreased MC and CHR. | Not performed. | [24,92–97] |
| | EGCG | 5-FU, IRI, CPT, OXA | S and G2-CCA, apoptosis, CYT $IC_{50}$ between 74.6 and 112.1 in CRC cell lines SW480, SW620, and LS411N. Decreased MC. | 30 mg/kg for 2 weeks decreased MC, tumor growth and induced apoptosis | 150 mg twice a day of green tea extract did not show any effect in CRC development risk | [18,99–107] |
| Terpenes | Geraniol | 5-FU | S-CCA. CYT $IC_{30}$ of 200 µM for 7 days treatment in Caco-2 cell line. | 250 mg/kg for 4 weeks prevented CRC precancerous lesions. Reduced tumor growth and apoptosis induction. | Not performed. | [116–118] |
| | Panaxadiol | 5-FU, IRI | CYT $IC_{50}$ lower than 10 µM in HCT116 cell line (72 h). Decreased AC (VEGF inhibition) | 30 mg/kg for 3 weeks reduced tumor growth and AC. | Not performed. | [119,123–125] |
| | Rg3 | 5-FU | CYT $IC_{50}$ 100–200 µM in HT-29 cell line (48 h). Induction of apoptosis and AC via AMPK dysregulation. | 25 mg/kg for 12 days reduced tumor vascularization and decreased CHR to 5-FU and OXA. | Not performed. | [121,122,125] |

AC (antiangiogenic capacity); BAV (bioavailability); CCA (cell cycle arrest), Comp. (Compound); CPT (cisplatin); CHR (chemoresistance); CRC (colorectal cancer); CYT (cytotoxicity); DOX (doxorubicin); EGCG (epigallocatechin gallate); EMT (epithelial-mesenchymal transition); Fam. (Family); 5-FU (5-fluorouracil); IRI (irinotecan); MC (metastatic capacity); OXA (oxaliplatin); Refs. (references); VEGF (vascular endothelial growth factor).

On the other hand, it has been observed that flavonoid compounds also have anti-carcinogenic potential. Among them, the most investigated in CRC have been quercetin and EGCG. These compounds exerted their cytotoxic effect by producing cycle arrest, inhibiting key pathways in tumor development such as PI3K/AKT/mTOR and the MAPK pathway, and inhibiting processes that are linked to tumor progression such as cell migra-

tion [93,99,100]. In addition, they showed a great chemosensitizing capacity in combination with traditional drugs such as doxorubicin, irinotecan, 5-FU, cisplatin, and oxaliplatin under in vitro and in vivo conditions. A study that was conducted by Hassanein et al. [133] showed the chemopreventive effect of EGCG administration together with sulindac, a non-steroidal anti-inflammatory drug, showing that it was able to decrease the production of neoplastic lesions in in vivo models of CRC. As polyphenols, these compounds have a low bioavailability, which is a limitation for their use in humans [18,24,87–89,97,101–103,105]. In this context, the synthesis of gold NPs encapsulating EGCG has been shown to be an effective therapy against tumor cells while it has been shown that the co-encapsulation of EGCG and 5-FU in NPs allows an increase in the effect of both compounds separately, producing an anti-angiogenic and pro-apoptotic effect [106,134]. The encapsulation of this compound in nanoformulations would increase the half-life of the compound in serum, increasing its bioavailability and increasing its antitumor effect [135].

The bibliographic analysis showed that terpenes are the least studied bioactive compounds as chemosensitizers in this type of cancer. Among this family, geraniol and ginsenosides have been the most studied compounds with sensitizing properties in CRC [114,117,118]. Due to the small number of studies that have been conducted on these compounds, it is complicated for these results to be transferred to clinical studies at present. These compounds exert their antiproliferative activity by producing cell cycle arrest and inducing apoptotic pathways. In addition, it has been observed that they suppress pathways essential for tumor development such as PI3K/AKT/mTOR [115,119,120]. Results in in vivo models showed that geraniol sensitized tumors that were induced in mice from a 5-FU-resistant CRC line to the drug, while the major ginsenoside (Rg3) showed synergy with 5-FU in tumors that were generated from the SW620 and LoVo cell lines. However, it has been shown that these compounds have clear preventive and therapeutic properties in CRC [115,116,123].

Therefore, after reviewing the existing literature, it is necessary to continue investigating the antitumor properties and possible chemosensitizing actions of these compounds, trying to transfer these results to future clinical trials in humans. In addition, it is important to study their bioavailability, trying to limit their elimination in blood using these natural compounds encapsulated in nanoformulations.

## 5. Conclusions

The bioactive compounds of plant origin that were described in this review have been shown to have therapeutic and chemosensitizing action in vitro and in vivo. However, their low bioavailability in the human body presents a serious limitation for their application in therapy. Future larger studies including clinical trials and the development of future effective nanoformulations to increase their bioavailability will be necessary to determine its real utility in improving the treatment of CRC.

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