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## **Sensitization of tumor cells to chemotherapy by natural products: a systematic review of preclinical data and molecular mechanisms**

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## **ABSTRACT**

**Purpose:** Tumor cells are spontaneously or adaptively resistant to chemotherapeutic drugs, eventually leading to the selection of multiresistant cells responsible for tumor growth and metastasis. Chemosensitization of tumor cells to conventional drugs using non-toxic natural products is a recent and innovative strategy aiming to increase the cytotoxic efficiency of anticancer drugs, limit their toxic side effects and delay the appearance of acquired chemoresistance. This systematic review summarizes data obtained from preclinical studies reporting the use of natural products to sensitize tumor cells to chemotherapeutic agents. It also details the cellular and molecular mechanisms involved in chemosensitization.

**Design:** Search terms were combined and used to retrieve English language reports in PubMed, Science Direct and Scopus databases, published until October 2017. All articles were carefully analyzed and data extraction was conducted through standardized forms. Methodological quality assessment of *in vivo* studies was also performed.

**Results:** From a total of 669 articles surveyed, 104 met the inclusion criteria established. The main studied compounds as chemosensitizers were phenolic derivatives (26.9%) and flavonoids (17.3%). Most reports were authored by researchers from China (33.7%) and USA (26.9%). A large number of articles were published from 2011 to 2015 (50.0%), suggesting that the use of natural products as chemosensitizers is a recent issue. *In vivo* studies were conducted mainly using xenograft models, which were considered of moderate methodological quality.

**Conclusion:** Several natural products, belonging to diverse chemical families, are potent chemosensitizers in tumor cells enhancing the cytotoxicity of conventional drugs. These molecules usually have a pleiotropic effect on different molecular targets, acting on several cellular and molecular processes with low selectivity. All studied molecules were obtained from terrestrial plants and major developments should arise from future studies, considering the chemodiversity of molecules purified from other terrestrial taxa and marine organisms.

**Keywords:** cancer; chemotherapy; chemosensitization; drug resistance; natural products

## 1. Introduction

Cancer is one of the most impactful diseases of the 21<sup>st</sup> century, affecting populations of diverse social, ethnic and economic characteristics. Although the genetic, epigenetic and pathophysiological mechanisms of cancer have been well described in recent years, cancer still represents the second cause of death in developed countries after heart disease [1,2].

To ensure their survival and proliferation, cancer cells acquire differentiated abilities compared to normal cells. In the development of malignant tumors, they may present constitutively active proto-oncogenes, which predisposes to carcinogenesis, maintaining proliferative signaling pathways active [3]. In addition, expression of tumor suppressor genes is usually decreased and the cell acquires sufficient autonomy to continue multiplying without the need for growth factors. Tumor cells also have replicative immortality mechanisms [4] and greater resistance to cell death mediated by the regulation of anti and pro-apoptotic proteins [5]. For tumor maintenance and progression, they stimulate the production of angiogenic factors and modulate cellular metabolism in order to obtain more nutrients [3,6].

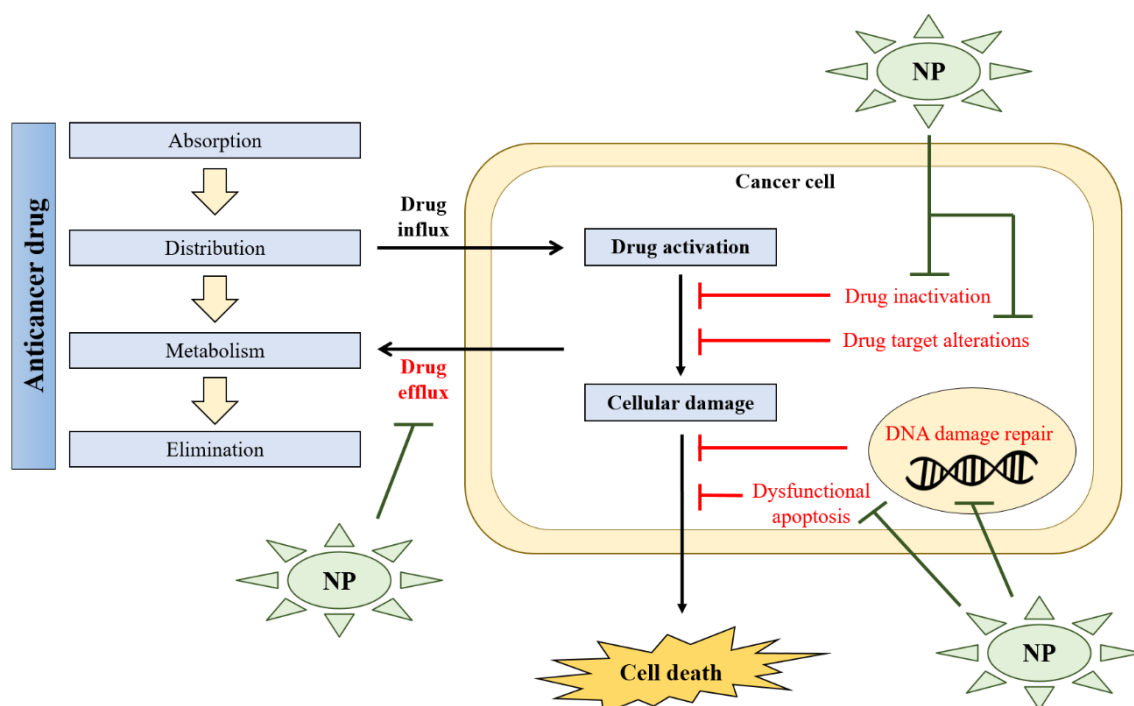
In this sense, chemotherapy is one of the main alternatives for cancer treatment, using molecules capable of inhibiting proliferative signaling pathways, replicative immortality mechanisms and angiogenesis, besides inducing apoptosis of tumor cells [7-10]. However, the efficacy of conventional chemotherapeutics has been limited by drug resistance mechanisms [11]. Several studies have recognized that tumors exhibit a high degree of molecular and genetic heterogeneity, making them adapted to the usual cytotoxic agents. Unsuccessful treatments have been attributed to increased rates of drug efflux, alterations in drug metabolism (drug inhibition and degradation), cell death inhibition, epigenetic factor and mutations of drug targets (Figure 1). These mechanisms can act independently or in combination and through numerous signaling pathways [11-13].

A wide variety of natural compounds has been reported for cancer therapy [14,15]. Natural products are an inexhaustible source of molecules with unique structural models and innovative mechanisms of action. In fact, natural compounds can be used in a versatile manner, especially in cancer management: a) as chemotherapeutic agents [16,17]; b) in cancer prevention (chemopreventive agents) [18,19]; c) or

improving the effectiveness of conventional chemotherapy (chemosensitizer agents) [20].

Most of the identified chemosensitizer natural compounds are phytochemicals, which are classified as phenolic derivatives, flavonoids, alkaloids, carotenoids, terpenoids, quinones, saponins and steroids depending on their molecular structure [20,21]. In general, these molecules act by increasing the residence time of chemotherapeutics in tumor cells, inducing cell death by up-regulation of pro-apoptotic targets, promoting DNA damage or regulating the expression of altered and unaltered drug targets (Figure 1). When associated, these mechanisms enhance the cytotoxic effect of anticancer drugs, promoting a synergistic effect even in cells with acquired resistance [22-24].

The present systematic review was designed to summarize and analyze reports involving the use of natural products as chemosensitizers. Our focus was on preclinical studies (*in vitro* and *in vivo* approaches) in order to demonstrate to readers how these experimental models can contribute to the achievement of alternative strategies for cancer therapy.



**Figure 1.** General drug resistance mechanisms implicated in cancer therapy and possibilities of intervention of natural products (NP) as chemosensitizer agents.

## 2. Materials and methods

## 2.1 Search strategy

A systematic review was conducted through a literature search performed in October 2017 and included all reports published to date. This literature search was performed on specialized databases (PubMed, Science Direct and Scopus) using different combinations of the following keywords: chemosensitization, cancer, tumor, natural products, phytotherapy, medicinal plants, marine products and marine drugs. We did not contact investigators and we did not attempt to identify unpublished data. This systematic review was performed in accordance with the criteria described on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [25].

## 2.2 Study selection

Manuscript selection was based on the inclusion criteria: pre-clinical (*in vitro* and *in vivo*) studies involving the use of natural compounds/secondary metabolites as chemosensitizer agents of tumor cells to chemotherapeutic drugs, as well as pre-clinical (*in vitro* and *in vivo*) studies involving associations/combinatorial treatment between natural compounds/secondary metabolites and conventional chemotherapeutic drugs for antitumor therapy; only articles published in English and containing keywords in the title or abstract were selected. Other review articles, meta-analysis, abstracts, conferences, editorials/letters, case reports, conference proceedings, manuscripts without full text available or articles that did not meet the inclusion criteria were excluded from this systematic review. Studies involving extracts, fractions, synthetic or semisynthetic derivatives were also excluded.

For the selection of the manuscripts, two independent investigators (RGOJ and CAAF) first selected the articles according to the title, then to the abstract and finally through an analysis of the full-text publication. In cases of non-consensus, a third independent review was consulted (JRGSA). The selected articles were carefully reviewed with the purpose of identifying and excluding the reports that did not fit the criteria described above. Additional papers were included in this review after the analysis of all references from the selected articles.

### 2.3 Data extraction

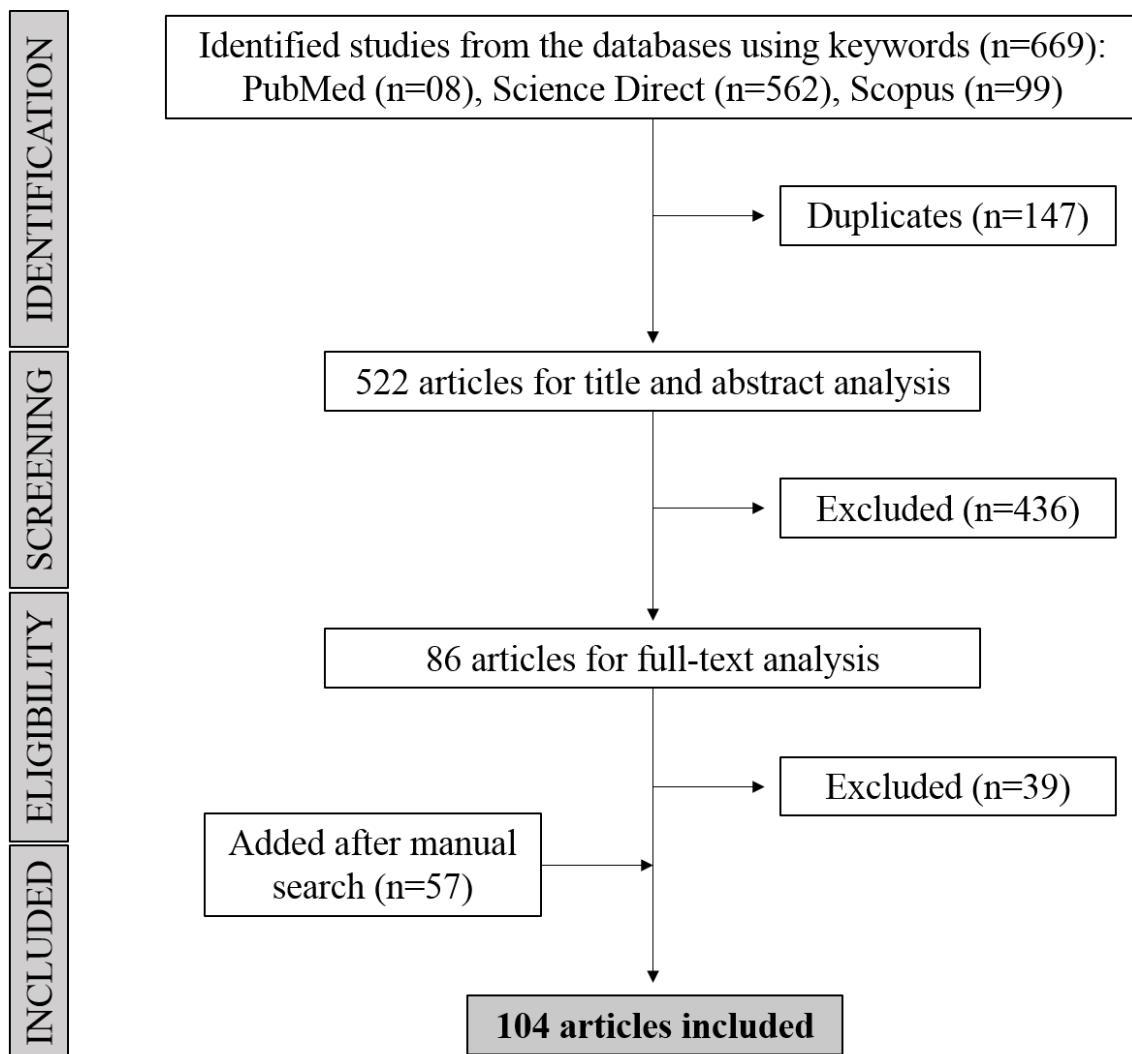
Data were collected and examined by the authors using standardized forms. The information from the selected manuscripts on studied natural compounds, experimental models, associated chemotherapeutic agent, doses or concentrations, route of administration, cell lines, biochemical assays, histological assessments and molecular mechanisms studied were extracted and assessed.

### 2.4 Methodological quality assessment

The risk of bias and quality of the *in vivo* preclinical investigations were assessed using a checklist adapted from Hooijmans et al. [26] and Siqueira-Lima et al. [27]. This analysis allowed evaluating the methodological quality of the selected studies regarding the randomization of the treatment allocation, blinded drug administration, blinded outcome assessment and outcome measurements. Studies that reported randomization of animals, blinding and outcome measurements were considered of higher methodological quality.

## 3. Results

The primary search identified 669 reports (08 from PubMed, 562 from Science Direct and 99 from Scopus). However, 147 manuscripts were indexed in two or more databases and were considered only once, resulting in 552 original articles. After an initial screening of titles and abstract, 436 articles were excluded since they did not meet the inclusion criteria or presented extremely different themes from the proposal of this systematic review. Finally, 86 articles were fully analyzed and among these 39 were excluded. A detailed analysis of the list of references from all selected articles was performed, leading to the addition of 57 papers pertinent to this review and that met all inclusion criteria established after title, abstract and full text analysis. In total, 104 articles were included for data extraction. A flowchart illustrating the progressive study selection and numbers at each stage is shown in Figure 2.



**Figure 2.** Flowchart detailing literature search according to PRISMA statement [25].

The articles selected for this review were categorically analyzed in relation to the country where the study was conducted, year of publication, natural compounds evaluated as chemosensitizers, cell lines and corresponding cancers. Table 1 summarizes the main informations contained in the selected *in vitro* and *in vivo* reports. In general, the studies were conducted by research groups located in about 20 different countries. However, most of the investigations were authored by researchers from China (35 reports, 33.7%) and USA (28 reports, 26.9%). Regarding the annual evolution of the publications, a large number of articles were published from 2011 to 2015 (52 reports, 50.0%). Only in the last two years, 18 articles (17.3%) have been published, suggesting that the use of natural products as chemosensitizers is a recent issue that has attracted researchers' attention.





**Table 1.** General characteristics of included studies (*in vitro* and *in vivo* reports).

<b>Authors, year, country</b>	<b>Model</b>	<b>Chemosensitizer</b>	<b>Combined conventional drug</b>	<b>Tumor cell line</b>	<b>Cancer</b>
<i>Alkaloids</i>					
Song et al. (2007) [28], China	<i>In vitro</i> and <i>in vivo</i>	Oxymatrine	NM-3	SGC-7901, MKN-45 and MKN-74	Gastric cancer
Banerjee et al. (2009) [29], USA	<i>In vitro</i> and <i>in vivo</i>	3,3-diindolylmethane	CIP, OXP and GCT	PANC-1, Colo-357 and PANC-28	Pancreatic cancer
Sung et al. (2010) [30], USA	<i>In vitro</i>	Noscapine	TNF, TLD, PTX and BTZ	KBM-5 and U266	Leukemia
Chougule et al. (2011) [31], USA	<i>In vitro</i> and <i>in vivo</i>	Noscapine	GCT	A549 and H460	Lung cancer
Tong et al. (2012a) [32], China	<i>In vitro</i>	Berberine	DOX	A549; HeLa; HepG2	Lung cancer; cervical cancer; hepatocellular carcinoma
Qi et al. (2013) [33], USA	<i>In vitro</i> and <i>in vivo</i>	Noscapine	TMZ, BCE and CIP	U87MG	Glioblastoma
Wang et al. (2013a) [34], China	<i>In vitro</i> and <i>in vivo</i>	Sinomenine	5FU	Eca-109	Esophageal carcinoma
Guo et al. (2014) [35], China	<i>In vitro</i>	Berberine	RPM	SMMC7721 and HepG2	Hepatocellular carcinoma

Liu et al. (2015a) [36], China	<i>In vitro</i> and <i>in vivo</i>	Oxymatrine	5FU	Hep-G2 and SMMC-7721	Hepatocellular carcinoma
Doddapaneni et al. (2016) [37], USA	<i>In vitro</i>	Noscapine	DTX	MDA-MB231	Breast cancer
Zhao et al. (2016) [38], China	<i>In vitro</i>	Berberine	CIP	MCF-7	Breast cancer

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#### *Carotenoids*

Rajendran et al. (2010) [39], Singapore	<i>In vitro</i>	$\gamma$ -Tocotrienol	DOX and PTX	HepG2, C3A, SNU-387, and PLC/PRF5	Hepatocellular carcinoma
Liu et al. (2015b) [40], China	<i>In vitro</i> and <i>in vivo</i>	$\alpha$ -carotene	PTX	LLC**	Lung cancer
Zhang et al. (2016) [41], China	<i>In vitro</i> and <i>in vivo</i>	$\beta$ -carotene	5FU	EC1 and Eca109	Esophageal carcinoma

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#### *Coumarins*

Kim et al. (2014) [42], South Korea	<i>In vitro</i>	Bergamottin	BTZ and TLD	U266	Multiple myeloma
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#### *Flavonoids*

Stammler and Volm (1997) [43], Germany	<i>In vitro</i>	Epigallocatechin-3-gallate	DOX	SSW620-dox	Colon cancer
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Dhanalakshmi et al. (2003) [44], USA	<i>In vitro</i>	Silibinin	CIP and CAP	DU145	Prostate cancer
Chisholm et al. (2004) [45], New Zealand	<i>In vitro</i>	Epigallocatechin-3-gallate	TOF	MDA-MB-231	Breast cancer
Peng et al. (2007) [46], USA	<i>In vitro</i>	Deguelin	DOX and DTX	SKBR-3, MCF-7 and MCF 10A	Breast cancer
Siddiqui et al. (2008) [47], USA	<i>In vitro</i>	Epigallocatechin-3-gallate	TRAIL	LNCaP	Prostate cancer
Shervington et al. (2009) [48], UK	<i>In vitro</i>	Epigallocatechin-3-gallate	CIP and TOF	1321N1; U87-MG	Astrocytoma; glioblastoma
Zhang et al. (2009) [49], China	<i>In vitro</i> and <i>in vivo</i>	Naringenin	DOX	A549; HepG2; MCF-7 and MCF-7/DOX	Lung cancer; hepatocellular carcinoma; breast cancer
Jin et al. (2011) [50], South Korea	<i>In vitro</i>	Naringenin	TRAIL	A549	Lung cancer
Stearns and Wang (2011) [51], USA	<i>In vitro</i> and <i>in vivo</i>	Epigallocatechin-3-gallate	TXN	PC-3ML	Prostate cancer
Hönicke et al. (2012) [52], Germany	<i>In vitro</i>	Epigallocatechin-3-gallate	IL-1Ra	U-2 OS	Osteosarcoma
Wu et al. (2012) [53], China	<i>In vivo</i>	Epigallocatechin-3-gallate	CCT	BGC-823	Gastric cancer

Kwak et al. (2013) [54], South Korea	<i>In vitro</i>	Epigallocatechin-3-gallate	VOR	HuCC-T1	Cholangiocarcinoma
Suzuki et al. (2014) [55], USA	<i>In vitro</i> and <i>in vivo</i>	Genistein	5FU	MIA PaCa-2	Pancreatic cancer
Wang et al. (2014a) [56], China	<i>In vitro</i> and <i>in vivo</i>	Myricetin	5FU	EC9706	Esophageal carcinoma
Abaza et al. (2015) [57], Kuwait	<i>In vitro</i>	Naringenin	CPT, 5FU, DOX, CIP, ELP, ETP, CAP and CPA	SW1116 and SW837; HTB26 and HTB132	Colon cancer; breast cancer
Wang et al. (2015) [58], USA	<i>In vitro</i>	Epigallocatechin-3-gallate + quercetin	DTX	LAPC-4-AI and PC-3	Prostate cancer
García-Vilas et al. (2016) [59], Spain	<i>In vitro</i>	Epigallocatechin-3-gallate	4MU	MDA-MB231	Breast cancer
Krajnovic et al. (2016) [60], Serbia	<i>In vitro</i> and <i>in vivo</i>	Isoxanthohumol	PTX	B16, A375 and B16F10	Melanoma

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*Naphthodianthrones*

Lin et al. (2016) [61], China	<i>In vitro</i>	Hypericin	OXA	HCT8 and HCT116	Colon cancer
Lin et al. (2017) [62], China	<i>In vitro</i>	Hypericin	OXF	HCT116 and HCT8	Colon cancer

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*Phenolic derivatives*

Anuchapreeda et al. (2002) [63], Thailand	<i>In vitro</i>	Curcumin	VBL	KB-V1	Cervical cancer
Hour et al. (2002) [64], China	<i>In vitro</i>	Curcumin	DOX, 5FU and PTX	PC-3 and DU145	Prostate cancer
Fulda and Debatin (2004) [65], Germany	<i>In vitro</i>	Resveratrol	DOX, VP16, ACD, PTX, MET, CYT, 5FU, CHM, MMS, TMD and NCD	SHEP; U373MG; PANC1; MCF7; LNCaP; Jurkat T-cell and Reh B-cell	Neuroblastoma; malignant glioma; pancreatic cancer; breast cancer; prostate cancer; leukemia
Wu et al. (2004) [66], China	<i>In vivo</i>	Resveratrol	5FU	H <sub>22</sub>	Hepatocellular carcinoma
Aggarwal et al. (2005) [67], USA	<i>In vitro</i> and <i>in vivo</i>	Curcumin	PTX	MDA-MB-435	Breast cancer
Bava et al. (2005) [68], India	<i>In vitro</i>	Curcumin	PTX	HeLa, SiHa, CaSki, and ME-180	Cervical cancer
Li et al. (2007) [69], USA	<i>In vitro</i> and <i>in vivo</i>	Curcumin	OXA	LoVo and Colo205	Colon cancer
Chen et al. (2009) [70], Taiwan	<i>In vitro</i>	Tannic acid	ATO	HL-60	Leukemia
Harikumar et al. (2009) [71], USA	<i>In vitro</i> and <i>in vivo</i>	Resveratrol	GCT	AsPC-1, MIA PaCa-2 and PANC1	Pancreatic cancer
Kunnumakkara et al.	<i>In vitro</i> and	Curcumin	CCT	HCT116, HT29 and	Colon cancer

(2009) [72], USA	<i>in vivo</i>			SW620	
Yu et al. (2009) [73], USA	<i>In vitro</i>	Curcumin	FOLFOX	HCT116 and HT29	Colon cancer
Hartojo et al. (2010) [74], USA	<i>In vitro</i>	Curcumin	5FU and CIP	Flo-1 and OE33	Esophageal adenocarcinoma
Bava et al. (2011) [75], India	<i>In vitro</i>	Curcumin	PTX	HeLa	Cervical cancer
Sreekanth et al. (2011) [76], India	<i>In vitro</i> and <i>in vivo</i>	Curcumin	PTX	3-MC*	Cervical cancer
Osman et al. (2012) [77], Saudi Arabia	<i>In vitro</i>	Resveratrol	DOX	MCF-7	Breast cancer
Saleh et al. (2012) [78], Egypt	<i>In vitro</i>	Curcumin	ETP	MCF-7; HeLa; HCT116; HepG2; U251	Breast cancer; cervical cancer; colon cancer; hepatocellular carcinoma; glioblastoma
Wang et al. (2012a) [79], China	<i>In vitro</i>	Curcumin	LAP	RS4;11, Reh and Jurkat	Acute lymphoblastic leukemia
Amiri et al. (2013) [80], Iran	<i>In vitro</i>	Resveratrol	ETP	HepG2; HCT116	Hepatocellular carcinoma; colon cancer
Díaz-Chávez et al. (2013) [81], Mexico	<i>In vitro</i>	Resveratrol	DOX	MCF-7	Breast cancer
Shakibaei et al.	<i>In vitro</i>	Curcumin	5FU	HCT116 and	Colon cancer

(2013) [82], Germany				HCT116+ch3	
Carlson et al. (2014) [83], USA	<i>In vitro</i>	Curcumin + resveratrol	DOX	SKOV-3	Ovarian cancer
Qian et al. (2014) [84], China	<i>In vitro</i>	Curcumin	ADM	HepG2	Hepatocellular carcinoma
Buhrmann et al. (2015) [85], Germany	<i>In vitro</i>	Resveratrol	5FU	HCT116, HCT116R, SW480 and SW480R	Colon cancer
Cote et al. (2015) [86], USA	<i>In vitro</i>	Resveratrol + quercetin	DOX	SKOV-3	Ovarian cancer
Shakibaei et al. (2015) [87], Germany	<i>In vitro</i>	Curcumin	5FU	HCT116 and HCT116R	Colon cancer
Abaza et al. (2016) [88], Kuwait	<i>In vitro</i>	Methylferulate	CPT, 5FU, DOX, OXP, PTX, VBL, VCR, ETP, ELP, AMS, HHG and APD	SW1116 and SW837	Colon cancer
Ooko et al. (2016) [89], Germany	<i>In vitro</i>	Curcumin	DOX	CCRF-CEM and CEM/ADR5000	Acute lymphoblastic leukemia
Tyagi et al. (2017) [90], USA	<i>In vitro</i>	Calebin A	5FU and TLD	KBM-5	Chronic myeloid leukemia

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*Quinones*

Jafri et al. (2010) [91], USA	<i>In vitro</i> and <i>in vivo</i>	Thymoquinone	CIP	NCI-H460 and NCI-H146	Lung cancer
Li et al. (2010) [92], Singapore	<i>In vitro</i>	Thymoquinone	BTZ and TLD	U266 and RPMI 8226	Multiple myeloma
Sandur et al. (2010) [93], USA	<i>In vitro</i>	Plumbagin	BTZ and TLD	U266 and MM.1S	Multiple myeloma
Effenberger-Neidnicht and Schobert (2011) [94], Germany	<i>In vitro</i>	Thymoquinone	DOX	HL-60; 518A2; HT-29; KB-V1; MCF-7	Leukemia; melanoma; colon cancer; cervical cancer; breast cancer
Wang et al. (2014b) [95], China	<i>In vitro</i> and <i>in vivo</i>	Shikonin	GCT	PANC-1, BxPC-3 and AsPC-1	Pancreatic cancer
Daqian et al. (2015) [96], China	<i>In vitro</i>	Chimaphilin	DOX	U-2OS and U-2OSMR	Osteosarcoma
He et al. (2016) [97], China	<i>In vitro</i> and <i>in vivo</i>	Shikonin	CIP	HCT116, HT29 and SW620	Colon cancer
Song et al. (2016) [98], China	<i>In vitro</i> and <i>in vivo</i>	Shikonin	ATO	HepG2, Hep3B, Huh7	Hepatocellular carcinoma
Wang et al. (2017) [99], China	<i>In vitro</i>	Cryptotanshinone	PTX	CAL 27 and SCC 9	Tongue squamous cell carcinoma

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*Saponins*

Choi et al. (2003) [100], South Korea	<i>In vitro</i>	Protopanaxatriol	DOX	AML-2/D100 and AML-2/DX100	Acute myeloid leukemia
Kim et al. (2010) [101], South Korea	<i>In vitro</i>	Ginsenoside Rg3	DTX	LNCaP, PC-3 and DU145	Prostate cancer
Ming et al. (2010) [102], China	<i>In vitro</i>	$\beta$ -aescin	5FU	SMMC-7721	Hepatocellular carcinoma
Wang et al. (2012b) [103], China	<i>In vitro</i> and <i>in vivo</i>	Escin	GCT	L6, BxPC-3, PANC-1, CFPAC-1 and SW-1990	Pancreatic cancer
Yang et al. (2012) [104], China	<i>In vivo</i>	Ginsenoside Rg3	PTX	MCF-7	Breast cancer
Wang et al. (2013b) [105], China	<i>In vitro</i> and <i>in vivo</i>	Steroidal saponin	DOX, 5FU, PTX and CIP	HepG2 and R-HepG2	Hepatocellular carcinoma
Chang et al. (2014) [106], China	<i>In vivo</i>	Ginsenoside Rg3	PTX + CIP	Eca- 109	Esophageal carcinoma
Lee et al. (2014) [107], South Korea	<i>In vitro</i>	Ginsenoside Rg3	CIP	HTB5, J82, JON, UMUC14 and T24	Bladder cancer
Liu et al. (2017) [108], China	<i>In vitro</i>	Paris saponin I	CPT	H1299; H520; H460; H446	Lung adenocarcinoma; lung squamous cell carcinoma; lung large cell carcinoma

Yuan et al. (2017) [109], China	<i>In vitro</i> and <i>in vivo</i>	Ginsenoside Rg3	PTX	MDA-MB-231, MDA-MB-453 and BT-549	Breast cancer
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*Steroids*

Lee et al. (2009) [110], South Korea	<i>In vitro</i>	Withaferin A	TRAIL	Caki, Huh7, SK-Hep1 and Hep3B	Renal cancer
Chen et al. (2010) [111], South Africa	<i>In vitro</i>	Cucurbitacin B	CIP	SRB1, SRB12, SCC13 and COLO160	Cutaneous squamous carcinoma
Iwanski et al. (2010) [112], USA	<i>In vivo</i>	Cucurbitacin B	GCT	PANC-1	Pancreatic cancer
Lee et al. (2011) [113], USA	<i>In vitro</i> and <i>in vivo</i>	Cucurbitacin B	MET	U2OS, G292, MG-63, HT-161, HOS, SAOS-2, and SJSA	Osteosarcoma
Cohen et al. (2012) [114], USA	<i>In vitro</i>	Withaferin A	SOF	BCPAP and SW1736	Thyroid cancer
Fong et al. (2012) [115], USA	<i>In vitro</i> and <i>in vivo</i>	Withaferin A	DOX	A2780, A2780/CP70 and CaOV3	Ovarian cancer
El-Senduny et al. (2015) [116], USA	<i>In vitro</i>	Cucurbitacin B	CIP	A2780 and A2780CP	Ovarian cancer
Li et al. (2015) [117], China	<i>In vitro</i> and <i>in vivo</i>	Withaferin A	OXF	PANC-1, MIAPaCa-2 and SW1990	Pancreatic cancer

Ben-Eltriki et al. (2016) [118], Canada	<i>In vitro</i>	20(S)-protopanaxadiol	CAL	LNCaP and C4-2	Prostate cancer
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*Terpenoids*

Holland et al. (2006) [119], Australia	<i>In vitro</i>	Cannabidiol, $\Delta^9$ -tetrahydrocannabinol	VBL	CCRF-CEM and CEM/VLB <sub>100</sub>	Acute T-lymphoblastoid leukemia
Sieber et al. (2009) [120], Germany	<i>In vitro</i>	Artesunate	RUX	Ramos	B-lymphoma
He et al. (2011) [121], China	<i>In vitro</i>	Lupeol	TRAIL	SMMC7721 and HepG2	Hepatocellular carcinoma
Kannaiyan et al. (2011) [122], Singapore	<i>In vitro</i>	Celastrol	TLD and BTZ	U266, RPMI 8226, RPMI-8226 and RPMI-8226-LR-5	Multiple myeloma
Torres et al. (2011) [123], Spain	<i>In vitro</i> and <i>in vivo</i>	Cannabidiol and $\Delta^9$ -tetrahydrocannabinol	TMZ	U87MG (U87), A172, SW1783, U373MG (U373), T98G (T98), SW1088, and LN405	Glioma
Prasad et al. (2012) [124], USA	<i>In vivo</i>	Ursolic acid	CCT	HCT116, HT29, and Caco2	Colon cancer
Tong et al. (2012b) [125], China	<i>In vitro</i>	Pseudolaric acid B	ABT-737****	LNCaP, PC-3 and DU145	Prostate cancer
Wang et al. (2012c)	<i>In vitro</i>	Pristimerin	GCT	BxPC-3, PANC-1 and	Pancreatic cancer

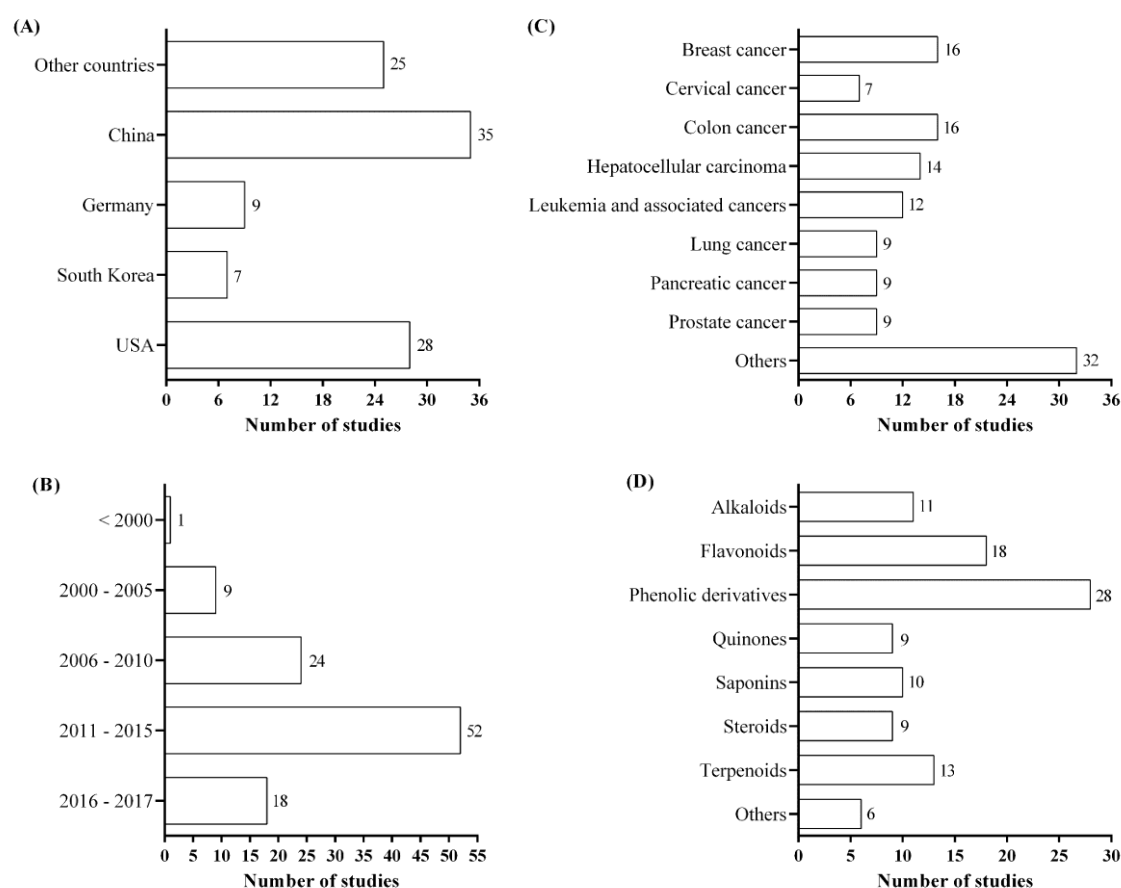
[126], China				AsPC-1	
Butturini et al. (2013) [127], Italy	<i>In vitro</i>	Cynaropicrin	CIP and DTX	THP-1	Monocytic leukemia
Liu et al. (2013) [128], China	<i>In vitro</i> and <i>in vivo</i>	Lupeol	S14161	HepG2 and SMMC7721	Hepatocellular carcinoma
Bamodu et al. (2015) [129], Taiwan	<i>In vitro</i>	Ovatodiolide	DOX	MDA-MB-231, HS578T and MCF-7	Breast cancer
Liu et al. (2016) [130], China	<i>In vitro</i> and <i>in vivo</i>	Lupeol	5FU	SGC7901 and BGC823	Gastric carcinoma
Reis et al. (2016) [131], Portugal	<i>In vitro</i>	Euphowelwitschines A and B, welwitschene, epoxywelwitschene and esulatin M	DOX	L5178Y	T-lymphoma

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4-methylumbelliferone (4MU); 5-fluorouracil (5FU); adriamycin (ADM); amsacrine (AMS); actinomycin D (ACD); aphidicolin (APD); arsenic trioxide (ATO); *bis*-chloroethylnitrosourea (BCE); bortezomib (BTZ); calcitrol (CAL); camptothecin (CPT); capecitabine (CCT); carboplatin (CAP); cisplatin (CIP); cyclophosphamide (CPA); cycloheximide (CHM); cytarabine (CYT); docetaxel (DTX); doxorubicin (DOX); ellipticine (ELP); etoposide (ETP); 5FU + oxilaplatin (FOLFOX); gemcitabine (GCT); homoharringtonine (HHG); ifosfamide (IFO); IL-1 receptor antagonist (IL-Ra); L-asparaginase (LAP); methotrexate (MET); mimosine (MMS); nocodazole (NCD); oxaliplatin (OXP); paclitaxel (PTX); rapamycin (RPM); rituximab (RUX); sorafenib (SOF); tamoxifen (TOF); taxane (TXN): DTX + PTX; temozolamide (TMZ); thalidomide (TLD); thymidine (TMD); TNF-Related Apoptosis Inducing Ligand (TRAIL); vinblastine (VBL); vincristine (VCR); vorinostat (VOR). \*3-Methylcholanthrene (3-MC)-induced tumorigenesis in Swiss albino mice. \*\*LLC: mouse Lewis lung cancer cell line. \*\*\*ABT-737: Bcl-2 inhibitor.



Combinatorial therapy (natural compounds and conventional chemotherapeutic) were used in various types of cancer. Breast and colon cancer were the most cited (16 reports each), followed by leukemia and associate cancers, lung, pancreatic, prostate and cervical cancer. Concerning the conventional anticancer drugs mentioned, about 40 different chemotherapeutic agents have been reported in combination with one or more natural molecules, varying according to the type of cancer studied, as shown in Table 1. Similarly, a wide variety of natural compounds have been reported as chemosensitizer agents. Most of the molecules studied belong to the class of phenolic derivatives (28 reports, 26.9%) and flavonoids (18 reports, 17.3%). Besides these, terpenoids, alkaloids, saponins, quinones and steroids were also considerably cited. These and other important outcomes are graphically presented in figure 3.



**Figure 3.** Distribution of the selected studies by country (A), year of publication (B), type of cancer studied (C) and chemical class of natural product evaluated as chemosensitizer (D).

Our systematic review consisted of 67 *in vitro* studies, 6 *in vivo* studies, and 31 reports presenting *in vitro* and *in vivo* outcomes. *In vitro* investigations included biochemical and molecular analysis, specially colorimetric and enzymatic assays, flow cytometry, western blot and immunofluorescence techniques. *In vivo* reports were performed using allograft or xenograft model, as shown in Table 2. In general, natural compounds potentiated the antitumor effect of chemotherapeutics by reducing tumor volume and weight. In some cases, synergistic inhibition of metastasis and increased apoptosis index were also observed. Combinatorial treatments were performed on the same day or on alternate days for 1 to 4 weeks. The used chemotherapy drugs varied according to the type of cancer studied. All natural products tested *in vivo* were also assayed *in vitro*, providing relevant findings on molecular targets implicated in their pharmacological effect. The chemical structures of these compounds are shown in Figure 4.

Concerning to methodological quality, all *in vivo* studies were carefully analyzed through a standard checklist adapted for preclinical trials. As shown in Figure 5, all studies described the objectives, outcomes to be measured and main findings obtained. In general, combinatorial treatments (chemosensitizer and conventional chemotherapeutic, doses, routes of administration and frequency of treatment) were properly reported. Most of the studies (31 reports, 83.8%) have also reported randomization of animal allocation. On the other hand, none of the included articles reported sample size calculations. In addition, no information on blinding strategy was provided.



**Table 2.** *In vivo* studies involving natural compounds as chemosensitizer agents.

<b>Chemosensitizer</b>	<b>Dose (route)</b>	<b>Combined drug</b>	<b>Dose (route)</b>	<b>Model (animal/sex)</b>	<b>Main outcomes (Cancer)</b>	<b>R</b>	<b>B</b>	<b>Reference</b>
3,3'-diindolylmethane	5 mg/day (p.o.)	OXP	15 mg/kg (i.v.)	Xenograft (Mi/F)	Synergistic decrease in tumor weight and appearance of nodal metastasis (pancreatic cancer)	Y	N	Banerjee et al. (2009) [29]
Cucurbitacin B	0.5 or 1 mg/kg/day (i.p.)	GCT	25 mg/kg/day (i.p.)	Xenograft (Mi/F)	Synergistic decrease in tumor volume and weight, synergistic inhibition of metastasis (pancreatic cancer)	Y	N	Iwanski et al. (2010) [112]
	0.5 or 1 mg/kg (i.p.)	MET	50 or 150 mg/kg (i.p.)	Xenograft (Mi/F)	Synergistic decrease in tumor volume and weight (osteosarcoma)	Y	N	Lee et al. (2011) [113]
Curcumin	2% w/w/day (p.o.)	PTX	10 mg/kg/week (i.p.)	Xenograft (Mi/F)	Synergistic inhibition of breast cancer metastasis to the lung (breast cancer)	Y	N	Aggarwal et al. (2005) [67]
	1 g/kg/day (p.o.)	CCT	60 mg/kg/twice weekly (p.o.)	Xenograft (Mi/M)	Synergistic decrease in tumor volume, synergistic inhibition of metastasis (colon cancer)	Y	N	Kunnumakkara et al. (2009) [72]
Curcumin (liposomal formulation)	40 mg/kg/thrice	OXP	5 mg/kg/thrice	Xenograft (Mi/F)	Synergistic decrease in tumor volume, synergistic	Y	N	Li et al. (2007) [69]

	weekly (i.v.)		weekly (i.p.)		inhibition of angiogenesis (colon cancer)			
	25 mg/kg/thrice weekly (i.p.)	PTX	10 mg/kg/twice weekly (i.p.)	Xenograft (Mi/F)	Synergistic decrease in tumor volume, improvement of apoptosis (cervical cancer)	Y	N	Sreekanth et al. (2011) [76]
Epigallocatechin-3-gallate	228 mg/kg/week (i.p.)	DTX + PTX	5 or 12.5 + 15 mg/kg/week (i.p.)	Xenograft (Mi/NR)	Synergistic decrease in tumor volume (prostate cancer)	Y	N	Stearns and Wang (2011) [51]
	1.5 mg/day (i.p.)	CCT	200 mg/kg/day (p.o.)	Xenograft (Mi/F)	Synergistic decrease in tumor volume and inhibition of microvessel formation (gastric cancer)	Y	N	Wu et al. (2012) [53]
Escin	2 mg/kg/day (i.p.)	GCT	100 mg/kg/twice weekly (i.p.)	Xenograft (Mi/M)	Synergistic decrease in tumor volume, improvement of apoptosis (pancreatic cancer)	Y	N	Wang et al. (2012b) [103]
Genistein	1.3 mg/kg/day (i.p.)	5FU	60 mg/kg/day (i.p.)	Xenograft (Mi/F)	Synergistic decrease in tumor volume, improvement of apoptosis (pancreatic cancer)	Y	N	Suzuki et al. (2014) [55]
Ginsenoside Rg3	6 mg/kg/day (p.o.)	PTX + CIP	10 + 5 mg/kg/day (i.p.)	Xenograft (Mi/F)	Synergistic decrease in tumor volume and weight (esophageal carcinoma)	Y	N	Chang et al. (2014) [106]

	10 mg/kg/day (p.o.)	PTX	20 mg/kg/day (p.o.)	Xenograft (Mi/F)	Synergistic decrease in tumor volume (breast cancer)	Y	N	Yang et al. (2012) [104]
	6 mg/kg/day (p.o.)	PTX	10 mg/kg/week (i.p.)	Xenograft (Mi/NR)	Synergistic decrease in tumor volume and weight, improvement of apoptosis (breast cancer)	Y	N	Yuan et al. (2017) [109]
Isoxanthohumol	20 mg/kg/day (NR)	PTX	3 mg/kg (NR)	Allograft (Mi/NR)	Synergistic decrease in tumor volume (melanoma)	Y	N	Krajnovic et al. (2016) [60]
Lupeol	20 mg/kg/thrice weekly (i.p.)	S14161	20 mg/kg/day (i.p.)	Xenograft (Mi/F)	Synergistic decrease in tumor volume (hepatocellular carcinoma)	Y	N	Liu et al. (2013) [128]
	30 mg/kg/day (i.p.)	5FU	10 mg/kg/day (i.p.)	Xenograft (Mi/NR)	Synergistic decrease in tumor volume and weight, improvement of apoptosis (gastric cancer)	N	N	Liu et al. (2016) [130]
Myricetin	25 mg/kg	5FU	20 mg/kg	Xenograft (Mi/NR)	Synergistic decrease in tumor volume (esophageal carcinoma)	N	N	Wang et al. (2014a) [56]
Naringenin	50 mg/kg/day (p.o.)	DOX	5 mg/kg/week (p.o.)	Allograft (Mi/F)	Synergistic decrease in tumor volume (lung cancer)	N	N	Zhang et al. (2009) [49]
Noscapine	300	GCT	30 mg/kg	Xenograft	Synergistic decrease in	Y	N	Chougule et al.

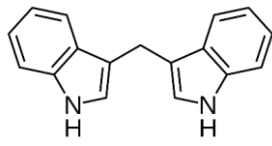
	mg/kg/day (p.o.)		(i.v.)	(Mi/F)	tumor volume and inhibition of angiogenesis in tumor tissue (lung cancer)			(2011) [31]
	200 mg/kg/day (i.g.)	TMZ or CIP	2 mg/kg/day (i.p.)	Xenograft (Mi/F)	Synergistic decrease in tumor volume and weight (glioblastoma)	Y	N	Qi et al. (2013) [33]
Oxymatrine	40 mg/kg/day (i.p.)	5FU	10 mg/kg/day (i.p.)	Xenograft (Mi/NR)	Synergistic decrease in tumor volume and weight (hepatocellular carcinoma)	N	N	Liu et al. (2015a) [36]
	1, 2 or 4 g/l/thrice weekly (i.p.)	NM-3	10 mg/kg/thrice weekly (i.p.)	Xenograft (Mi/NR)	Synergistic decrease in tumor volume (gastric cancer)	Y	N	Song et al. (2007) [28]
Resveratrol	40 mg/kg/day (p.o.)	GCT	25 mg/kg/twice weekly (i.p.)	Xenograft (Mi/M)	Synergistic decrease in tumor volume (pancreatic cancer)	Y	N	Harikumar et al. (2009) [71]
	5, 10 and 15 mg/kg/day	5FU	5, 10 and 20 mg/kg	Allograft (Mi/NR)	Synergistic decrease in tumor area (hepatocellular carcinoma)	Y	N	Wu et al. (2004) [66]
Shikonin	4 mg/kg/day (i.p.)	CIP	10 mg/kg/day (i.p.)	Xenograft (Mi/F)	Synergistic decrease in tumor volume and weight (colon cancer)	N	N	He et al. (2016) [97]
	3 mg/kg/day (i.p.)	ATO	10 mg/kg/day (i.p.)	Xenograft (Mi/NR)	Synergistic decrease in tumor volume and weight (hepatocellular carcinoma)	Y	N	Song et al. (2016) [98]

	2 mg/kg/day (i.p.)	GCT	100 mg/kg/twice weekly (i.p.)	Xenograft (Mi/M)	Synergistic decrease in tumor volume, synergistic inhibition of microvessel formation and induction of apoptosis (pancreatic cancer)	Y	N	Wang et al. (2014b) [95]
Sinomenine	25 mg/kg/twice weekly (i.t.)	5FU	12 mg/kg/twice weekly (i.t.)	Xenograft (Mi/M)	Synergistic decrease in tumor volume and weight (esophageal carcinoma)	Y	N	Wang et al. (2013a) [34]
Steroidal saponin	5, 10 or 15 mg/kg/day (i.v.)	DOX	8 mg/kg/day (i.v.)	Xenograft (Mi/NR)	Synergistic decrease in tumor volume (hepatocellular carcinoma)	N	N	Wang et al. (2013b) [105]
Thymoquinone	5 or 20 mg/kg/day (s.c.)	CIP	2.5 mg/kg/week (i.p.)	Xenograft (Mi/F)	Synergistic decrease in tumor volume (lung cancer)	Y	N	Jafri et al. (2010) [91]
Ursolic acid	250 mg/kg/day (p.o.)	CCT	60 mg/kg/twice weekly (p.o.)	Xenograft (Mi/M)	Synergistic decrease in tumor volume and weight, synergistic inhibition of metastasis (colon cancer)	Y	N	Prasad et al. (2012) [124]
Withaferin A	2 mg/kg/day (i.p.)	DOX	1 mg/kg/day (i.p.)	Xenograft (Mi/NR)	Synergistic decrease in tumor volume and weight, synergistic inhibition of microvessel formation and induction of autophagy (ovarian cancer)	Y	N	Fong et al. (2012) [115]

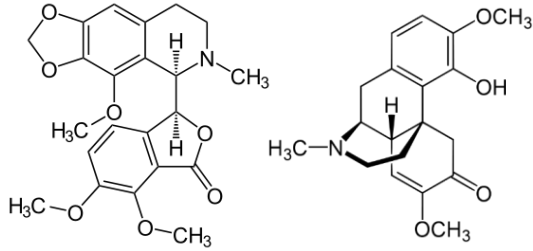
	3 mg/kg/day (i.p.)	OXP	10 mg/kg/twice weekly (i.p.)	Xenograft (Mi/M)	Synergistic decrease in tumor volume and weight, synergistic induction of apoptosis (pancreatic cancer)	Y	N	Li et al. (2015) [117]
$\alpha$ -carotene	5 mg/kg/day (p.o.)	PTX	6 mg/kg/day (i.p.)	Xenograft (Mi/M)	Synergistic decrease in lung metastasis (lung cancer)	Y	N	Liu et al. (2015b) [40]
$\beta$ -carotene	5 mg/kg/thrice weekly (i.g.)	5FU	5 mg/kg/thrice weekly (i.p.)	Xenograft (Mi/M)	Synergistic decrease in tumor volume and weight, improvement of apoptosis (esophageal carcinoma)	Y	N	Zhang et al. (2016) [41]
$\Delta^9$ - Tetrahydrocannabinol	15 mg/kg (i.t.)	TMZ	5 mg/kg (i.t.)	Xenograft (Mi/NR)	Synergistic decrease in tumor volume and weight (glioma)	Y	N	Torres et al. (2011) [123]

Combined drugs: 5-fluorouracil (5FU); arsenic trioxide (ATO); capecitabine (CCT); cisplatin (CIP); docetaxel (DTX); doxorubicin (DOX); gemcitabine (GCT); methotrexate (MET); oxaliplatin (OXP); paclitaxel (PTX); temozolamide (TMZ). Routes: i.g. (intra-gastric), i.t. (intratumoral), i.p. (intra-peritoneal), i.v. (intravenous), p.o. (per oral), s.c. (subcutaneous). F: female. M: male. NR: not reported. Mi: mice. R: reporting of randomization. B: reporting of blinding.

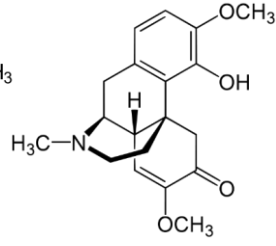
**Alkaloids**



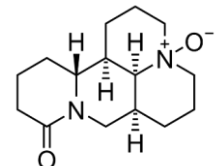
**3,3'-diindolylmethane**



**Noscapine**

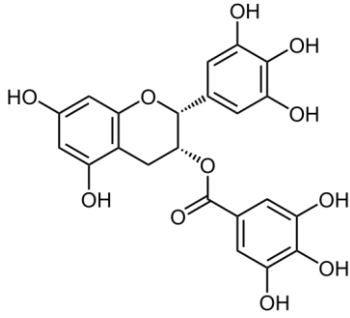


**Sinomenine**

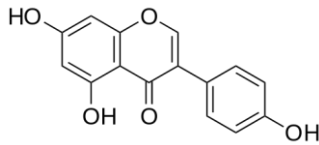


**Oxymatrine**

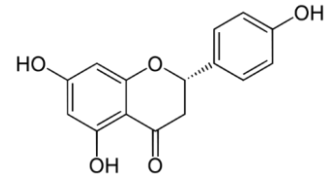
**Flavonoids and phenolic derivatives**



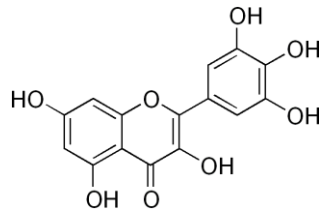
**Epigallocatechin-3-gallate**



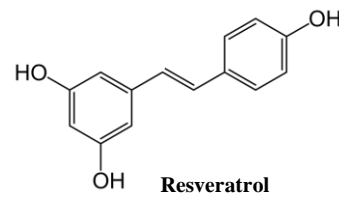
**Genistein**



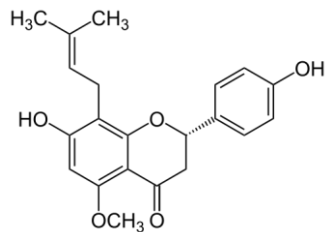
**Naringenin**



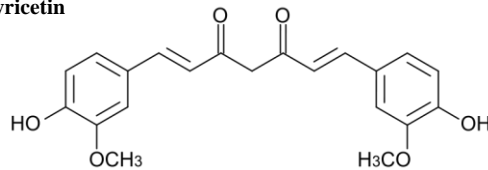
**Myricetin**



**Resveratrol**

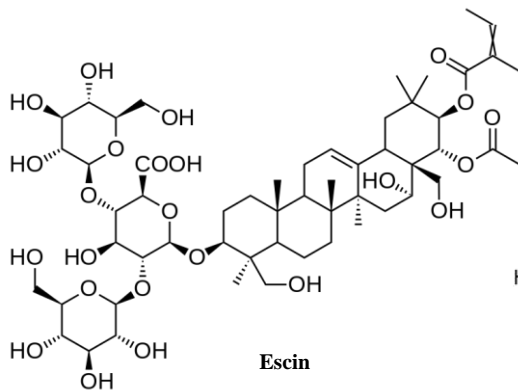


**Isoxanthohumol**

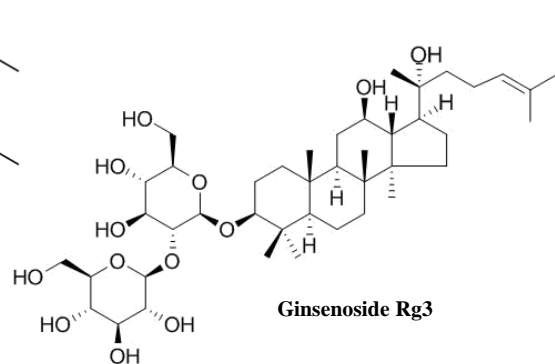


**Curcumin**

**Saponins**



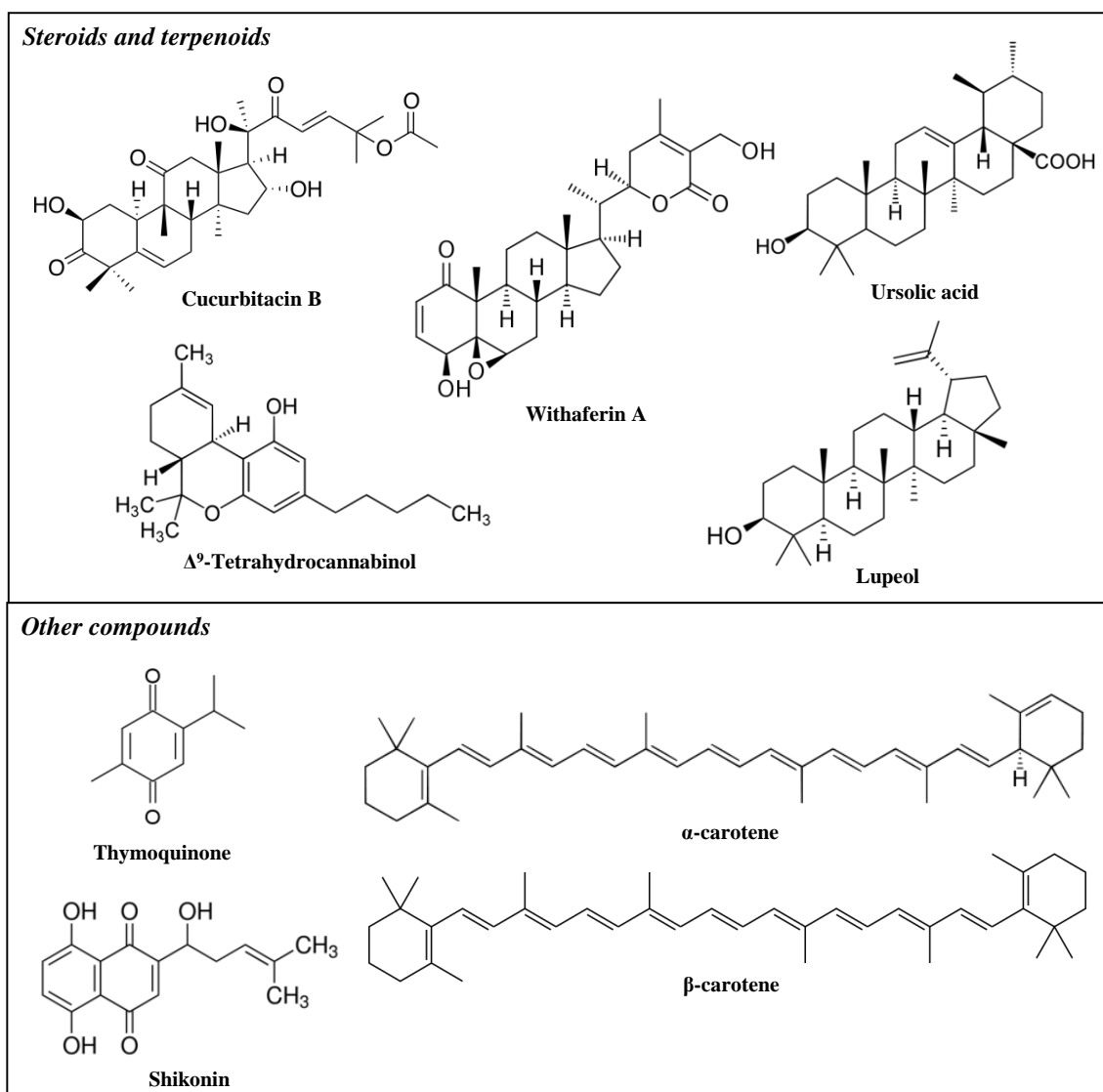
**Escin**



**Ginsenoside Rg3**

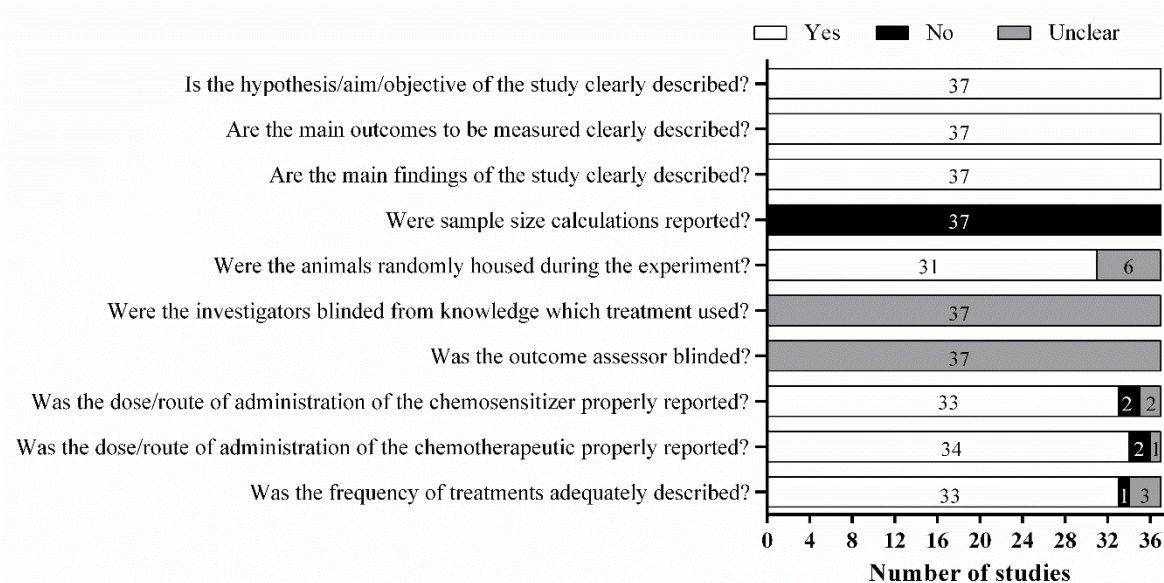
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**Figure 4.** Chemical structure of the major natural compounds evaluated as chemosensitizer agents (*in vitro* and *in vivo* evidences).





**Figure 5.** Methodological quality assessment of included *in vivo* studies. *Light bars* indicate the proportion of articles that met each criterion; *dark bars* indicate the proportion of studies that did not and *white gray bars* indicate the proportion of studies with unclear or insufficient answers.

#### 4. Discussion

Cancer therapy is based on the use of one or more treatment strategies, including surgical removal of the tumor, radiotherapy, immunotherapy, phototherapy and chemotherapy. Although chemotherapy is recognized as one of the most effective strategies in the treatment of various types of cancer, the phenomenon of chemoresistance has become increasingly frequent, representing an obstacle to the use of anticancer drugs [132]. Tumor cells may develop a multidrug-resistant phenotype depending on the carcinogenic process *per se*, or even due to exposure to conventional chemotherapeutics [133]. In this sense, chemosensitization represents an alternative for overcoming chemoresistance. It consists in the use of molecules capable of improving the activity of another through the modulation of one or more mechanisms of resistance (Figure 1).

Historically, natural products have been shown to be more effective than conventional anticancer drugs because of their multi-target potential and low toxicity. Such compounds are already widely known as promising anti-tumor and chemopreventive agents. Fortunately, several research groups have also investigated the

role of natural products in sensitizing tumor cells. In this systematic review, most of the included studies were published after 2011 (Figure 3), indicating that the use of natural compounds as chemosensitizer agents is still recent.

Interestingly, China has been the country that most explores the use of natural products as chemosensitizers (Figure 3). In fact, Traditional Chinese Medicine (TCM) has contributed to the development of new pharmaceutical products based on plant extracts or even molecules with unique chemical structures and innovative mechanisms of action [134]. In cancer therapy, TCM has provided molecules with antitumor and chemopreventive properties [135] and, more recently, chemosensitizing potential. Shikonin, a natural naphthoquinone derived from the Chinese medicinal herb *Lithospermum erythrorhizon*, showed synergistic effect with gemcitabine, cisplatin and arsenic trioxide against pancreatic [95], colon [97] and hepatocellular [98] cancer, respectively. Song et al. [28] and Liu et al. [36] have also demonstrated the chemosensitizing effect of oxymatrine, one of the major components extracted from *Sophora flavescens*, widely used in TCM. In addition, several phenolic derivatives and flavonoids commonly found in Chinese medicinal plants were investigated as chemosensitizers, including resveratrol [65], curcumin [64], naringenin [49] and myricetin [56].

Concerning to *in vivo* studies included, natural products were investigated using xenograft model. In this model, human tumor cells are transplanted via subcutaneous inoculation or into the organ type in which the tumor originated, into immunocompromised animals that do not reject human cells [136]. Xenograft models have been used not only to determine the *in vivo* activity of new anticancer drugs, but also to determine drug dose, treatment schedules and routes of administration [137]. In this context, *in vivo* reports included in this review were appropriately described. In addition to *in vitro* protocols, these models offer a wealth of information on the mechanisms of action involved in the chemosensitizing effect of natural products.

However, animal experiments should be well designed, efficiently executed and data must to be correctly analyzed and interpreted [138]. Regarding the methodological quality assessment, we found that most of studies were conducted randomly, but no information on blinding was provided (Figure 5). In addition, no study reported sample size calculations. Although these parameters are often required in clinical trials, the need of randomization and blinding have been strongly recommended for preclinical protocols in order to minimize the risk of bias and avoid unexpected outcomes in

clinical trials [139-141]. For this reason, we consider that the *in vivo* studies included in this review presented moderate methodological quality.

In general, phenolic derivatives and flavonoids were the most cited compounds (Figure 3). Curcumin, resveratrol and epigallocatechin-3-gallate have been extensively evaluated in combinatorial treatment with clinically used chemotherapeutics. These compounds are widely found in various medicinal plants and foods, such as red wine, fruits, vegetables and spices. The use of these molecules has been increasingly encouraged in cancer treatment mainly because of their low toxicity and immediate availability. Besides, phenolic compounds possess a strong antitumor activity by modulating different pathways involved in cell proliferation, invasion, metastasis and angiogenesis [19-22]. Usually, when cancer cells were treated by natural products in combination with chemotherapeutic drugs, there was an additive cytotoxic effect caused by the activation of alternative signaling pathways that induce cell death, or even by increasing the residence time of the anticancer drug in the cell, improving its performance.

Next, we selected the natural compounds most cited in this review in order to better understand the different mechanisms of action involved in the sensitization of tumor cells. All findings described below were extracted from *in vitro* and *in vivo* included studies.

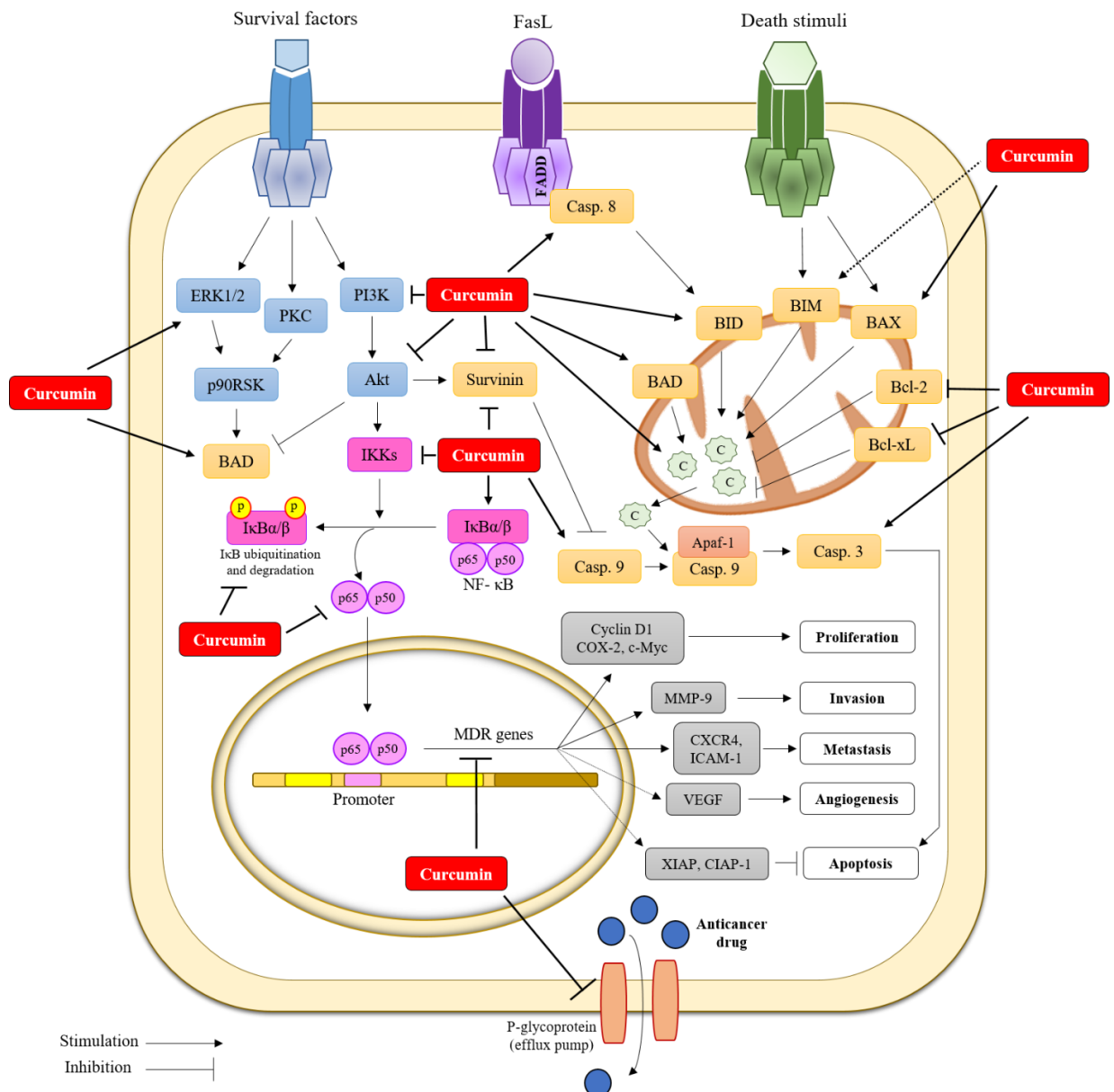
#### 4.1 Curcumin

Curcumin (diferuloyl methane) is a naturally occurring phenolic pigment found in rhizomes of *Curcuma longa* Linn., commonly known as turmeric. Usually, curcumin content in turmeric varies from 1 to 5% and it is widely used in foods, as a cosmetic ingredient, and in some medicinal preparations [142]. It has potent anti-inflammatory, anticancer and chemopreventive properties, but without exhibiting toxic effects in animal models even at high doses [143-145]. Curcumin has demonstrated multiple anticancer effects, including inhibition of cell proliferation, induction of apoptosis, inhibition of angiogenesis and metastasis. Several mechanisms have been implicated in these effects, such as activation of pro-apoptotic proteins and inhibition of nuclear factor  $\kappa$ B (NF- $\kappa$ B) and phosphatidylinositol (PI)3-kinase/Akt (PI3K/Akt) pathways, commonly activated in multiresistant tumor cells [20]. In figure 6, we show the main mechanisms involved in the chemosensitizing effect of curcumin.

In contrast to healthy cells, NF- $\kappa$ B pathway is constitutively active in the majority of solid and hematopoietic tumor cell lines. Additionally, chemotherapeutic agents and pro-inflammatory cytokines also activate NF- $\kappa$ B over time, contributing to chemoresistance of tumor cells. NF- $\kappa$ B is a tumorigenic transcription factor associated with evasion of apoptosis, sustained cell proliferation, invasion, metastasis and angiogenesis. It is a complex protein composed of different subunits (p50, p52, p65, RelB and c-Rel), mainly p50/p65. Under normal conditions, NF- $\kappa$ B is retained in the cytoplasm by its interaction with inhibitors of  $\kappa$ B (I $\kappa$ B $\alpha$ , I $\kappa$ B $\beta$  or I $\kappa$ B $\epsilon$ ). However, I $\kappa$ B kinases (IKKs) are able to phosphorylate I $\kappa$ B portion, resulting in its subsequent ubiquitination and proteasome-mediated degradation, and consequently in the release of NF- $\kappa$ B, which then translocates to the nucleus [74, 146]. In this review, we have identified that curcumin down-regulates NF- $\kappa$ B activation induced by chemotherapeutic agents, such as paclitaxel [67,68,75], 5-fluorouracil [82] and capecitabine [72] in cervical, breast and colon cancer. Western blot and immunohistochemical analysis showed that curcumin inhibits NF- $\kappa$ B (p65 subunit), I $\kappa$ B $\alpha$ / $\beta$  phosphorylation and IKK activation, resulting in synergistic antitumor effect when combined with conventional chemotherapeutic agents [64,87].

NF- $\kappa$ B can also be stimulated via the PI3K/Akt signaling pathway. Initially, exposure to cellular survival factors (growth factors, cytokines, etc.) hyperactivates PI3K, leading to high Akt activation, conferring cell survival and resistance to chemotherapy-induced apoptosis. In fact, Akt protects apoptosis by stimulating anti-apoptotic proteins (e.g. survivin) and inhibiting pro-apoptotic signals (e.g. BAD). Furthermore, Akt induces the release of NF- $\kappa$ B through activation of IKK [79, 147]. Once available, NF- $\kappa$ B upregulates the expression of multiple MDR genes in tumor cells that play a role in apoptosis, cell proliferation, invasion, metastasis and angiogenesis [72]. In this sense, pharmacological investigations have demonstrated that curcumin potentiates anticancer effects of chemotherapeutics not only by inhibiting PI3K, Akt and NF- $\kappa$ B factors [68,75,79,82], but also the proteins expressed by the activation of these signaling pathways, including those involved in cell proliferation (e.g. Cyclin D1, COX-2, c-Myc), invasion (e.g. MMP-9), metastasis (e.g. CXCR4 and ICAM-1) and angiogenesis (e.g. VEGF) [72,79,87]. Finally, curcumin also acts synergistically with chemotherapeutics in the induction of apoptosis through stimulation of pro-apoptotic (e.g. BAD, BID, BIM, BAX, caspases 3, 8 and 9) proteins and inhibition of anti-apoptotic proteins (e.g. Bcl-2, Bcl-xL and survivin) [72,75,84].

MDRs may also involve efflux pumps that reduce the residence time of chemotherapeutic drugs in cancer cells. Anuchapreeda et al. [63] have investigated the role of curcumin in P-glycoprotein (Pgp) expression. Pgp, also known as multidrug resistance protein, is an important transmembrane protein that pumps many foreign drugs out of cells. Many synthetic Pgp modulators successfully reverse the MDR phenotype *in vitro*. On the other hand, the use of these compounds has been discouraged due to their toxicity profile observed in animal models and clinical trials. In this review, Pgp expression was found to be decreased by 11, 31, 60 and 64% in response to 1, 2, 3 and 4 days of treatment with 25  $\mu$ M curcumin, respectively, enhancing sensitivity of KB-V1 cells (cervical cancer) to vinblastine [63]. Since curcumin is considered a safe natural product, it has served as a prototype for obtaining new Pgp-modulating drugs [89].



**Figure 6.** Molecular mechanisms of curcumin-mediated chemosensitization. Curcumin modulates signaling pathways involved in apoptosis, cell proliferation, invasion, metastasis and angiogenesis

#### 4.2 Resveratrol

Resveratrol (*trans*-3,5,4'-trihydroxystilben) is a natural compound produced by the action of stilbene synthase in response to environmental stress, widely found in grapes, red wine, medicinal plants, various berries and nuts. This phenolic derivative possesses a wide spectrum of pharmacological activities, including anticancer properties. Resveratrol has presented an ability to target multiple signaling pathways

implicated in tumor cell survival, inflammation, invasion, metastasis and angiogenesis [148-149]. Several studies showed its antitumor activity in human cancer from different origin, including skin, breast, prostate, liver, pancreas, colon, lung and stomach [80, 150]. In recent years, resveratrol has been evaluated not only as a chemopreventive or chemotherapeutic agent, but also as a chemosensitizer. In our review, *in vitro* and *in vivo* evidences demonstrated that resveratrol potentiates the antitumor effect of several chemotherapeutics, mainly doxorubicin [65,77,81], 5-Fluorouracil [65,66,85], etoposide [80] and gemcitabine [71].

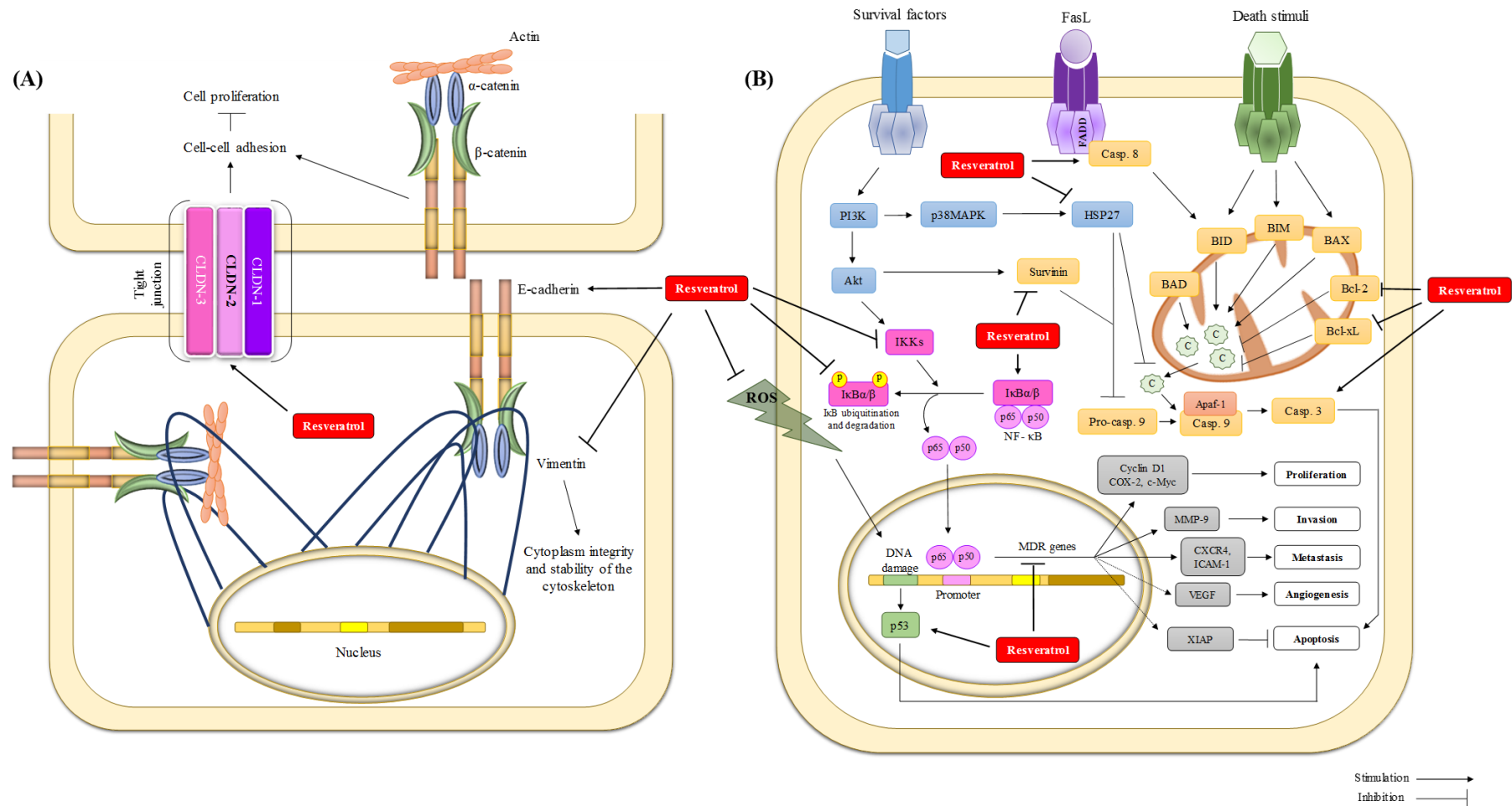
Similar to curcumin, resveratrol sensitizes tumor cells by inhibiting the NF- $\kappa$ B signaling pathway [85], as shown in figure 7. In addition, this phenolic derivative modulates the expression of MDR genes by down-regulating targets related to cell proliferation (e.g. cyclin D1, COX-2 and c-Myc), invasion (e.g. MMP-9), metastasis (e.g. CXCR4 and ICAM-1) and angiogenesis (e.g. VEGF) [71,85]. Resveratrol also enhances the cytotoxicity of chemotherapeutics through the induction of apoptosis by regulating the expression of pro (e.g. p53, caspases 3 and 8) and anti-apoptotic (e.g. Bcl-2, Bcl-xL, XIAP and survivin) mediators in tumor cells [65,71,80,85].

Díaz-Chávez et al. [81] showed that resveratrol sensitizes breast cancer cells to doxorubicin therapy by inhibiting HSP27 expression. HSP27 is present in several cell types, located mainly in the cytosol, but also in the perinuclear region, endoplasmic reticulum and nucleus. It is usually overexpressed during different stages of cell development and differentiation. High HSP27 expression has been observed in several types of cancer, suggesting that it plays an important role in cell proliferation, metastasis and chemoresistance. HSP27 acts as an independent ATP chaperone by inhibiting protein aggregation and stabilizing partially denatured proteins. In apoptosis, it interacts with mitochondrial membranes, interfering with the activation of the cytochrome-c/Apaf-1 complex and consequently preventing the activation of pro-caspase 9 [151].

Interestingly, resveratrol also enhances the efficacy of chemotherapeutics not only by interfering with intracellular signaling pathways, but also by modulating the expression of transmembrane proteins involved in cell proliferation and cytoskeleton stabilization. Buhrmann et al. [85] showed that resveratrol induces chemosensitization of colon cancer cells to 5-fluorouracil through up-regulation of intercellular junctions, epithelial-to-mesenchymal transition and apoptosis. In this investigation, resveratrol increased the expression of adhesion molecules, such as E-cadherin and claudin-2 (also

involved in tight junctions), ensuring greater cell adhesion and consequently preventing mechanisms of cell proliferation. Furthermore, resveratrol significantly attenuated drug resistance by inhibiting epithelial-mesenchymal transition factors, such as vimentin. This protein is attached to the nucleus, endoplasmic reticulum and mitochondria, laterally or terminally. The vimentin filaments are associated with the nuclear and plasma membranes, maintaining the position of the nucleus and the mitotic spindle and guaranteeing flexibility to the cell. It is a component of the cytoskeleton that interacts closely with microtubules, ensuring their stabilization [152]. Once inhibited by resveratrol, vimentin disperses in aggregates, causing loss of cytoplasmic integrity and changes in cellular morphology (Figure 7).





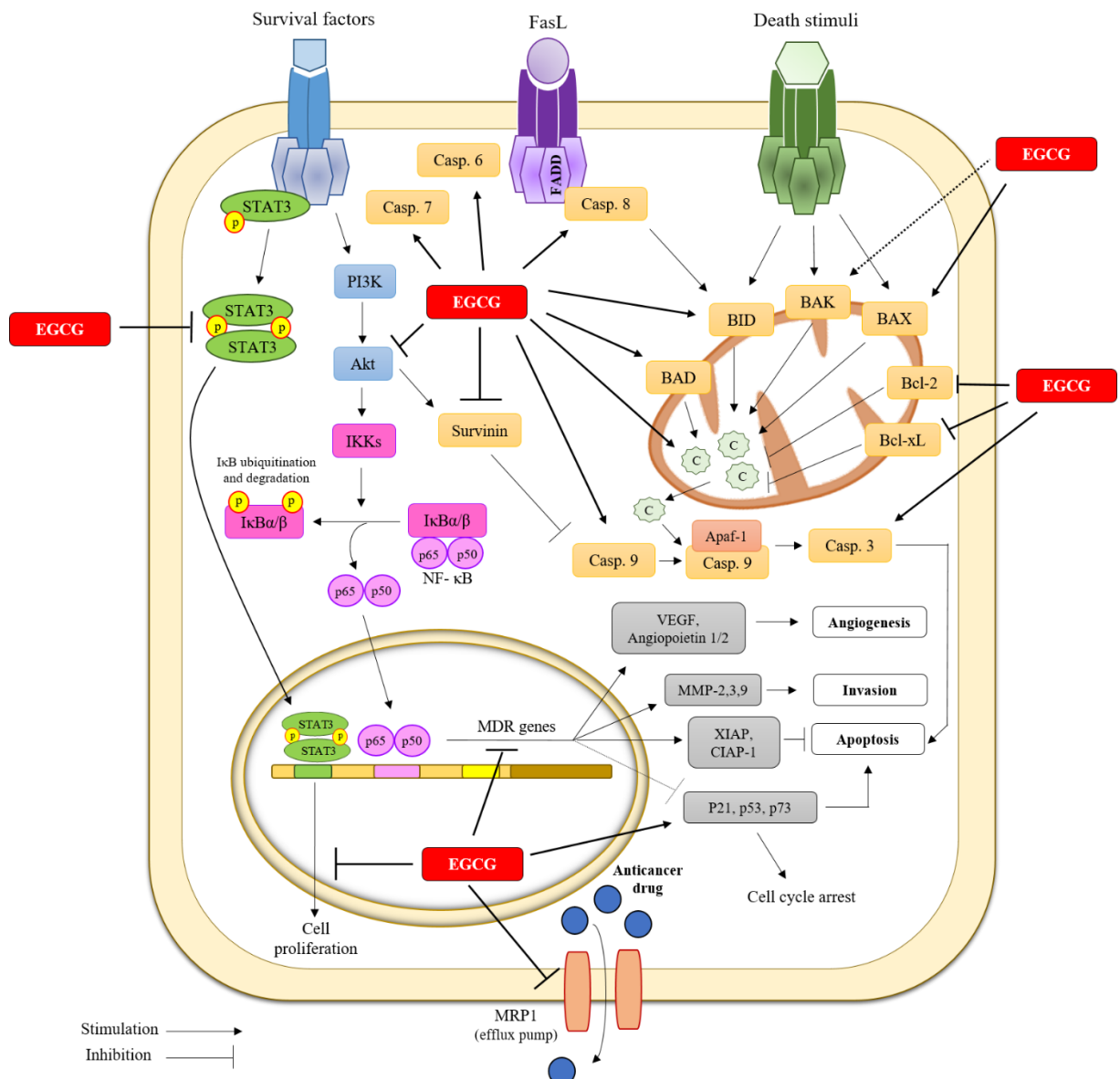
**Figure 7.** Molecular mechanisms of resveratrol-mediated chemosensitization. Resveratrol interferes in the expression of adhesion molecules and in the stability of the cell cycle (A), and modulates signaling pathways involved in apoptosis, cell proliferation, invasion, metastasis and angiogenesis (B).

### 4.3 Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG) is a major flavonoid found in green tea (*Camelia sinensis*) that possesses a broad spectrum of pharmacological activities, including antiangiogenic [153], anticarcinogenic [154], antimetastatic [155,156] and chemopreventive effects [157]. These properties are attributed to its antioxidant potential, cell signaling modulation, apoptosis induction, cell cycle arrest and inhibition of different MMPs (matrix metalloproteinases). In recent years, EGCG has been shown to be effective in sensitizing tumor cells to conventional chemotherapy. In fact, EGCG potentiates the antitumor effect of TRAIL (TNF $\alpha$ -related apoptosis-inducing ligand) [47], 4-MU (4-methylumbelliferone) [59], taxane [51], IL-1Ra (IL-1 receptor antagonist) [52], capecitabine [53], vorinostat [54], cisplatin [48], tamoxifen [45,48], docetaxel [58] and doxorubicin [43] in various types of cancer, mainly breast [45,59] and prostate cancer [47,51,58].

*In vitro* and *in vivo* assays have demonstrated that EGCG enhances the antitumor effect of other drugs by inducing apoptosis. In general, EGCG up-regulates apoptotic proteins (e.g. BAD, BAK, BAX, caspases 3, 6, 7, 8 and 9) and down-regulates anti-apoptotic factors (e.g. Bcl-2, Bcl-xL, XIAP, CIAP-1, survivin and Smac/Diablo) [47, 54, 58]. EGCG also induces the expression of genes that are directly associated with cell cycle arrest and apoptosis, such as p53, p73 and p21 [51].

Several studies have demonstrated that EGCG synergistically inhibits biomarkers associated with angiogenesis (e.g. VEGF, angiopoietin 1 and 2), invasion and metastasis (MMP-2, 3, and 9) [47, 52-54], improving the performance of chemotherapy in reducing tumor weight and/or volume in xenograft models [53]. Although inhibition of the NF- $\kappa$ B pathway does not appear to be directly involved in the mechanism of EGCG-induced tumor cell sensitization, this flavonoid inhibits the Akt pathway, indirectly resulting in lower expression of factors associated with cell proliferation, invasion, metastasis, angiogenesis, and apoptosis. In addition, Wang et al. [58] showed that EGCG combined with quercetin inhibits STAT3 (signal transducer and activator of transcription 3) expression, contributing to sensitization of prostate cancer cells to docetaxel. In the same study, the authors also demonstrated the potential of these flavonoids to block MRP1 (multidrug resistance-associated protein 1), increasing the residence time of docetaxel in tumor cells. All mechanisms involved in the sensitization of tumor cells by EGCG are summarized in figure 8.



**Figure 8.** Molecular mechanisms of epigallocatechin-3-gallate (EGCG)-mediated chemosensitization. EGCG modulates signaling pathways involved in apoptosis, cell proliferation, invasion, metastasis and angiogenesis

## 5. Conclusion

This systematic review unified information from the literature on the use of natural compounds as chemosensitizers in cancer therapy. *In vitro* and *in vivo* studies demonstrated that natural products act synergistically with drugs traditionally used in cancer therapy, enhancing their antitumor efficacy through various mechanisms, including induction of apoptosis and inhibition of cell proliferation, invasion, metastasis, and angiogenesis. Although the *in vivo* tests presented moderate

methodological quality, this report highlights the potential of natural products as anticancer drug candidates in future clinical research for combinatorial treatments. Considering that chemosensitization of cancer cells by natural products is a recent strategy and that only few resources have been explored at the moment, this research field should be expanding rapidly in the coming years and provide efficient alternatives to manage tumor chemoresistance.

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## **CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.

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