



HAL
open science

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

Raimundo Gonçalves de Oliveira Júnior, Christiane Adrielly Alves Ferraz, Jackson Roberto Guedes da Silva Almeida, Raphaël Grougnet, Valérie Thiéry, Laurent Picot

► To cite this version:

Raimundo Gonçalves de Oliveira Júnior, Christiane Adrielly Alves Ferraz, Jackson Roberto Guedes da Silva Almeida, Raphaël Grougnet, Valérie Thiéry, et al.. Sensitization of tumor cells to chemotherapy by natural products: a systematic review of preclinical data and molecular mechanisms. *Fitoterapia*, 2018, 129, pp.383-400. 10.1016/j.fitote.2018.02.025 . hal-01807405

HAL Id: hal-01807405

<https://univ-rochelle.hal.science/hal-01807405v1>

Submitted on 4 Jun 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Raimundo Gonçalves de Oliveira Júnior¹, Christiane Adrielly Alves Ferraz², Jackson Roberto Guedes da Silva Almeida², Raphaël Grougnet³, Valérie Thiéry¹, Laurent Picot^{1*}

¹ UMRi CNRS 7266 LIENSs, University of La Rochelle, 17042 La Rochelle, France.

² Center for Studies and Research of Medicinal Plants, Federal University of San Francisco Valley, 56306-000 Petrolina, Brazil.

³ UMR CNRS 8638 Laboratory of Pharmacognosy, Paris Descartes University, 75006 Paris, France.

*Corresponding author at: UMRi CNRS 7266 LIENSs, Université de La Rochelle, Curie B101 Faculté des Sciences et Technologies, Avenue Michel Crépeau, 17042 La Rochelle, France. E-mail address: laurent.picot@univ-lr.fr (L. Picot).

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 21st 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.

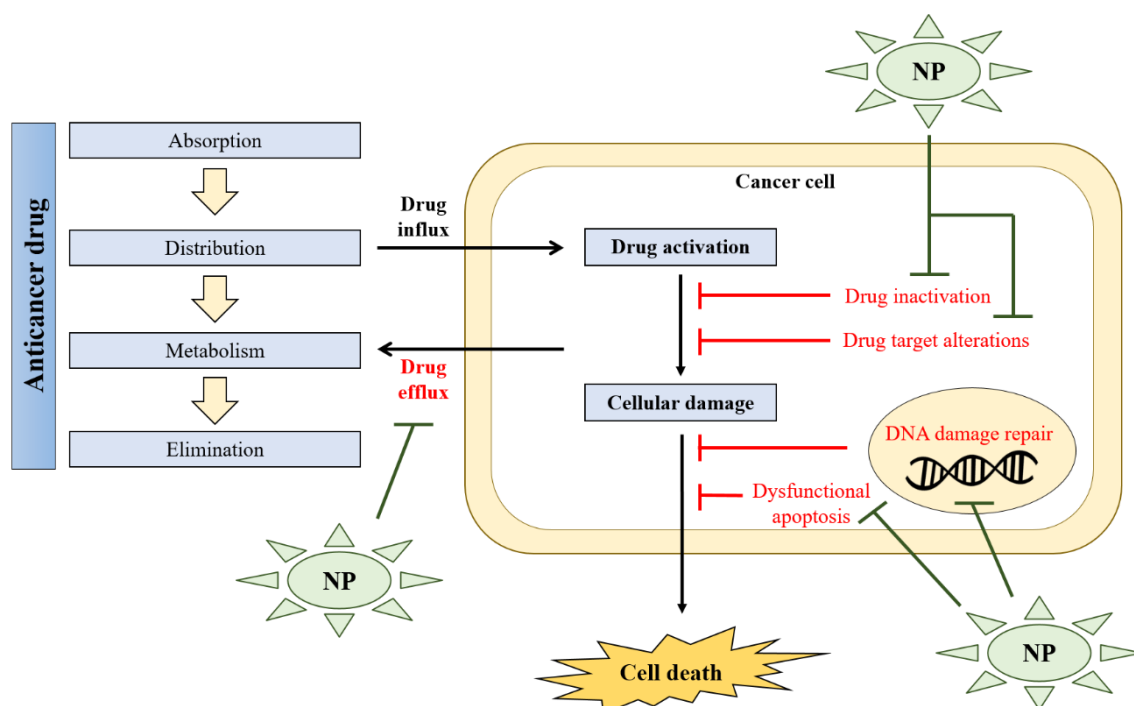


Figure 1. General drug resistance mechanisms implicated in cancer therapy and possibilities of intervention of natural products (NP) as chemosensitizer agents.

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.

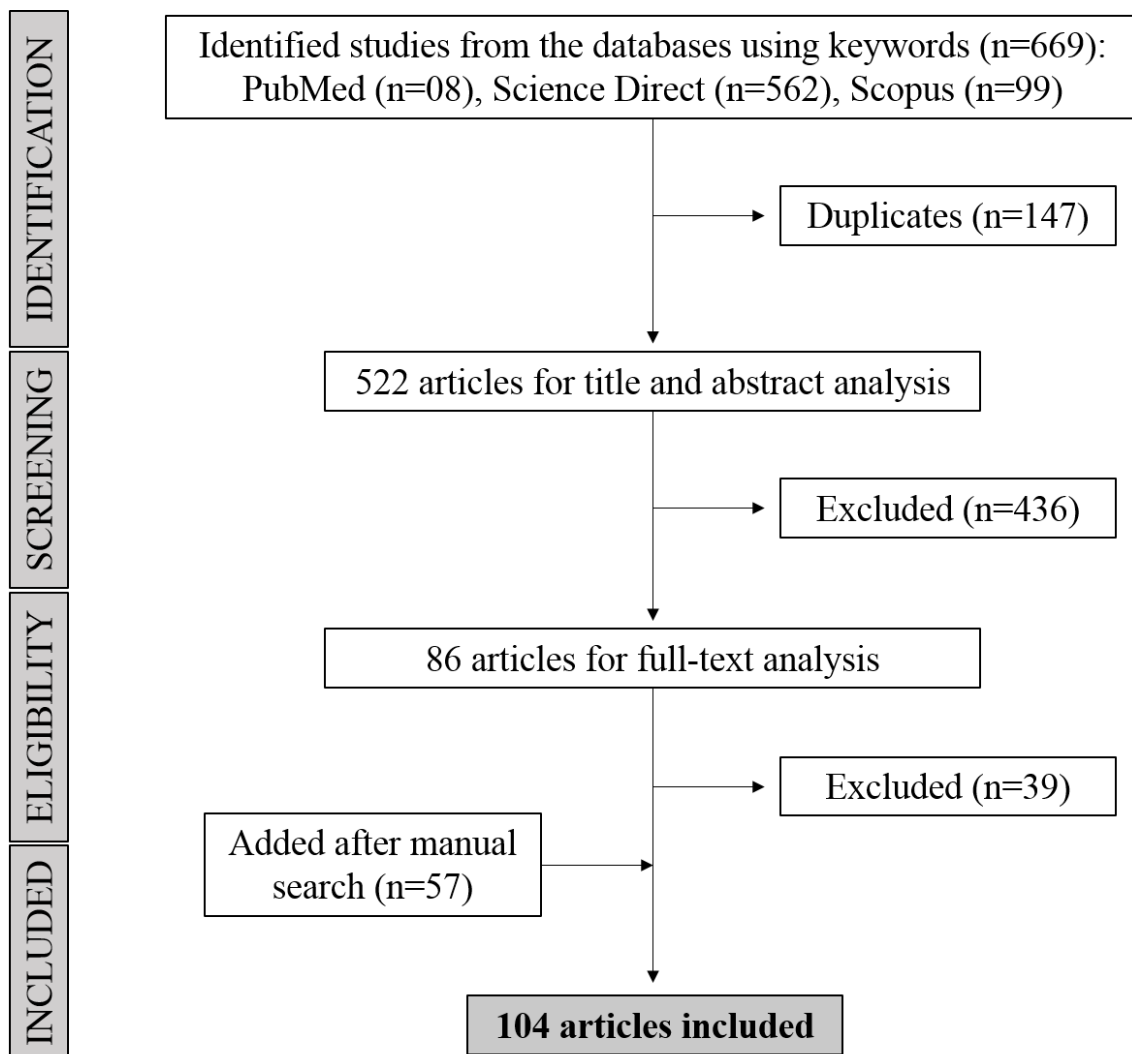


Figure 2. Flowchart detailing literature search according to PRISMA statement [25].

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).

Authors, year, country	Model	Chemosensitizer	Combined conventional drug	Tumor cell line	Cancer
<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

Carotenoids

Rajendran et al. (2010) [39], Singapore	<i>In vitro</i>	γ -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>	α -carotene	PTX	LLC**	Lung cancer
Zhang et al. (2016) [41], China	<i>In vitro</i> and <i>in vivo</i>	β -carotene	5FU	EC1 and Eca109	Esophageal carcinoma

Coumarins

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

Flavonoids

Stammler and Volm (1997) [43], Germany	<i>In vitro</i>	Epigallocatechin-3-gallate	DOX	SSW620-dox	Colon cancer
--	-----------------	----------------------------	-----	------------	--------------

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

*Naphthodianthrone*s

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

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 ₂₂	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

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

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>	β -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
---------------------------------	------------------------------------	-----------------	-----	--------------------------------------	---------------

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
---	-----------------	-----------------------	-----	----------------	-----------------

Terpenoids

Holland et al. (2006) [119], Australia	<i>In vitro</i>	Cannabidiol, Δ^9 -tetrahydrocannabinol	VBL	CCRF-CEM and CEM/VLB ₁₀₀	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 Δ^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

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.

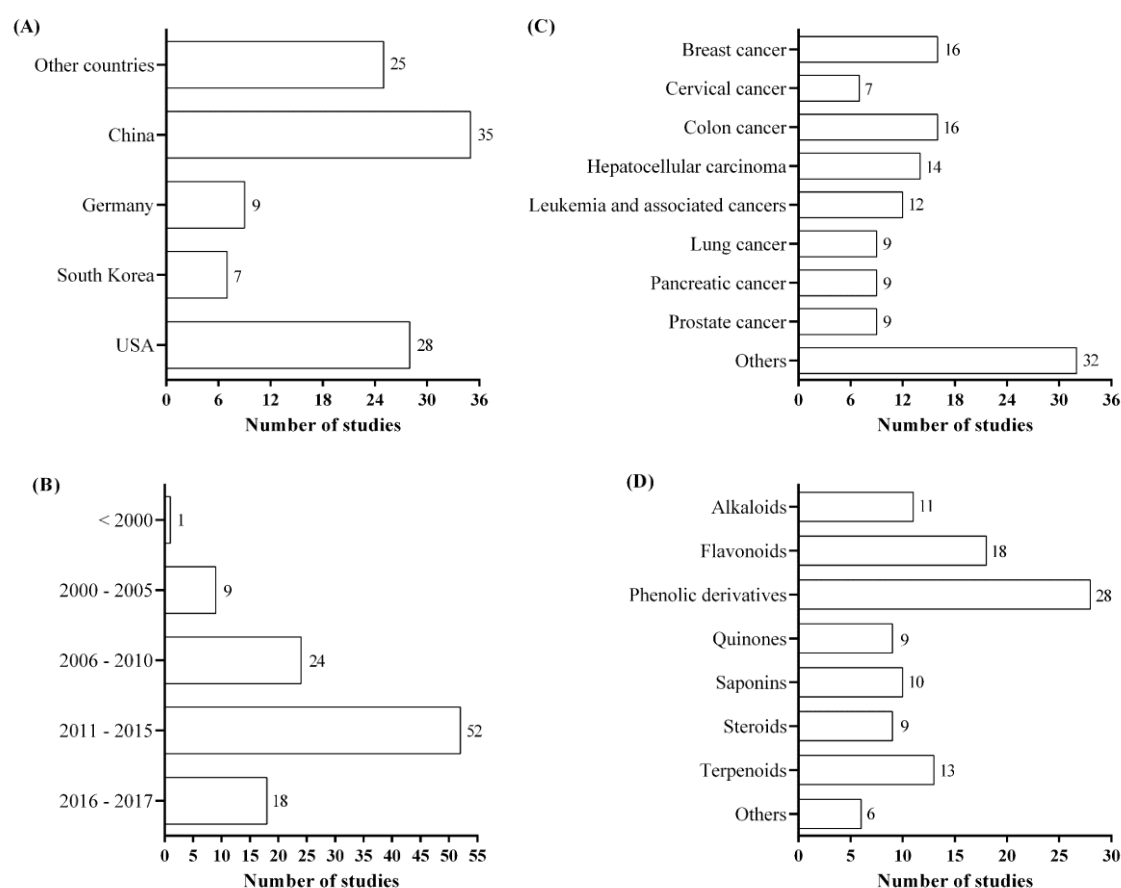


Figure 3. Distribution of the selected studies by country (A), year of publication (B), type of cancer studied (C) and chemical class of natural product evaluated as chemosensitizer (D).

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.

Chemosensitizer	Dose (route)	Combined drug	Dose (route)	Model (animal/sex)	Main outcomes (Cancer)	R	B	Reference
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.

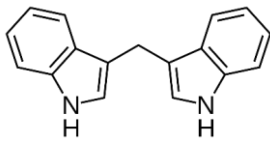
	mg/kg/day (p.o.)		(i.v.)	(Mi/F)	tumor volume and inhibition of angiogenesis in tumor tissue (lung cancer)			(2011) [31]
	200 mg/kg/day (i.g.)	TMZ or CIP	2 mg/kg/day (i.p.)	Xenograft (Mi/F)	Synergistic decrease in tumor volume and weight (glioblastoma)	Y	N	Qi et al. (2013) [33]
Oxymatrine	40 mg/kg/day (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]

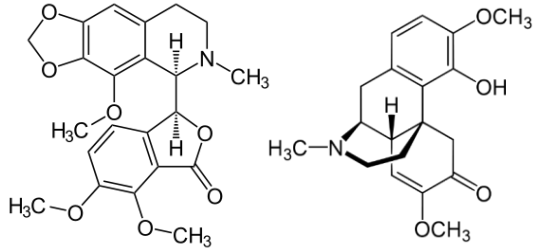
	3 mg/kg/day (i.p.)	OXP	10 mg/kg/twice weekly (i.p.)	Xenograft (Mi/M)	Synergistic decrease in tumor volume and weight, synergistic induction of apoptosis (pancreatic cancer)	Y	N	Li et al. (2015) [117]
α -carotene	5 mg/kg/day (p.o.)	PTX	6 mg/kg/day (i.p.)	Xenograft (Mi/M)	Synergistic decrease in lung metastasis (lung cancer)	Y	N	Liu et al. (2015b) [40]
β -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]
Δ^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.

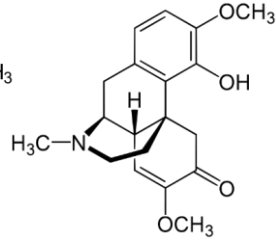
Alkaloids



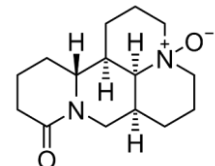
3,3'-diindolylmethane



Noscapine

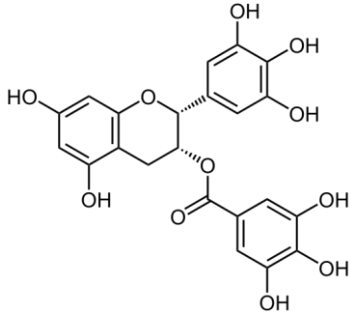


Sinomenine

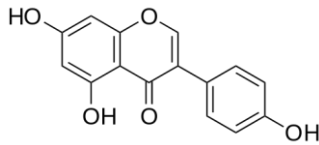


Oxymatrine

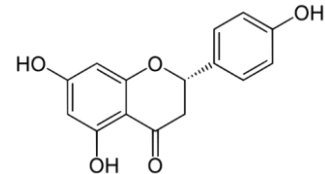
Flavonoids and phenolic derivatives



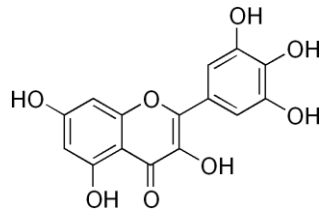
Epigallocatechin-3-gallate



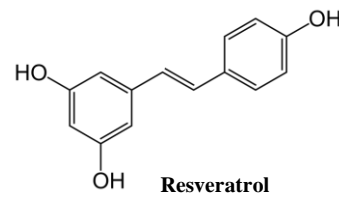
Genistein



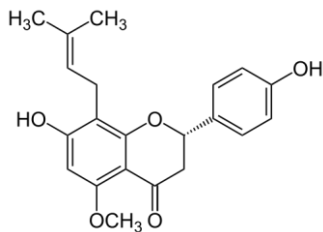
Naringenin



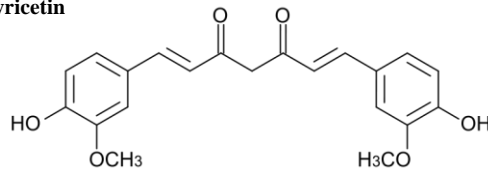
Myricetin



Resveratrol

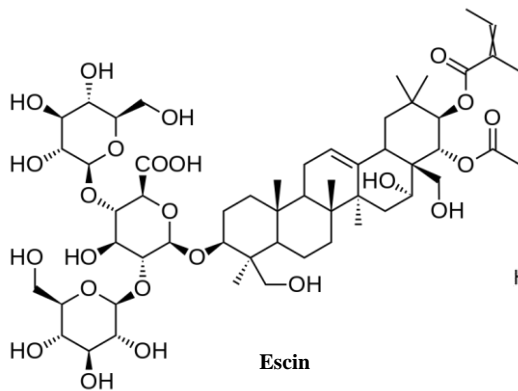


Isoxanthohumol

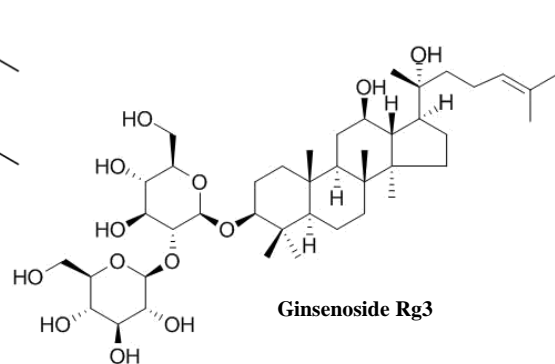


Curcumin

Saponins



Escin



Ginsenoside Rg3

(continued on next page)

(continued)

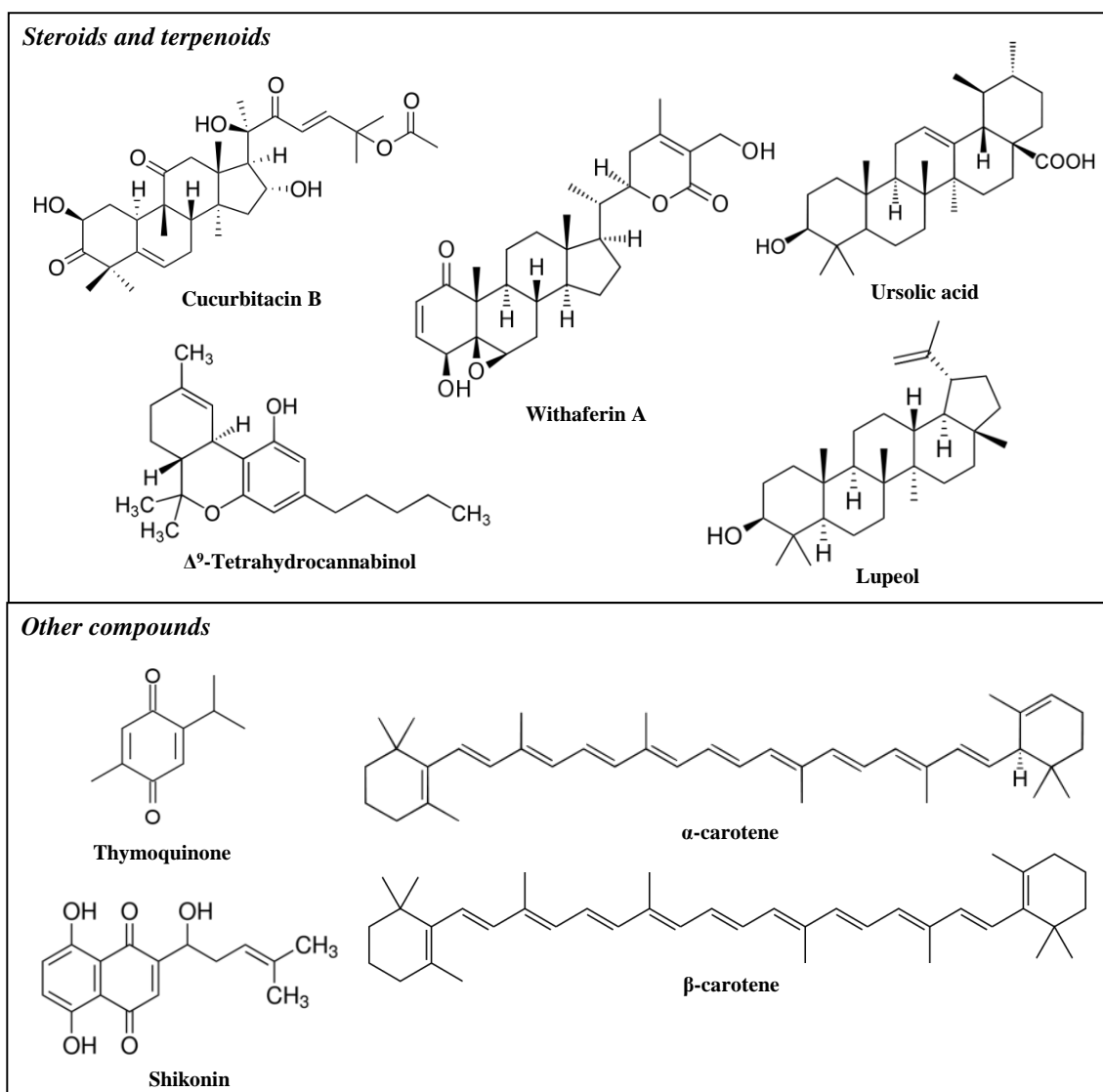


Figure 4. Chemical structure of the major natural compounds evaluated as chemosensitizer agents (*in vitro* and *in vivo* evidences).

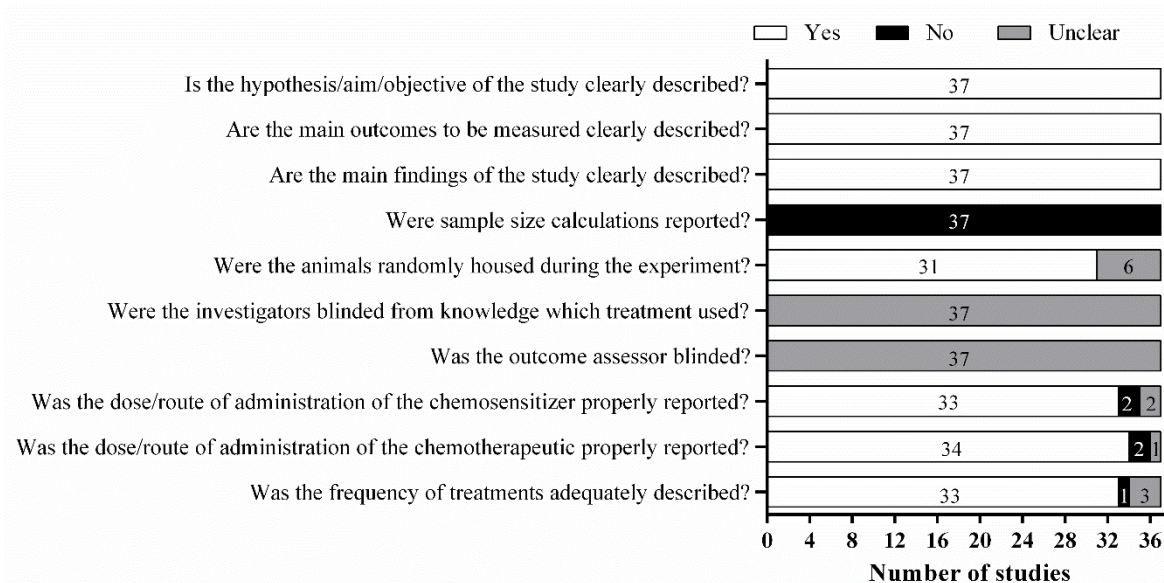


Figure 5. Methodological quality assessment of included *in vivo* studies. *Light bars* indicate the proportion of articles that met each criterion; *dark bars* indicate the proportion of studies that did not and *white gray bars* indicate the proportion of studies with unclear or insufficient answers.

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 κ B (NF- κ 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- κ 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- κ B over time, contributing to chemoresistance of tumor cells. NF- κ 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- κ B is retained in the cytoplasm by its interaction with inhibitors of κ B (I κ B α , I κ B β or I κ B ϵ). However, I κ B kinases (IKKs) are able to phosphorylate I κ B portion, resulting in its subsequent ubiquitination and proteasome-mediated degradation, and consequently in the release of NF- κ B, which then translocates to the nucleus [74, 146]. In this review, we have identified that curcumin down-regulates NF- κ 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- κ B (p65 subunit), I κ B α / β phosphorylation and IKK activation, resulting in synergistic antitumor effect when combined with conventional chemotherapeutic agents [64,87].

NF- κ 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- κ B through activation of IKK [79, 147]. Once available, NF- κ 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- κ 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 μ 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].

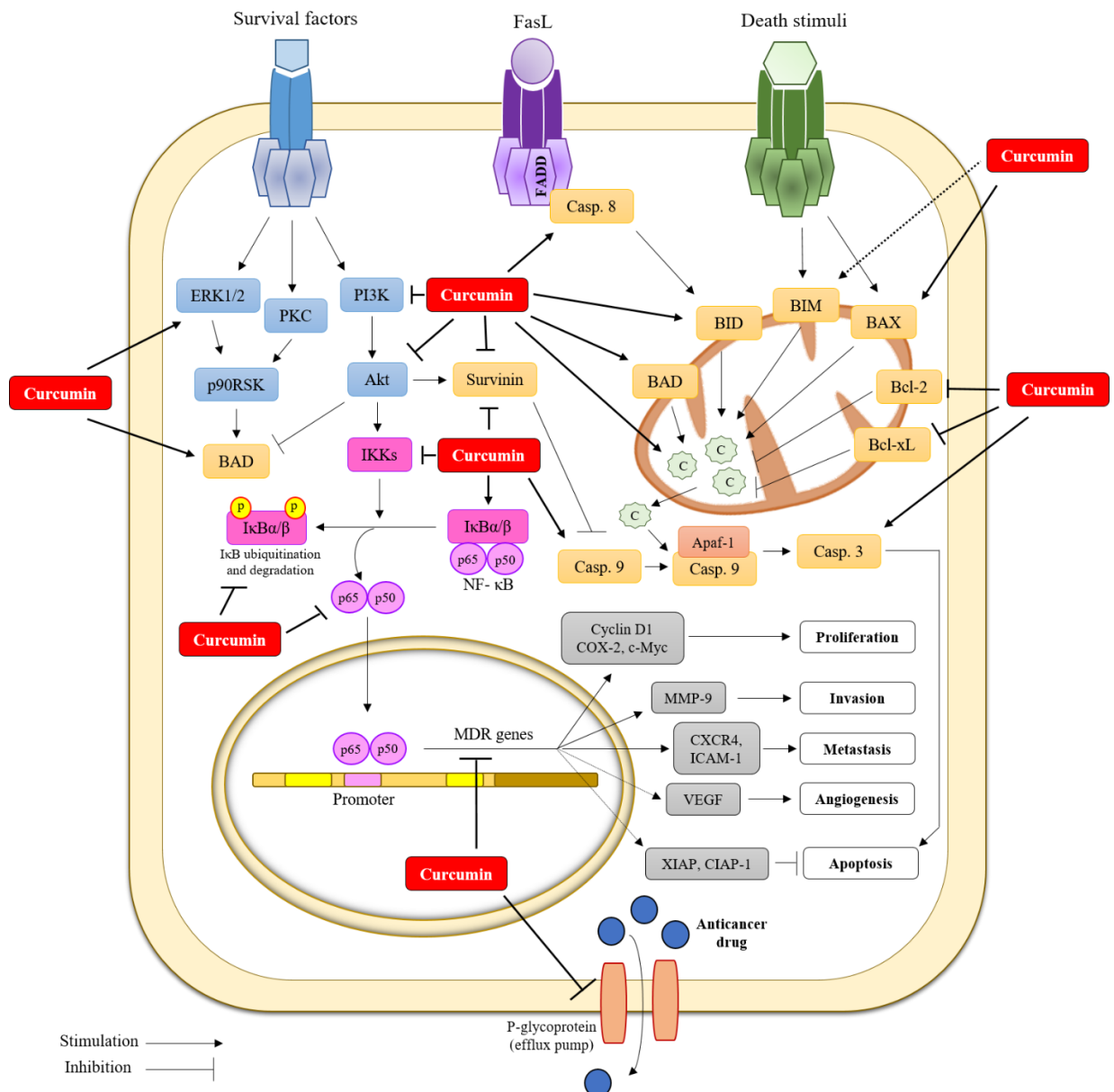


Figure 6. Molecular mechanisms of curcumin-mediated chemosensitization. Curcumin modulates signaling pathways involved in apoptosis, cell proliferation, invasion, metastasis and angiogenesis

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- κ 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).

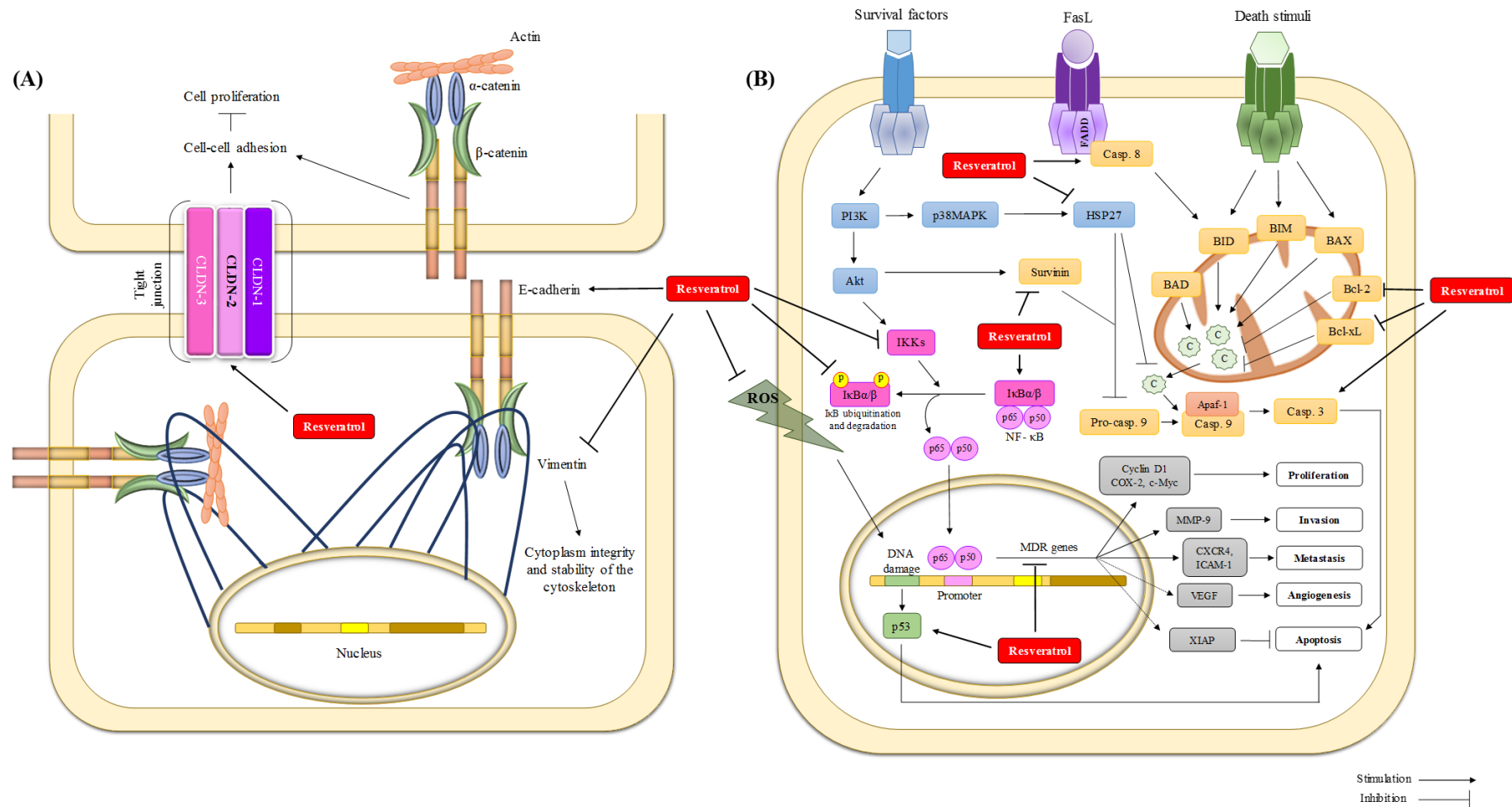


Figure 7. Molecular mechanisms of resveratrol-mediated chemosensitization. Resveratrol interferes in the expression of adhesion molecules and in the stability of the cell cycle (A), and modulates signaling pathways involved in apoptosis, cell proliferation, invasion, metastasis and angiogenesis (B).

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 α -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- κ 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.

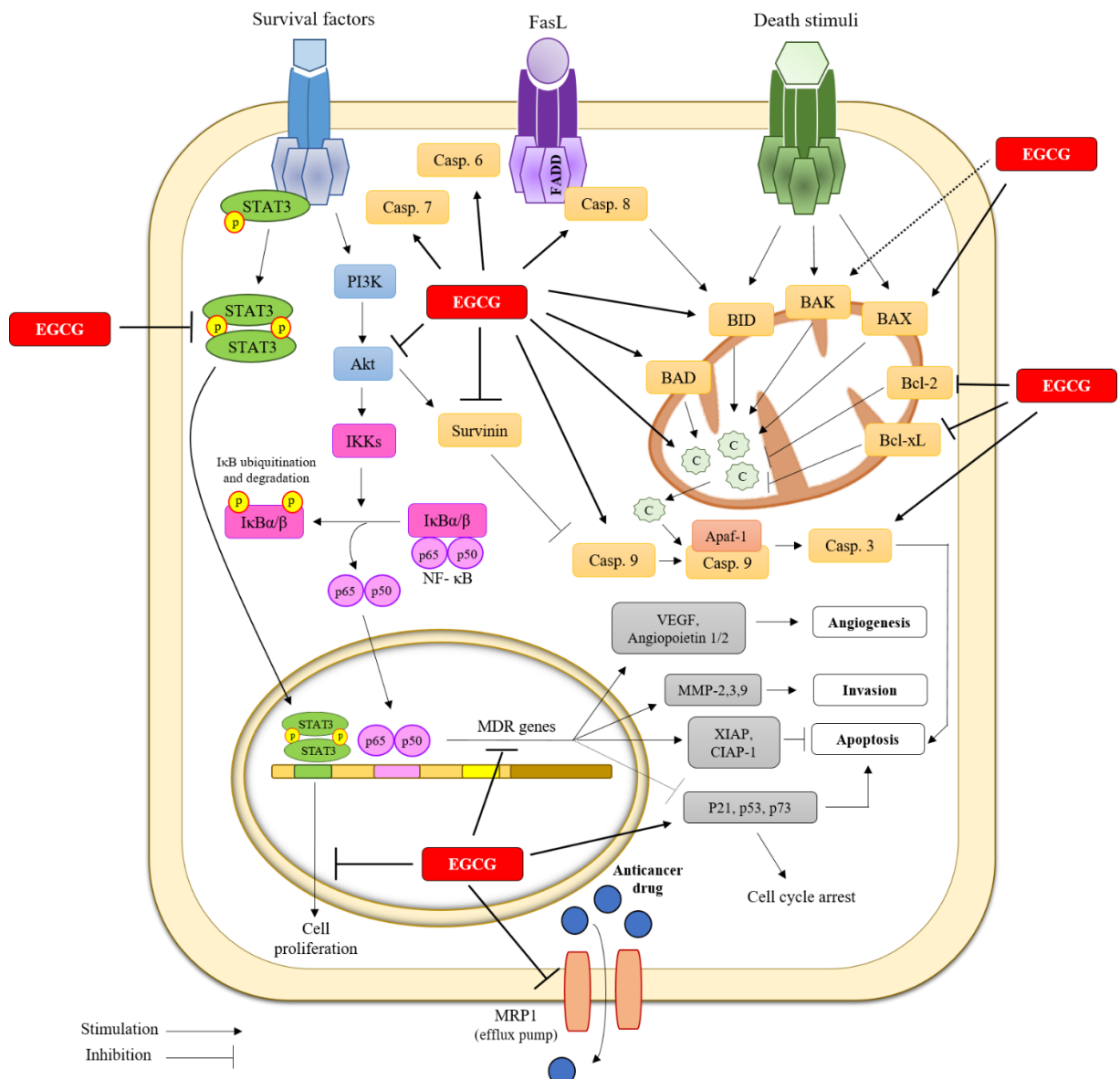


Figure 8. Molecular mechanisms of epigallocatechin-3-gallate (EGCG)-mediated chemosensitization. EGCG modulates signaling pathways involved in apoptosis, cell proliferation, invasion, metastasis and angiogenesis

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.

ACKNOWLEDGEMENTS

We are grateful to the French Ministry of Research and Higher Education for funding RGOJ's PhD grant. We thank the French cancer league (Comité 17 de la Ligue Nationale contre le Cancer) for financial support and the "Cancéropôle Grand Ouest, axe Valorisation des produits de la mer en cancérologie" and Brazilian Society of Pharmacognosy for scientific support.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

- [1] J.S. You, P.A. Jones, Cancer Genetics and Epigenetics: Two Sides of the Same Coin? *Cancer Cell*. 22 (2012) 9–20. doi: 10.1016/j.ccr.2012.06.008.
- [2] T.J. Harris, F. McCormick, The molecular pathology of cancer, *Nat. Rev. Clin. Oncol.* 7 (2010) 251–265. doi: 10.1038/nrclinonc.2010.41.
- [3] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, *Cell*. 144 (2011) 646–674. doi: 10.1016/j.cell.2011.02.013.
- [4] J.W. Shay, W.E. Wright, Role of telomeres and telomerase in cancer, *Semin. Cancer. Biol.* 21 (2011) 349–353. doi: 10.1016/j.semcancer.2011.10.001.
- [5] M. Hassan, H. Watari, A. AbuAlmaaty, et al., Apoptosis and Molecular Targeting Therapy in Cancer, *Biomed. Res. Int.* 2014 (2014) 150845. doi: 10.1155/2014/150845.
- [6] Y.A. Fouad, C. Aanei, Revisiting the hallmarks of cancer, *Am. J. Cancer Res.* 7 (2017) 1016–1036.
- [7] R.S.Y. Wong, Apoptosis in cancer: from pathogenesis to treatment, *J. Exp. Clin. Cancer Res.* 30 (2011) 87. doi: 10.1186/1756-9966-30-87.

- [8] L. Zitvogel, L. Galluzzi, M.J. Smyth, et al., Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance, *Immunity*. 39 (2013) 74–88. doi: 10.1016/j.immuni.2013.06.014.
- [9] T. Otto, P. Sicinski, Cell cycle proteins as promising targets in cancer therapy, *Nat. Rev. Cancer*. 17 (2017) 93–115. doi: 10.1038/nrc.2016.138.
- [10] L. Galluzzi, O. Kepp, M.G.V. Heiden, et al., Metabolic targets for cancer therapy, *Nat. Rev. Drug Discov.* 12 (2013) 829–846. doi: 10.1038/nrd4145.
- [11] G. Housman, S. Byler, S. Heerboth, et al., Drug resistance in cancer: an overview, *Cancers (Basel)*. 6 (2014) 1769–1792. doi: 10.3390/cancers6031769.
- [12] I.A. Cree, P. Charlton, Molecular chess? Hallmarks of anti-cancer drug resistance, *BMC Cancer*. 17 (2017) 10. doi: 10.1186/s12885-016-2999-1
- [13] C. Holohan, S. Van Schaeybroeck, D.B. Longley, et al., Cancer drug resistance: an evolving paradigm, *Nat. Rev. Cancer*. 13 (2013) 714–726. doi: 10.1038/nrc3599.
- [14] S. Shukla, A. Mehta, Anticancer potential of medicinal plants and their phytochemicals: a review, *Braz. J. Bot.* 38 (2015) 199–210. doi: 10.1007/s40415-015-0135-0
- [15] V. Ruiz-Torres, J.A. Encinar, M. Herranz-López, et al., An Updated Review on Marine Anticancer Compounds: The Use of Virtual Screening for the Discovery of Small-Molecule Cancer Drugs, *Molecules*. 22 (2017) E1037. doi: 10.3390/molecules22071037.
- [16] S. Sukhdev, B. Sharma, S.S. Kanwar, et al., Lead Phytochemicals for Anticancer Drug Development, *Front. Plant. Sci.* 7 (2016) 1667. doi: 10.3389/fpls.2016.01667.
- [17] C. Calcabrini, E. Catanzaro, A. Bishayee, et al., Marine Sponge Natural Products with Anticancer Potential: An Updated Review, *Mar. Drugs*. 15 (2017) E310. doi: 10.3390/md15100310.
- [18] R. Kotecha, A. Takami, J.L. Espinoza, Dietary phytochemicals and cancer chemoprevention: a review of the clinical evidence, *Oncotarget*. 7 (2016) 52517–52529. doi: 10.18632/oncotarget.9593.
- [19] H. Wang, T.O. Khor, L. Shu, et al., Plants Against Cancer: A Review on Natural Phytochemicals in Preventing and Treating Cancers and Their Druggability, *Anticancer Agents Med. Chem.* 12 (2012) 1281–1305.

- [20] B.S. Vinod, T.T. Maliekal, R.J. Anto, Phytochemicals as chemosensitizers: from molecular mechanism to clinical significance, *Antioxid. Redox. Signal.* 18 (2013) 1307–1348. doi: 10.1089/ars.2012.4573.
- [21] P. Dandawate, S. Padhye, A. Ahmad, et al., Novel strategies targeting cancer stem cells through phytochemicals and their analogs, *Drug. Deliv. Transl. Res.* 3 (2013) 165–182. doi: 10.1007/s13346-012-0079-x.
- [22] S.A. Hussain, A.A. Sulaiman, C. Balch, et al., Natural Polyphenols in Cancer Chemoresistance, *Nutr. Cancer.* 6 (2016) 879–891. doi: 10.1080/01635581.2016.1192201.
- [23] G. Jacquemin, S. Shirley, O. Micheau, Combining naturally occurring polyphenols with TNF-related apoptosis-inducing ligand: a promising approach to kill resistant cancer cells? *Cell. Mol. Life. Sci.* 67 (2010) 3115–3130. doi: 10.1007/s00018-010-0407-6.
- [24] S.C Gupta, R. Kannappan, S. Reuter, et al., Chemosensitization of tumors by resveratrol, *Ann. N. Y. Acad. Sci.* 1215 (2011) 150–160. doi: 10.1111/j.1749-6632.2010.05852.x.
- [25] D. Moher, A. Liberati, J. Tetzlaff, et al., Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, *PLoS Med.* 6 (2009) e1000097. doi: 10.1371/journal.pmed.1000097.
- [26] C.R. Hooijmans, M.M. Rovers, R.B. de Vries, et al., SYRCLE's risk of bias tool for animal studies, *BMC Med. Res. Methodol.* 14 (2014) 43. doi: 10.1186/1471-2288-14-43.
- [27] P.S. Siqueira-Lima, J.C. Silva, J.S.S. Quintans, et al., Natural products assessed in animal models for orofacial pain – a systematic review, *Braz. J. Pharmacog.* 27 (2017) 124–134. doi: 10.1016/j.bjp.2016.06.005.
- [28] M.Q. Song, J.S. Zhu, J.L. Chen, et al., Synergistic effect of oxymatrine and angiogenesis inhibitor NM-3 on modulating apoptosis in human gastric cancer cells, *World J. Gastroenterol.* 13 (2007) 1788–1793. doi: 10.3748/wjg.v13.i12.1788
- [29] S. Banerjee, Z. Wang, D. Kong, et al., 3,3'-Diindolylmethane enhances chemosensitivity of multiple chemotherapeutic agents in pancreatic cancer, *Cancer Res.* 69 (2009) 5592–5600. doi: 10.1158/0008-5472.CAN-09-0838.
- [30] B. Sung, K.S. Ahn, B.B. Aggarwal, Noscapine, a benzyloquinoline alkaloid, sensitizes leukemic cells to chemotherapeutic agents and cytokines by

- modulating the NF-kappaB signaling pathway, *Cancer Res.* 70 (2010) 3259–3268. doi: 10.1158/0008-5472.CAN-09-4230.
- [31] M.B. Chougule, A. Patel, P. Sachdeva, et al., Enhanced anticancer activity of gemcitabine in combination with nescapine via antiangiogenic and apoptotic pathway against non-small cell lung cancer, *PLoS One*, 6 (2011) e27394. doi: 10.1371/journal.pone.0027394.
- [32] N. Tong, J. Zhang, Y. Chen, et al., Berberine sensitizes multiple human cancer cells to the anticancer effects of doxorubicin *in vitro*, *Oncol. Lett.* 3 (2012) 1263–1267. doi: 10.3892/ol.2012.644.
- [33] Q. Qi, X. Liu, S. Li, et al., Synergistic suppression of nescapine and conventional chemotherapeutics on human glioblastoma cell growth, *Acta. Pharmacol. Sin.* 34 (2013) 930–938. doi: 10.1038/aps.2013.40.
- [34] J. Wang, Z.R. Yang, W.G. Dong, et al., Cooperative inhibitory effect of sinomenine combined with 5-fluorouracil on esophageal carcinoma, *World J. Gastroenterol.* 19 (2013) 8292–8300. doi: 10.3748/wjg.v19.i45.8292.
- [35] N. Guo, A. Yan, X. Gao, et al., Berberine sensitizes rapamycin-mediated human hepatoma cell death *in vitro*, *Mol. Med. Rep.* 10 (2014) 3132–3138. doi: 10.3892/mmr.2014.2608.
- [36] Y. Liu, T. Bi, W. Dai, et al., Oxymatrine synergistically enhances the inhibitory effect of 5-fluorouracil on hepatocellular carcinoma *in vitro* and *in vivo*, *Tumour Biol.* 37 (2016) 7589–7597. doi: 10.1007/s13277-015-4642-1.
- [37] R. Doddapaneni, K. Patel, N. Chowdhury, et al., Nescapine chemosensitization enhances docetaxel anticancer activity and nanocarrier uptake in triple negative breast cancer, *Exp. Cell Res.* 346 (2016) 65–73. doi: 10.1016/j.yexcr.2016.05.006.
- [38] Y. Zhao, Z. Jing, Y. Li, et al., Berberine in combination with cisplatin suppresses breast cancer cell growth through induction of DNA breaks and caspase-3-dependent apoptosis, *Oncol. Rep.* 36 (2016) 567–572. doi: 10.3892/or.2016.4785.
- [39] P. Rajendran, F. Li, K.A. Manu, et al., γ -Tocotrienol is a novel inhibitor of constitutive and inducible STAT3 signalling pathway in human hepatocellular carcinoma: potential role as an antiproliferative, pro-apoptotic and chemosensitizing agent, *Br. J. Pharmacol.* 163 (2011) 283–298. doi: 10.1111/j.1476-5381.2010.01187.x.

- [40] Y.Z. Liu, C.M. Yang, J.Y. Chen, et al., Alpha-carotene inhibits metastasis in Lewis lung carcinoma *in vitro*, and suppresses lung metastasis and tumor growth in combination with taxol in tumor xenografted C57BL/6 mice, *J. Nutr. Biochem.* 26 (2015) 607–615. doi: 10.1016/j.jnutbio.2014.12.012.
- [41] Y. Zhang, X. Zhu, T. Huang, et al., β -Carotene synergistically enhances the anti-tumor effect of 5-fluorouracil on esophageal squamous cell carcinoma *in vivo* and *in vitro*, *Toxicol. Lett.* 261 (2016) 49–58. doi: 10.1016/j.toxlet.2016.08.010.
- [42] S.M. Kim, J.H. Lee, G. Sethi, et al., Bergamottin, a natural furanocoumarin obtained from grapefruit juice induces chemosensitization and apoptosis through the inhibition of STAT3 signaling pathway in tumor cells, *Cancer Lett.* 354 (2014) 153–163. doi: 10.1016/j.canlet.2014.08.002.
- [43] G. Stammer, M. Volm, Green tea catechins (EGCG and EGC) have modulating effects on the activity of doxorubicin in drug-resistant cell lines, *Anticancer Drugs.* 8 (1997) 265–268.
- [44] S. Dhanalakshmi, P. Agarwal, L.M. Glode, et al., Silibinin sensitizes human prostate carcinoma DU145 cells to cisplatin- and carboplatin-induced growth inhibition and apoptotic death, *Int. J. Cancer.* 106 (2003) 699–705.
- [45] K. Chisholm, B.J. Bray, R.J. Rosengren, Tamoxifen and epigallocatechin gallate are synergistically cytotoxic to MDA-MB-231 human breast cancer cells, *Anticancer Drugs.* 15 (2004) 889–897.
- [46] X.H. Peng, P. Karna, R.M. O'Regan, Down-regulation of inhibitor of apoptosis proteins by deguelin selectively induces apoptosis in breast cancer cells, *Mol. Pharmacol.* 71 (2007) 101–111.
- [47] I.A. Siddiqui, A. Malik, V.M. Adhami, et al., Green tea polyphenol EGCG sensitizes human prostate carcinoma LNCaP cells to TRAIL-mediated apoptosis and synergistically inhibits biomarkers associated with angiogenesis and metastasis, *Oncogene.* 27 (2008) 2055–2063.
- [48] A. Shervington, V. Pawar, S. Menon, et al., The sensitization of glioma cells to cisplatin and tamoxifen by the use of catechin, *Mol. Biol. Rep.* 36 (2009) 1181–1186. doi: 10.1007/s11033-008-9295-3.
- [49] F.Y. Zhang, G.J. Du, L. Zhang, et al., Naringenin enhances the anti-tumor effect of doxorubicin through selectively inhibiting the activity of multidrug resistance-associated proteins but not P-glycoprotein, *Pharm. Res.* 26 (2009) 914–925. doi: 10.1007/s11095-008-9793-y.

- [50] C.Y. Jin, C. Park, H.J. Hwang, et al., Naringenin up-regulates the expression of death receptor 5 and enhances TRAIL-induced apoptosis in human lung cancer A549 cells, *Mol. Nutr. Food Res.* 55 (2011) 300–309. doi: 10.1002/mnfr.201000024.
- [51] M.E. Stearns, M. Wang, Synergistic Effects of the Green Tea Extract Epigallocatechin-3-gallate and Taxane in Eradication of Malignant Human Prostate Tumors, *Transl. Oncol.* 4 (2011) 147–156.
- [52] A.S. Hönicke, S.A. Ender, J. Radons, Combined administration of EGCG and IL-1 receptor antagonist efficiently downregulates IL-1-induced tumorigenic factors in U-2 OS human osteosarcoma cells, *Int. J. Oncol.* 41 (2012) 753–758. doi: 10.3892/ijo.2012.1498.
- [53] H. Wu, Y. Xin, C. Xu, et al., Capecitabine combined with (-)-epigallocatechin-3-gallate inhibits angiogenesis and tumor growth in nude mice with gastric cancer xenografts, *Exp. Ther. Med.* 3 (2012) 650–654. doi: 10.3892/etm.2012.448.
- [54] T.W. Kwak, D.H. Kim, C.W. Chung, et al., Synergistic Anticancer Effects of Vorinostat and Epigallocatechin-3-Gallate against HuCC-T1 Human Cholangiocarcinoma Cells, *Evid. Based Complementary Altern. Med.* 2013 (2013) 18515. doi: 10.1155/2013/185158.
- [55] R. Suzuki, Y. Kang, X. Li, et al., Genistein potentiates the antitumor effect of 5-Fluorouracil by inducing apoptosis and autophagy in human pancreatic cancer cells, *Anticancer Res.* 34 (2014) 4685–4692.
- [56] L. Wang, J. Feng, X. Chen, et al., Myricetin enhance chemosensitivity of 5-fluorouracil on esophageal carcinoma *in vitro* and *in vivo*, *Cancer Cell Int.* 14 (2014) 71. doi: 10.1186/s12935-014-0071-2.
- [57] M.S. Abaza, K.Y. Orabi, E. Al-Quattan, et al., Growth inhibitory and chemosensitization effects of naringenin, a natural flavanone purified from *Thymus vulgaris*, on human breast and colorectal cancer, *Cancer Cell Int.* 15 (2015) 46. doi: 10.1186/s12935-015-0194-0.
- [58] P. Wang, S.M. Henning, D. Heber, et al., Sensitization to docetaxel in prostate cancer cells by green tea and quercetin, *J. Nutr. Biochem.* 26 (2015) 408–415. doi: 10.1016/j.jnutbio.2014.11.017.
- [59] J.A. García-Vilas, A.R. Quesada, M.A. Medina, Screening of synergistic interactions of epigallocatechin-3-gallate with antiangiogenic and antitumor compounds, *Synergy.* 3 (2016) 5–13. doi: 10.1016/j.synres.2016.05.001.

- [60] T. Krajnović, G.N. Kaluđerović, L.A. Wessjohann, et al., Versatile antitumor potential of isoxanthohumol: Enhancement of paclitaxel activity *in vivo*, *Pharmacol. Res.* 105 (2016) 62–73. doi: 10.1016/j.phrs.2016.01.011.
- [61] S. Lin, K. Lei, W. Du, et al., Enhancement of oxaliplatin sensitivity in human colorectal cancer by hypericin mediated photodynamic therapy via ROS-related mechanism, *Int. J. Biochem. Cell Biol.* 71 (2016) 24–34. doi: 10.1016/j.biocel.2015.12.003.
- [62] S. Lin, L. Yang, H. Shi, et al., Endoplasmic reticulum-targeting photosensitizer Hypericin confers chemo-sensitization towards oxaliplatin through inducing pro-death autophagy, *Int. J. Biochem. Cell Biol.* 87 (2017) 54–68. doi: 10.1016/j.biocel.2017.04.001.
- [63] S. Anuchapreeda, P. Leechanachai, M.M. Smith, et al., Modulation of P-glycoprotein expression and function by curcumin in multidrug-resistant human KB cells, *Biochem. Pharmacol.* 64 (2002) 573–582.
- [64] T.C. Hour, J. Chen, C.Y. Huang, et al., Curcumin enhances cytotoxicity of chemotherapeutic agents in prostate cancer cells by inducing p21(WAF1/CIP1) and C/EBPbeta expressions and suppressing NF-kappaB activation, *Prostate.* 51 (2002) 211–218.
- [65] S. Fulda, K.M. Debatin, Sensitization for anticancer drug-induced apoptosis by the chemopreventive agent resveratrol, *Oncogene.* 23 (2004) 6702–6711.
- [66] S.L. Wu, Z. J. Sun, L. Yu, et al., Effect of resveratrol and in combination with 5-FU on murine liver cancer, *World J. Gastroenterol.* 10 (2004) 3048–3052.
- [67] B.B. Aggarwal, S. Shishodia, Y. Takada, et al., Curcumin suppresses the paclitaxel-induced nuclear factor-kappaB pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice, *Clin. Cancer Res.* 11 (2005) 7490–7498.
- [68] S.V. Bava, V.T. Puliappadamba, A. Deepti, et al., Sensitization of taxol-induced apoptosis by curcumin involves down-regulation of nuclear factor- κ B and the serine/threonine kinase Akt and is independent of tubulin polymerization, *J. Biol. Chem.* 280 (2005) 6301–6308. doi:10.1074/jbc.M410647200.
- [69] L. Li, B. Ahmed, K. Mehta, R. Kurzrock, Liposomal curcumin with and without oxaliplatin: effects on cell growth, apoptosis, and angiogenesis in colorectal cancer, *Mol. Cancer Ther.* 6 (2007) 1276–1282. doi:10.1158/1535-7163.MCT-06-0556.

- [70] K.S. Chen, Y.C. Hsiao, D.Y. Kuo, et al., Tannic acid-induced apoptosis and - enhanced sensitivity to arsenic trioxide in human leukemia HL-60 cells, *Leuk. Res.* 33 (2009) 297–307. doi:10.1016/j.leukres.2008.08.006.
- [71] K.B. Harikumar, A.B. Kunnumakkara, G. Sethi, et al., Resveratrol, a multitargeted agent, can enhance antitumor activity of gemcitabine *in vitro* and in orthotopic mouse model of human pancreatic cancer, *Int. J. Cancer.* 127 (2010) 257–268. doi:10.1002/ijc.25041.
- [72] A.B. Kunnumakkara, P. Diagaradjane, P. Anand, et al., Curcumin sensitizes human colorectal cancer to capecitabine by modulation of cyclin D1, COX-2, MMP-9, VEGF and CXCR4 expression in an orthotopic mouse model, *Int. J. Cancer.* 125 (2009) 2187–2197. doi:10.1002/ijc.24593.
- [73] Y. Yu, S.S. Kanwar, B.B. Patel, et al., Elimination of Colon Cancer Stem-Like Cells by the Combination of Curcumin and FOLFOX, *Transl. Oncol.* 2 (2009) 321–328. doi:10.1593/tlo.09193.
- [74] W. Hartojo, A.L. Silvers, D.G. Thomas, et al., Curcumin promotes apoptosis, increases chemosensitivity, and inhibits nuclear factor kappaB in esophageal adenocarcinoma., *Transl. Oncol.* 3 (2010) 99–108. doi:10.1593/tlo.09235.
- [75] S. V. Bava, C.N. Sreekanth, A.K.T. Thulasidasan, et al., Akt is upstream and MAPKs are downstream of NF- κ B in paclitaxel-induced survival signaling events, which are down-regulated by curcumin contributing to their synergism, *Int. J. Biochem. Cell Biol.* 43 (2011) 331–341. doi:10.1016/j.biocel.2010.09.011.
- [76] C.N. Sreekanth, S. V Bava, E. Sreekumar, et al., Molecular evidences for the chemosensitizing efficacy of liposomal curcumin in paclitaxel chemotherapy in mouse models of cervical cancer, *Oncogene.* 30 (2011) 3139–3152. doi:10.1038/onc.2011.23.
- [77] A.M.M. Osman, H.M. Bayoumi, S.E. Al-Harthi, et al., Modulation of doxorubicin cytotoxicity by resveratrol in a human breast cancer cell line, *Cancer Cell Int.* 12 (2012) 47. doi:10.1186/1475-2867-12-47.
- [78] E.M. Saleh, R.A. El-awady, N.A. Eissa, et al., Antagonism between curcumin and the topoisomerase II inhibitor etoposide: A study of DNA damage, cell cycle regulation and death pathways, *Cancer Biol. Ther.* 13 (2012) 1058–1071. doi:10.4161/cbt.21078.
- [79] H. Wang, Q.R. Geng, L. Wang, et al., Curcumin potentiates antitumor activity of L-asparaginase via inhibition of the AKT signaling pathway in acute

- lymphoblastic leukemia., *Leuk. Lymphoma.* 53 (2012) 1376–82. doi:10.3109/10428194.2011.649478.
- [80] F. Amiri, A.H. Zarnani, H. Zand, et al., Synergistic anti-proliferative effect of resveratrol and etoposide on human hepatocellular and colon cancer cell lines, *Eur. J. Pharmacol.* 718 (2013) 34–40. doi:10.1016/j.ejphar.2013.09.020.
- [81] J. Díaz-Chávez, M.A. Fonseca-Sánchez, E. Arechaga-Ocampo, et al., Proteomic Profiling Reveals That Resveratrol Inhibits HSP27 Expression and Sensitizes Breast Cancer Cells to Doxorubicin Therapy, *PLoS One.* 8 (2013) 1–11. doi:10.1371/journal.pone.0064378.
- [82] M. Shakibaei, A. Mobasheri, C. Lueders, et al., Curcumin Enhances the Effect of Chemotherapy against Colorectal Cancer Cells by Inhibition of NF- κ B and Src Protein Kinase Signaling Pathways, *PLoS One.* 8 (2013) 1–13. doi:10.1371/journal.pone.0057218.
- [83] L.J. Carlson, B. Cote, A.W. Alani, et al., Polymeric micellar co-delivery of resveratrol and curcumin to mitigate *in vitro* doxorubicin-induced cardiotoxicity, *J. Pharm. Sci.* 103 (2014) 2315–2322. doi:10.1002/jps.24042.
- [84] H. Qian, Y. Yang, X. Wang, Curcumin enhanced adriamycin-induced human liver-derived Hepatoma G2 cell death through activation of mitochondria-mediated apoptosis and autophagy, *Eur. J. Pharm. Sci.* 43 (2011) 125–131. doi:10.1016/j.ejps.2011.04.002.
- [85] C. Buhrmann, P. Shayan, P. Kraehe, et al., Resveratrol induces chemosensitization to 5-fluorouracil through up-regulation of intercellular junctions, Epithelial-to-mesenchymal transition and apoptosis in colorectal cancer, *Biochem. Pharmacol.* 98 (2015) 51–58. doi:10.1016/j.bcp.2015.08.105.
- [86] B. Cote, L.J. Carlson, D.A. Rao, et al., Combinatorial resveratrol and quercetin polymeric micelles mitigate doxorubicin induced cardiotoxicity *in vitro* and *in vivo*, *J. Control. Release.* 213 (2015) 128–133. doi:10.1016/j.jconrel.2015.06.040.
- [87] M. Shakibaei, P. Kraehe, B. Popper, et al., Curcumin potentiates antitumor activity of 5-fluorouracil in a 3D alginate tumor microenvironment of colorectal cancer, *BMC Cancer.* 15 (2015) 250. doi:10.1186/s12885-015-1291-0.
- [88] M.S.I. Abaza, M. Afzal, R.J. Al-Attayah, et al., Methylferulate from *Tamarix aucheriana* inhibits growth and enhances chemosensitivity of human colorectal

- cancer cells: possible mechanism of action., *BMC Complement. Altern. Med.* 16 (2016) 384. doi:10.1186/s12906-016-1358-8.
- [89] E. Ooko, T. Alsalim, B. Saeed, et al., Modulation of P-glycoprotein activity by novel synthetic curcumin derivatives in sensitive and multidrug-resistant T-cell acute lymphoblastic leukemia cell lines, *Toxicol. Appl. Pharmacol.* 305 (2016) 216–233. doi:10.1016/j.taap.2016.06.002.
- [90] A.K. Tyagi, S. Prasad, M. Majeed, et al., Calebin A, a novel component of turmeric, suppresses NF- κ B regulated cell survival and inflammatory gene products leading to inhibition of cell growth and chemosensitization, *Phytomedicine.* 34 (2017) 171–181. doi:10.1016/j.phymed.2017.08.021.
- [91] S.H. Jafri, J. Glass, R. Shi, et al., Thymoquinone and cisplatin as a therapeutic combination in lung cancer: *In vitro* and *in vivo*., *J. Exp. Clin. Cancer Res.* 29 (2010) 87. doi:10.1186/1756-9966-29-87.
- [92] F. Li, P. Rajendran, G. Sethi, Thymoquinone inhibits proliferation, induces apoptosis and chemosensitizes human multiple myeloma cells through suppression of signal transducer and activator of transcription 3 activation pathway, *Br. J. Pharmacol.* 161 (2010) 541–554. doi:10.1111/j.1476-5381.2010.00874.x.
- [93] S.K. Sandur, M.K. Pandey, B. Sung, et al., 5-hydroxy-2-methyl-1,4-naphthoquinone, a vitamin K3 analogue, suppresses STAT3 activation pathway through induction of protein tyrosine phosphatase, SHP-1: potential role in chemosensitization., *Mol. Cancer Res.* 8 (2010) 107–18. doi:10.1158/1541-7786.MCR-09-0257.
- [94] K. Effenberger-Neidnicht, R. Schobert, Combinatorial effects of thymoquinone on the anti-cancer activity of doxorubicin, *Cancer Chemother. Pharmacol.* 67 (2011) 867–874. doi: 10.1007/s00280-010-1386-x.
- [95] Y. Wang, Y. Zhou, G. Jia, et al., Shikonin suppresses tumor growth and synergizes with gemcitabine in a pancreatic cancer xenograft model: Involvement of NF- κ B signaling pathway, *Biochem. Pharmacol.* 88 (2014) 322–333. doi:10.1016/j.bcp.2014.01.041.
- [96] W. Daqian, W. Chuandong, Q. Xinhua, et al., Chimaphilin inhibits proliferation and induces apoptosis in multidrug resistant osteosarcoma cell lines through insulin-like growth factor-I receptor (IGF-IR) signaling, *Chem. Biol. Interact.* 237 (2015) 25–30. doi:10.1016/j.cbi.2015.05.008.

- [97] G. He, G. He, R. Zhou, et al., Enhancement of cisplatin-induced colon cancer cells apoptosis by shikonin, a natural inducer of ROS *in vitro* and *in vivo*, *Biochem. Biophys. Res. Commun.* 469 (2016) 1075–1082. doi:10.1016/j.bbrc.2015.12.100.
- [98] J. Song, Z. Zhao, X. Fan, et al., Shikonin potentiates the effect of arsenic trioxide against human hepatocellular carcinoma *in vitro* and *in vivo*, *Oncotarget.* 7 (2016). doi:10.18632/oncotarget.12041.
- [99] Y. Wang, H.L. Lu, Y.D. Liu, et al., Cryptotanshinone sensitizes antitumor effect of paclitaxel on tongue squamous cell carcinoma growth by inhibiting the JAK/STAT3 signaling pathway, *Biomed. Pharmacother.* 95 (2017) 1388–1396. doi:10.1016/j.biopha.2017.09.062.
- [100] C.H. Choi, G. Kang, Y.D. Min, Reversal of P-glycoprotein-mediated multidrug resistance by protopanaxatriol ginsenosides from Korean red ginseng, *Planta Med.* 69 (2003) 235–240. doi:10.1055/s-2003-38483.
- [101] S.M. Kim, S.Y. Lee, J.S. Cho, et al., Hong, Combination of ginsenoside Rg3 with docetaxel enhances the susceptibility of prostate cancer cells via inhibition of NF- κ B, *Eur. J. Pharmacol.* 631 (2010) 1–9. doi:10.1016/j.ejphar.2009.12.018.
- [102] Z.J. Ming, Y. Hu, Y.H. Qiu, et al., Synergistic effects of β -aescin and 5-fluorouracil in human hepatocellular carcinoma SMMC-7721 cells, *Phytomedicine.* 17 (2010) 575–580. doi:10.1016/j.phymed.2009.12.009.
- [103] Y.W. Wang, S.J. Wang, Y.N. Zhou, et al., Escin augments the efficacy of gemcitabine through down-regulation of nuclear factor- κ B and nuclear factor- κ B-regulated gene products in pancreatic cancer both *in vitro* and *in vivo*, *J. Cancer Res. Clin. Oncol.* 138 (2012) 785–797. doi:10.1007/s00432-012-1152-z.
- [104] L.Q. Yang, B. Wang, H. Gan, et al., Enhanced oral bioavailability and anti-tumour effect of paclitaxel by 20(s)-ginsenoside Rg3 *in vivo*, *Biopharm. Drug Dispos.* 33 (2012) 425–436. doi: 10.1002/bdd.1806.
- [105] H. Wang, Z. Zhai, N. Li, et al., Steroidal saponin of *Trillium tschonoskii*. Reverses multidrug resistance of hepatocellular carcinoma, *Phytomedicine.* 20 (2013) 985–991. doi:10.1016/j.phymed.2013.04.014.
- [106] L. Chang, B. Huo, Y. Lv, et al., Ginsenoside Rg3 enhances the inhibitory effects of chemotherapy on esophageal squamous cell carcinoma in mice, *Mol. Clin. Oncol.* 2 (2014) 1043–1046. doi:10.3892/mco.2014.355.

- [107] Y.J. Lee, S. Lee, J.N. Ho, et al., Synergistic antitumor effect of ginsenoside Rg3 and cisplatin in cisplatin-resistant bladder tumor cell line, *Oncol. Rep.* 32 (2014) 1803–1808. doi:10.3892/or.2014.3452.
- [108] Z. Liu, Q. Zheng, W. Chen, et al., Chemosensitizing effect of Paris Saponin I on Camptothecin and 10-hydroxycamptothecin in lung cancer cells via p38 MAPK, ERK, and Akt signaling pathways, *Eur. J. Med. Chem.* 125 (2017) 760–769. doi:10.1016/j.ejmech.2016.09.066.
- [109] Z. Yuan, H. Jiang, X. Zhu, et al., Ginsenoside Rg3 promotes cytotoxicity of Paclitaxel through inhibiting NF- κ B signaling and regulating Bax/Bcl-2 expression on triple-negative breast cancer, *Biomed. Pharmacother.* 89 (2017) 227–232. doi:10.1016/j.biopha.2017.02.038.
- [110] T.J. Lee, H.J. Um, D.S. Min, et al., Withaferin A sensitizes TRAIL-induced apoptosis through reactive oxygen species-mediated up-regulation of death receptor 5 and down-regulation of c-FLIP, *Free Radic. Biol. Med.* 46 (2009) 1639–1649. doi:10.1016/j.freeradbiomed.2009.03.022.
- [111] W. Chen, A. Leiter, D. Yin, et al., Cucurbitacin B inhibits growth, arrests the cell cycle, and potentiates antiproliferative efficacy of cisplatin in cutaneous squamous cell carcinoma cell lines, *Int. J. Oncol.* 37 (2010) 737–743.
- [112] G.B. Iwanski, D.H. Lee, S. En-Gal, et al., Cucurbitacin B, a novel *in vivo* potentiator of gemcitabine with low toxicity in the treatment of pancreatic cancer, *Br. J. Pharmacol.* 160 (2010) 998–1007. doi:10.1111/j.1476-5381.2010.00741.x.
- [113] D.H. Lee, N.H. Thoennissen, C. Goff, et al., Synergistic effect of low-dose cucurbitacin B and low-dose methotrexate for treatment of human osteosarcoma, *Cancer Lett.* 306 (2011) 161–170. doi:10.1016/j.canlet.2011.03.001.
- [114] S.M. Cohen, R. Mukerji, B.N. Timmermann, et al., A novel combination of withaferin A and sorafenib shows synergistic efficacy against both papillary and anaplastic thyroid cancers, *Am. J. Surg.* 204 (2012) 895–901. doi:10.1016/j.amjsurg.2012.07.027.
- [115] M.Y. Fong, S. Jin, M. Rane, et al., Withaferin a synergizes the therapeutic effect of doxorubicin through ROS-mediated autophagy in ovarian cancer, *PLoS One.* 7 (2012) 1–16. doi:10.1371/journal.pone.0042265.

- [116] F.F. El-Senduny, F.A. Badria, A.M. EL-Waseef, et al., Approach for chemosensitization of cisplatin-resistant ovarian cancer by cucurbitacin B, *Tumor Biol.* 37 (2016) 685–698. doi:10.1007/s13277-015-3773-8.
- [117] X. Li, F. Zhu, J. Jiang, et al., Synergistic antitumor activity of withaferin A combined with oxaliplatin triggers reactive oxygen species-mediated inactivation of the PI3K/AKT pathway in human pancreatic cancer cells, *Cancer Lett.* 357 (2015) 219–230. doi:10.1016/j.canlet.2014.11.026.
- [118] M. Ben-Eltriki, S. Deb, H. Adomat, et al., Calcitriol and 20(S)-protopanaxadiol synergistically inhibit growth and induce apoptosis in human prostate cancer cells, *J. Steroid Biochem. Mol. Biol.* 158 (2016) 207–219. doi:10.1016/j.jsbmb.2015.12.002.
- [119] M.L. Holland, J.A. Panetta, J.M. Hoskins, et al., The effects of cannabinoids on P-glycoprotein transport and expression in multidrug resistant cells, *Biochem. Pharmacol.* 71 (2006) 1146–1154. doi:10.1016/j.bcp.2005.12.033.
- [120] S. Sieber, G. Gdynia, W. Roth, et al., Combination treatment of malignant B cells using the anti-CD20 antibody rituximab and the anti-malarial artesunate, *Int. J. Oncol.* 35 (2009) 149–158.
- [121] Y. He, F. Liu, L. Zhang, et al., Growth inhibition and apoptosis induced by lupeol, a dietary triterpene, in human hepatocellular carcinoma cells., *Biol. Pharm. Bull.* 34 (2011) 517–22. doi:10.1248/bpb.34.517.
- [122] R. Kannaiyan, H.S. Hay, P. Rajendran, et al., Celastrol inhibits proliferation and induces chemosensitization through down-regulation of NF- κ B and STAT3 regulated gene products in multiple myeloma cells, *Br. J. Pharmacol.* 164 (2011) 1506–1521. doi:10.1111/j.1476-5381.2011.01449.x.
- [123] S. Torres, M. Lorente, F. Rodriguez-Fornes, et al., A Combined Preclinical Therapy of Cannabinoids and Temozolomide against Glioma, *Mol. Cancer Ther.* 10 (2011) 90–103. doi:10.1158/1535-7163.MCT-10-0688.
- [124] S. Prasad, V.R. Yadav, B. Sung, et al., Ursolic acid inhibits growth and metastasis of human, colorectal cancer in an orthotopic nude mouse model by targeting multiple cell signaling pathways: Chemosensitization with capecitabine, *Clin. Cancer Res.* 18 (2012) 4942–4953. doi:10.1158/1078-0432.CCR-11-2805.

- [125] J. Tong, S. Yin, Y. Dong, et al., Pseudolaric Acid B Induces Caspase-Dependent Apoptosis and Autophagic Cell Death in Prostate Cancer Cells, *Phytother. Res.* 27 (2013) 885–891. doi: 10.1002/ptr.4808.
- [126] Y. Wang, Y. Zhou, H. Zhou, et al., Pristimerin Causes G1 Arrest, Induces Apoptosis, and Enhances the Chemosensitivity to Gemcitabine in Pancreatic Cancer Cells, *PLoS One.* 7 (2012) 1–12. doi:10.1371/journal.pone.0043826.
- [127] E. Butturini, A.C. Prati, G. Chiavegato, et al., Mild oxidative stress induces S-glutathionylation of STAT3 and enhances chemosensitivity of tumoural cells to chemotherapeutic drugs, *Free Radic. Biol. Med.* 65 (2013) 1322–1330. doi:10.1016/j.freeradbiomed.2013.09.015.
- [128] F. Liu, Y. He, Y. Liang, et al., PI3-kinase inhibition synergistically promoted the anti-tumor effect of lupeol in hepatocellular carcinoma., *Cancer Cell Int.* 13 (2013) 108. doi:10.1186/1475-2867-13-108.
- [129] O.A. Bamodu, W.C. Huang, D.T.W. Tzeng, et al., Ovatodiolide sensitizes aggressive breast cancer cells to doxorubicin, eliminates their cancer stem cell-like phenotype, and reduces doxorubicin-associated toxicity, *Cancer Lett.* 364 (2015) 125–134. doi:10.1016/j.canlet.2015.05.006.
- [130] Y. Liu, T. Bi, W. Dai, et al., Lupeol enhances inhibitory effect of 5-fluorouracil on human gastric carcinoma cells, *Naunyn. Schmiedebergs. Arch. Pharmacol.* 389 (2016) 477–484. doi:10.1007/s00210-016-1221-y.
- [131] M.A. Reis, O.B. Ahmed, G. Spengler, et al., Jatrophone diterpenes and cancer multidrug resistance - ABCB1 efflux modulation and selective cell death induction, *Phytomedicine.* 23 (2016) 968–978. doi:10.1016/j.phymed.2016.05.007.
- [132] B.C. Baguley, Multiple drug resistance mechanisms in cancer, *Mol. Biotechnol.* 46 (2010) 308–316. doi: 10.1007/s12033-010-9321-2.
- [133] Q. Wu, Z. Yang, Y. Nie, et al., Multi-drug resistance in cancer chemotherapeutics: mechanisms and lab approaches, *Cancer Lett.* 347 (2014) 159–166. doi: 10.1016/j.canlet.2014.03.013.
- [134] W.Y. Wu, J.J. Hou, H.L. Long, et al., TCM-based new drug discovery and development in China, *Chin. J. Nat. Med.* 12 (2014) 241–250. doi: 10.1016/S1875-5364(14)60050-9.

- [135] J. Liu, S. Wang, Y. Zhang, et al., Traditional Chinese medicine and cancer: History, present situation, and development, *Thorac. Cancer*. 6 (2015) 561–569. doi: 10.1111/1759-7714.12270.
- [136] A. Richmond, Y. Su, Mouse xenograft models vs GEM models for human cancer therapeutics, *Dis. Model Mech.* 1 (2008) 78–82. doi: 10.1242/dmm.000976.
- [137] J. Jung, Human Tumor Xenograft Models for Preclinical Assessment of Anticancer Drug Development, *Toxicol. Res.* 30 (2014) 1–5. doi: 10.5487/TR.2014.30.1.001.
- [138] M.F. Festing, D.G. Altman, Guidelines for the design and statistical analysis of experiments using laboratory animals, *ILAR J.* 43 (2002) 244–258.
- [139] J.A. Hirst, J. Howick, J.K. Aronson, et al., The need for randomization in animal trials: an overview of systematic reviews, *Plos One*. 9 (2014) e98856. doi: 10.1371/journal.pone.0098856.
- [140] P.J. Karanicolas, F. Farrokhyar, M. Bhandari, Blinding: Who, what, when, why, how? *Can. J. Surg.* 53 (2010) 345–348.
- [141] J.E. Aguilar-Nascimento, Fundamental steps in experimental design for animal studies, *Acta. Cir. Bras.* 20 (2005) 2–8.
- [142] V.S. Govindarajan, Turmeric: chemistry, technology, and quality, *Crit Rev Food Sci Nutr.* 12 (1980) 199–301.
- [143] N. Chainani-Wu, Safety and anti-inflammatory activity of curcumin: a component of tumeric (*Curcuma longa*), *J. Altern. Complement. Med.* 9 (2003) 161–168.
- [144] B. Chandran, A. Goel, A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis, *Phytother. Res.* 26 (2012) 1719–1725. doi: 10.1002/ptr.4639.
- [145] S.C. Gupta, S. Patchva, B.B. Aggarwal, Therapeutic Roles of Curcumin: Lessons Learned from Clinical Trials, *AAPS J.* 15 (2013) 195–218. doi: 10.1208/s12248-012-9432-8.
- [146] M. Karin, Nuclear factor- κ B in cancer development and progression, *Nature*. 441 (2006) 431–436.
- [147] I. Vivanco, C.L. Sawyers, The phosphatidylinositol 3-Kinase AKT pathway in human cancer, *Nat. Rev. Cancer*. 2 (2002) 489–501.

- [148] E.M. Varoni, A.F.L. Faro, J. Sharifi-Rad, et al., Anticancer Molecular Mechanisms of Resveratrol, *Front. Nutr.* 3 (2016). doi: 10.3389/fnut.2016.00008.
- [149] N.C. Whitlock, S.J. Baek, The anticancer effects of resveratrol – Modulation of transcription factors, *Nutr. Cancer.* 64 (2012) 493–502. doi: 10.1080/01635581.2012.667862.
- [150] J.K. Aluyen, Q.N. Ton, T. Tran, et al., Resveratrol: potential as anticancer agent, *J. Diet Suppl.* 9 (2012) 45–56. doi: 10.3109/19390211.2011.650842.
- [151] J. Acunzo, C. Andrieu, V. Baylot, et al., Hsp27 as a therapeutic target in cancers, *Curr. Drug Targets.* 15 (2014) 423–431.
- [152] A. Satelli, S. Li, Vimentin in cancer and its potential as a molecular target for cancer therapy, *Cell. Mol. Life Sci.* 68 (2011) 3033–3046. doi: 10.1007/s00018-011-0735-1.
- [153] Y. Sakamoto, N. Terashita, T. Muraguchi, et al., Effects of epigallocatechin-3-gallate (EGCG) on A549 lung cancer tumor growth and angiogenesis, *Biosci. Biotechnol. Biochem.* 77 (2013) 1799–1803.
- [154] H. Fujiki, S. Yoshizawa, T. Horiuchi, et al., Anticarcinogenic effects of (-)-epigallocatechin gallate, *Prev. Med.* 21 (1992) 503–509.
- [155] C. Braicu, C.D. Gherman, A. Irimie, et al., Epigallocatechin-3-Gallate (EGCG) inhibits cell proliferation and migratory behaviour of triple negative breast cancer cells, *J. Nanosci. Nanotechnol.* 13 (2013) 632–637.
- [156] S. Shankar, S. Ganapathy, S.R. Hingorani, et al., EGCG inhibits growth, invasion, angiogenesis and metastasis of pancreatic cancer, *Front. Biosci.* 1 (2008) 440–452.
- [157] J.D. Lambert, C.S. Yang, Mechanisms of cancer prevention by tea constituents, *J. Nutr.* 133 (2013) 3262S–3267S.