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Chapter

Cytotoxic and Antimicrobial Activities of Quinones Isolated from Different Organism

Nimsi Campos-Xolalpa, Julia Pérez-Ramos, Ana Esquivel-Campos, Cuauhtemoc Pérez-González, Leonor Sánchez-Pérez and Salud Pérez-Gutiérrez

Abstract

Cancer is a group of related diseases in which there is uncontrolled cell growth that spreads to the surrounding tissues and damages them. Cancer remains the disease with the leading cause of death worldwide, and incidence and mortality are increasing rapidly. The main cancer treatment is chemotherapy; however, the compounds used in this treatment have serious side effects for this reason, is necessary to develop new therapeutic strategies. Natural products are an excellent pharmacological alternative for the treatment of cancer and infections. In search of new compounds with cytotoxic and antimicrobial activity, we have found quinones that have a high pharmacological potency in the treatment of these health problems. Quinones are an aromatic system of one or diketone and are mainly isolated from plants, fungi, bacteria, and other organisms. These compounds are secondary metabolites derived from the oxidation of hydroquinones; they include benzoquinones, naphthoquinones, anthraquinones, and polyquinones. This review summarizes the activity of 152 anticancer and 30 antimicrobial quinones.

Keywords: quinones, cancer, cytotoxic, antimicrobial, natural product

1. Introduction

Cancer is a group of a collection of related diseases where there is uncontrolled cell growth and spread into surrounding tissues, producing damage to them. In many cases, these cells form tumors and some cancer cells travel through the lymphatic system or blood to other places of the body and form new tumors.

Cancer remains the disease with major cause of death globally. In 2018, there were reported about 18 million new cases of cancer [1] and approximately 9.6 million deaths from this disease [2]; in addition, all over the world, the incidence and mortality of cancer are increasing. The risk of incidence of cancer is associated with age, infections, and human habits like poor diet, consumption of alcohol, tobacco, and others [3]; also, there are genetic predisposition and immune conditions [4].

Diseases due to the infections of bacteria and fungi are a very important health problem throughout the world. In 2019, the incidence of infection transmitted by

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food and water increased. The treatment of infection by bacteria is the administration of antibiotics; however, these drugs have been losing effectiveness because there is increased bacterial drug resistance [5]. The main causes of bacterial resistance are unnecessary prescriptions [6] and the unregulated antibiotics sale in many countries, leading to inadequate and unnecessary consumption [7]. Then, infections treatments become more expensive and have less effective.

From ancient times, natural products have been used in the treatment of different diseases, for example, in Egypt around 1550 BC, the "Ebers Papyrus" reported the use of 700 drugs [8]. Nowadays, natural products are an important source of compounds with great potential for the treatment of infections and different forms of cancer [9].

Quinones are an important family of natural products. They have a variety of biological effects, such as anticancer and antimicrobial activities [10, 11]. The 1,4-naphthoquinones, since ancient times, have been used as cosmetics for coloring skin, as well as the treatment of some diseases. These compounds have several activities like anti-inflammatory, antiviral, anticancer, and antibacterial, among others.

For example, juglone and plumbagin show an antimicrobial effect on bacteria and fungi, and they are defensive compounds in the plant. Cytosporaquine A-D and physcion exhibited cytotoxic activity against several human cell cancer lines.

The cytotoxic and antimicrobial activities of 1,4 naphthoquinones are due mainly to two carbonyl groups present in these compounds, which can accept one or two electrons to form a semiquinone radical or di-anion species and for their acid–base properties [10].

The present review focuses on the anticancer and antimicrobial activities of 182 quinones isolated from natural sources in the last 5 years (**Tables 1** and **2**).

2. Anticancer and antimicrobial activity of quinones obtained from plants, animals, and microorganisms

The incidence of cancer has increased; in 2018, around 9.6 million deaths in the world were due to this disease. The drugs used in chemotherapy have side effects and the cancer cells can have resistance to these drugs. Therefore, the study of new molecules with anticancer activity has become important.

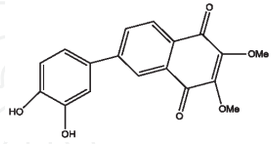
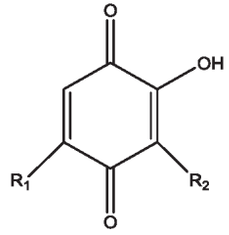
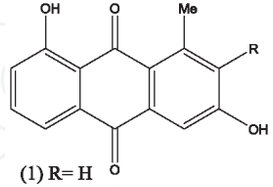
Infectious diseases are an international health public problem, especially in undeveloped countries. For the treatment of these diseases are used antibiotics; however, several microorganisms present resistance to these drugs.

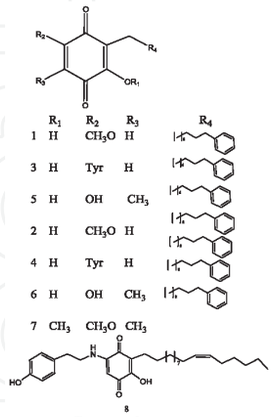
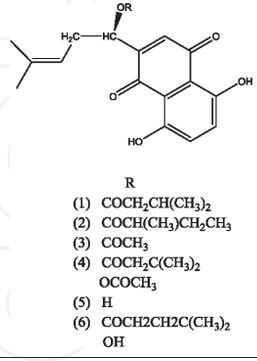
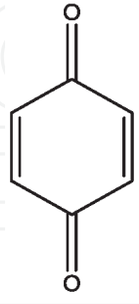
The search for new compounds with these activities has become important. Plants, marine organisms, fungi, and bacteria are natural sources to obtain substances with pharmacological effects.

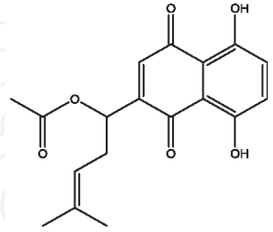
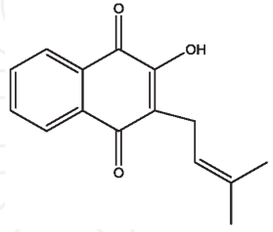
Quinones are natural products with different pharmacological activities, such as anticancer and antimicrobial effects. These compounds can be obtained by synthesis or the structure modified to increase their activity.

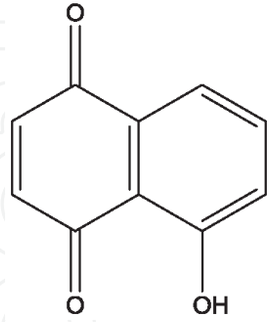
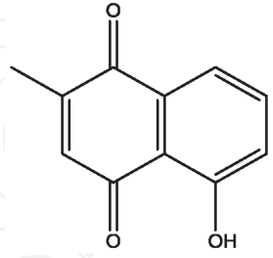
This chapter shows the revision of the literature generated in the last 5 years of quinones isolated from 65 plant species, bacteria, fungi, algae, or sponges. The plants were the most different species studied, followed by fungi with 10 species, Streptomyces with 4 strain investigated, and bacteria with only one studied. Nowadays, the study of marine organisms has become more important, with 3 species of sponges studied and from which these compounds have been isolated, and there was 1 scorpion studied.

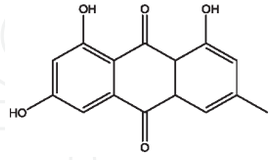
The cytotoxic properties of isolated quinones in the period 2015 to 2020 were mainly determined by in vitro and in vivo studies. This was due to some factors such as the sensitivity of these tests and the consumption of small amounts of

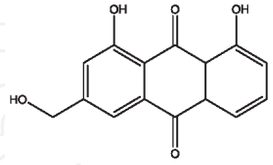
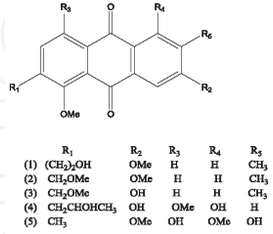
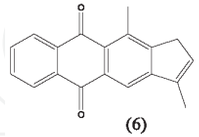
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Plants				
7-(3′,4′-dihydroxy-benzene)-2,3-dimethoxy-1,4-naphthoquinone. (ajaniquinone). *Ajania salicifolia*		MTT assay Hela HepG2 K562	IC_{50} (μM) 19.68 28.71 13.75	[12]
2-hydroxy-5-ethoxy-3-nonyl-1,4-benzoquinone (1). 5-*O*-butyl-embelin (2). 5-O-methylembelin (3). 5-O-methyl-rapanone (4). 5-O-ethylembelin (5). *Aegiceras corniculatum*	 R1 / R_2 1) $OCCH_2CH_3$ / C_9H_{19} 2) $OC(CH_2)2CH_3$ / $C11H_{23}$ 3) OCH_3 / $C_{11}H_{23}$ 4) OCH_3 / $C_{13}H_{27}$ 5) $OCH2CH_3$ / $C_{11}H_{23}$	MTT assay	IC_{50} μM HL-60 HepG2 BGC-823 A2780 (1) 18 48.2 24 20 (2) 8.77 38.6 9.70 14.48 (3) 8.79 43.08 10.63 15.60 (4) 7.60 40.10 10.40 14.50 (5) 11.65 > 100 13.07 10.58	[13]
Aloesaponarin II (1). Aloesaponarin I (2). *Aloe megalacantha*	 (1) R= H (2) R= COOMe	CAF KB-3-1	IC_{50} μM (1) 0.98 (2) 16	[14]

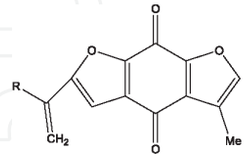
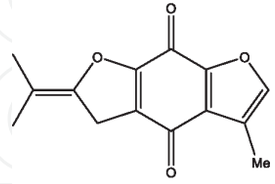
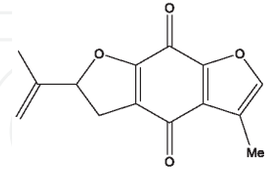
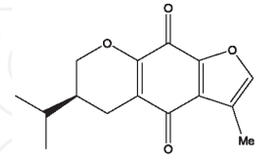
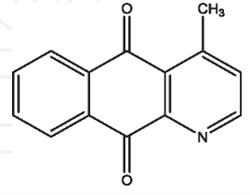
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Ardisiaquinone A (1) Ardisiaquinone B (2) Ardisiaquinone C (3) Ardisiaquinone D (4) Ardisiaquinone E (5) Ardisiaquinone F (6) Ardisiaquinone G (7) Ardisiaquinone H (8) *Ardisia quinquegona*		MTT assay A549	IC_{50} μM (1) 55.7 (2) 44.2 (3) 67.9 (4) 75.6 (5) 12.7 (6) 15.2 (7) 47.5 (8) 67.0	[15]
Isovalerylalkannin (1) α-methyl-n-butyl alkannin (2) Acetylalkanni (3) β-acetoxy isovalerylalkannin (4) Alkannin (5) 4-hydroxy 4-methyl valeryl alkannin (6) *Arnebia densiflora*		MTT assay L929 HeLa HEp-2	IC_{50} μg/mL Range 26.34–172.35	[16]
Benzoquinone *Artemisia asiática*		MTT assay A431 SYF	IC_{50} μM 54.1 52.3	[17]

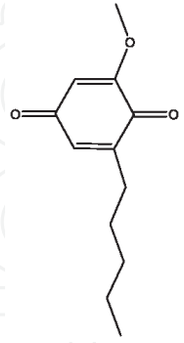
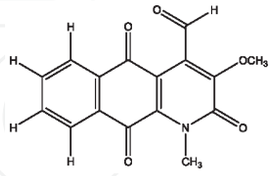
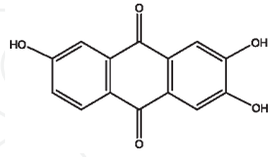
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Acetylshikonin *Lithospermum erythrorhizon* *Onosma visianii*		WST-1 cell viability assay HepG2 MTT assay MDA-MB231 4 T1 MDA-MB231 HCT-116	IC_{50} μM 2 IC_{50} μM 24 h 48 h 72 h 9.11 3.34 1.83 4.98 2.61 1.74 IC_{50} μg/mL 72 h 80.2 24.6	[18] [19] [20]
Shikonin *Lithospermum erythrorhizon*. Different species of *Boraginaceae* family		MTT assay HL-60 Western blotting flow cytometry D gel electrophoresis MTT assay MDA-MB231 4 T1 Immunofluorescence microscopy Experiments *in vivo* MHTBDE Huh7	IC_{50} μM 3.83 at 48 h Induced apoptosis in HL-60 strong alteration in cell proteome ERP57 is overexpressed in AML cells and is downregulated by shikonin IC_{50} μM 24 h 48 h 72 h 4.48 2.31 1.13 1.79 1.02 0.83 shikonin-mediated suppression of β-catenin signaling via increased levels of GSK-3β in MDA-MB-231 cells Shikonin inhibits lung metastasis and β-catenin signaling in NOD/SCID mice inoculated with MDA-MB-231 cells. IC_{50} M $5 X10^{-6}$	[21] [19] [22]

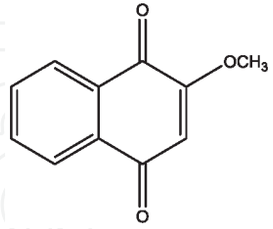
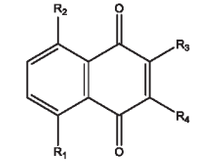
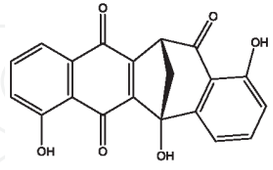
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Juglone (5-hydroxy-1,4-naphthalenedione) *Juglans nigra* *Juglans mandshurica*		MTT assay F98 BGC-823 HCT-15 K562 HepG-2 WST-8 assay U87 SHG62 SHG66	% cell viability (50 μM) 20% (5 μM) 41% (0.5 μM) 59% IC_{50} μM 9.6 27.8 35.5 8.14 Cell viability % (10, 20, and 40 μM) 85, 60, 38 88, 62, 41 80, 55, 35	[23] [24] [25] [26]
Plumbagin *Nempenthes alata* Different species of *Plumbago* *Rumex dentatus, R. abyssinicus, R. usambarensis, R. bequaertii, R. ruwenzoriensis, R. crispus; Plumbago zeylanica,Myrsine Africana, Maesa lanceolata, Rapanea melanphloes, Aloe Saponaria* Several plants of the families: *Plumbaginaceae, Iridaceae, Drosophyllaceae, Droseraceae, Ebenceae* and *Nepenthaceae*		MTT assay MCF7 SK-OV-3 In mice bearing MCF7 cell xenografts MCF-10A MDA-MB231 MCF-7 Single cell gel electrophoresis assay. Clonogenic assay, Migration assay Western blot analysis NR assay A549 SPC212 DLD-1 Caco-2 MCF-7 HepG2 CRL2120. Annexin V-FITC binding assay MTT; Comet assay; PCR 786–0 cells	IC_{50} μM 3.5 13.1 Reduced tumor growth and weight without apparent side effects. Exerted its growth suppressive activity in MCF-7 by inducing apoptotic-related proteins. This compound is cytotoxic and caused cell membrane rupture in starting from 7.5 μM. Increase in the tail moment parameter with 7.5 μM. 3 1.5 3 Induced cytotoxicity in human breast cancer cells along with cell cycle arrest, DNA damage and cell death leading to apoptosis. Also found to suppress the telomerase activity in cancer cells accompanied by telomere attrition. IC_{50} μM 1.14	[27] [28] [29] [30]

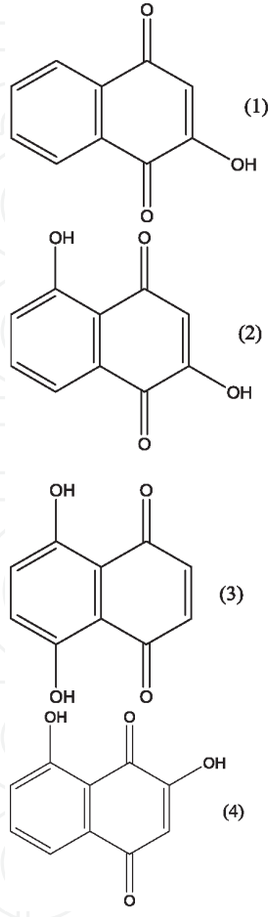
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
			0.27 0.98 0.07 0.06 1.01 67.66 Reduced mRNA levels of MTOR and BCL2, and it did not affect the expression of CYP-encoding genes.	
Emodin (1,3,8-trihydroxy-6-methyl anthraquinone), *Rumex dentatus, R. abyssinicus, R. usambarensis, R. bequaertii, R. ruwenzoriensis, R. crispus; Plumbago zeylanica,Myrsine Africana, Maesa lanceolata, Rapanea melanphloes, Aloe saponaria* *Rheum palmatum* *Rhamnus sphaerosperma*		NR assay. A549 SPC212 DLD-1 Caco-2 MCF-7 HepG2 CRL2120. Flow cytometric assay Combination of IDH2 knockdown and emodin treatment on cell cycle disturbance. Cytomorphological Viability HaCaT SiHa C33A HSC-3 Annexin-V Cell Caspase-3 Activity Emodin using 12.5–50 μg/mL Western Blot DNA Damage Analysis	IC_{50} μM 66.3 99.31 77.28 73.63 37.57 71.7 >148.15 Suppression of IDH2 activity results in perturbation of the cellular redox balance and, ultimately, exacerbate emodin-induced apoptotic cell death in B16F10 cells. This result suggests that the combination of IDH2 downregulation and emodin treatment has negative effects on cancer cell growth Showed higher cytotoxic effects Induced apoptosis and necrosis independent of the caspase-3 activation pathway decreased the activation of AKT in all tumor cells, induction of reversible damage (DNA). Changed the Levels of BAX and BCL-2 Inhibited AKT.	[29] [31] [32]

Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Aloe-emodin (AE) *Rheum palmatum* and *Aloe vera*		Formation of AE-derived glutathione conjugate (AE-GSH) and incubations containing AE and GSH, along with 3′-phosphoadenosine-5′-phosphosulfate (PAPS). The apoptotic induction by inverted phase contrast and fluorescence microscopes were used to evaluate apoptotic induction. Flow cytometry was used to determine the effects of aloe emodin on ΛΨm and cell cycle phase distribution.	AE undergoes sulfation, and the resulting AE-derived sulfate is chemically reactive to thiols. The phase II metabolism of AE may be a factor responsible for AE-induced cytotoxicity. This compound inhibits cancer cell growth MIAPaCa-2 and PANC-1 cell lines mediated by both ways, cell cycle arrest and loss of mitochondrial membrane potential.	[33] [34]
Fistulaquinones A (1). Fistulaquinones B(2). Fistulaquinones C (3). Isorhodoptilometrin-1-methyl ether (4). 7-hydroxyemodin-68-methyl ether (5). Sterequinone A (6). *Cassia fstula*	 (1) $(CH_2)_2OH$ OMe H H CH_3 (2) CH_2OMe OMe H H CH_3 (3) CH_2OMe OH H H CH_3 (4) $CH_2CHOHCH_3$ OH OMe OH H (5) CH_3 OMe OH OMe OH  (6)	MTT-assay	IC_{50} μM NB4 A549 SHSYSY (1) 6.2 > 10 8.4 (2) >10 5.5 > 10 (3) 9 > 10 > 10 (4) 2.8 4.3 3.6 (5) >10 > 10 > 10 (6) 8.8 7.4 > 10 PC3 MCF7 (1) >10 > 10 (2) >10 > 10 (3) 7.2 > 10 (4) 4.2 5 (5) 9.4 > 10 (6) >10 5.5	[35]

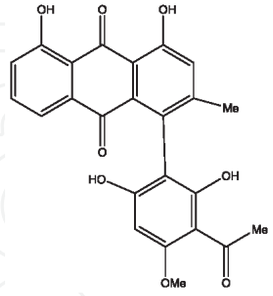
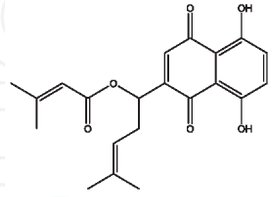
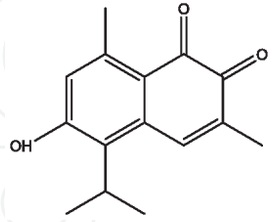
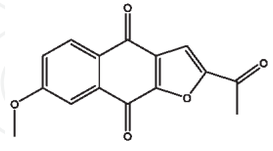
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Cyperaquinone (1) Hydroxycyperaquinone (2) Dihydrocyperaquinone (3) Tetrahydrocyperaquinone(4) Scabequinone (5) *Cyperus spp.*	 R (1) CH_2 (2) CH_2OH  (3)  (4)  (5)	MTT assay Annexin V/7-AAD	IC_{50} μM A549 AGS MRC-5 (1) 11.3 3.0 8.7 (2) 3.0 1.7 1.7 (3) 45.3 1.8 > 50 (4) >50 > 50 > 50 (5) 46.6 27.4 28.7 None of the five compounds exert an effect upon caspase-9 activity nor caspase-3.	[36]
Cleistopholine *Enicosanthellum pulchrum*		MTT assay CAOV-3 SKOV-3 Assessment of apoptosis morphology using acridine orange 86 (AO)/propidium iodide (PI) double staining Annexin-V-FITC.	IC_{50} μM 61.4 67.3 CAOV-3 cells showed morphological changes, evidenced by cell membrane blebbing, chromatin compression and formation of apoptotic bodies.	[37]

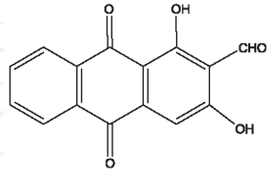
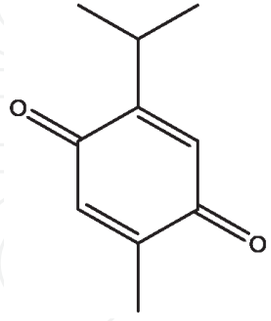
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
		Caspase 3, 8 and 9 Real-time PCR Western blot	Stimulated caspases 3 and 9 upregulated the mRNA expression levels of Bax, caspase 3 and caspase 9	
Primin *Eugenia hiemalis*		MTT assay K562 Jurkat MM.1S	IC_{50} μM 24 h 48 h 72 h 7.54 4.93 2.65 4.16 1.50 0.55 5.31 5.11 1.36 Apoptosis appears to be related to a decreased Bcl-2 expression and increased Bax expression	[38]
marcanine G *Goniothalamus marcanii*		SRB assay A549 MCF-7 MRCS	IC_{50} μM 14.87 15.18 15.45	[39]
2,7-Dihydroxy-3-methylanthraquinone (DDMN) *Hedyotis difusa*		MTT assay SGC-7901 Flow cytometry assay. Xenograft assay	IC_{50} μM 20.92 Induces death by apoptosis. Tumor growth on nude mice could be significantly inhibited during the 20 days period (40 mg / kg / d)	[40]

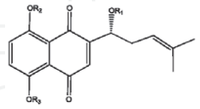
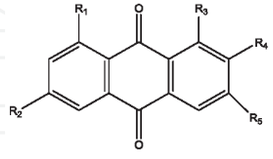
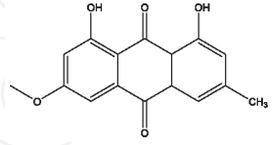
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
2-methoxy-1,4-naphthoquinone *Impatiens glandulifera*		MTT assay A549 SKMEL-28 V373	IC_{50} μM. 3 2 3	[41]
5-methoxy-1,4-naphthoquinone (1). 5,8-dihydroxy-1,4-naphthoquinone (2). 2-hydroxy-1,4-naphthoquinone (3). 2,5-dihydroxy-1,4-naphthoquinone (4). 3,5-dihydroxy-1,4-naphthoquinone (5). 3-methoxy juglone (6). 2-methoxy juglone (7). 3-ethoxy juglone (8). 2-ethoxy juglone (9). Engelharquinone (10). *Juglans mandshurica*	 R_1 R_2 R_3 R_4 (1) OCH_3 H H H (2) OH OH H H (3) H H OH H (4) OH H OH H (5) OH H H OH (6) OH H H OCH_3 (7) OH H OCH_3 H (8) OH H H OCH_2CH_3 (9) OH H OC_2H_5 H  (10)	MTT assay HepG-2	IC_{50} μM (1) 68.72 (2) 16.11 (3) 18.83 (4) 15.37 (5) 7.33 (6) 43.54 (7) 22.38 (8) 30.42 (9) 32.51 (10) 34.80	[25]

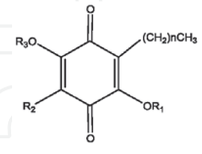
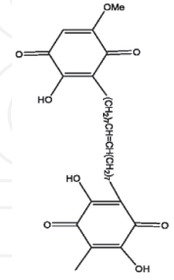
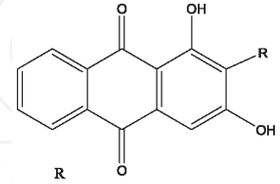
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
2-hydroxy-1,4-naphthoquinone (1). 2,5-dihydroxy-1,4-naphthoquinone (2). 5,8-dihydroxy-1,4-naphthoquinone (3). 3,5-dihydroxy-1,4-naphthoquinone (4). *Juglans mandshurica*		MTT Assay	IC_{50} μM BGC-823 HCT-15 K562 (1) —— 37.4 —— (2) 33.8 97.9 39.7 (3) 28.2 —— —— (4) 19.0 —— ——	[24]

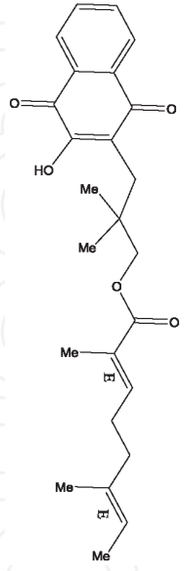
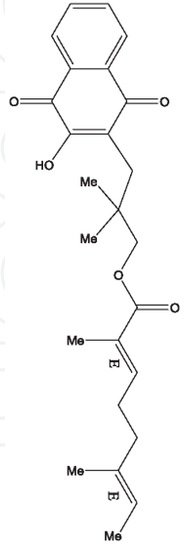
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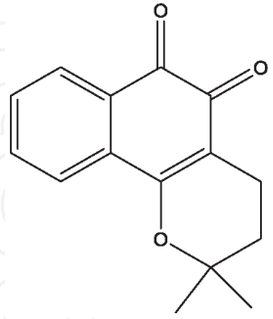
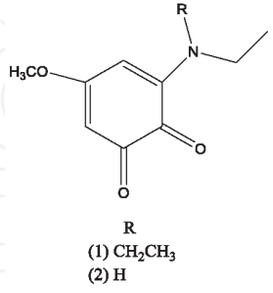
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Knipholone *Kniphofia foliosa* Hochst		MTT assay Jurkat HEK29 SH-SY5Y	Cell viability % 62–95% at 50 μM	[42]
β,β-dimethylacrylshikonin *Lithospermum erythrorhizon*		MTT assay MDA MB231 4 T1	IC_{50} μM 24 h 48 h 72 h 18.7 11.6 4.30 14.7 7.88 4.13	[19]
Mansonone-G (MG). *Mansonia gagei*		SRB assay MCF HeLa HCT-116 HepG2	IC_{50} μM 23 18.8 63.4 49.4	[43]
2-acetyl-7-methoxynaphtho[2,3-b]furan-4,9-quinone *Milletia versicolor*		The resazurin reduction assay CCRF-CEM CEM/ADR5000 MDA-MB231 MDAB231/*BCRP* HCT116 *(p53+/+)* HCT116*(p53−/−)* U87MG U87MG.*ΔEGFR* HepG2 AML12	IC_{50} μg/mL 0.16 0.28 0.58 0.89 0.27 0.61 0.27 0.26 0.22 >40	[44]

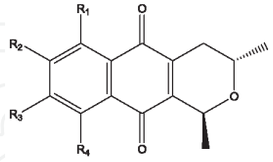
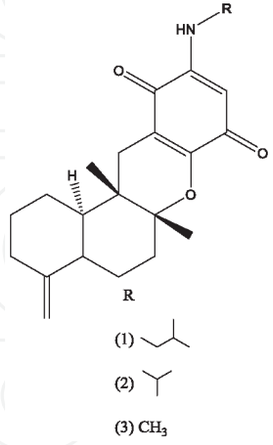
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Nordamnacanthal (NDAM) *Morinda citrifolia* L		MTT assay TBE assay In vivo study of the antitumor effect of NDAM using 4 T1-bearing BALB/C mice. Flow cytometry Immunophenotyping analysis of CD3, CD4 and CD8-stained splenocytes.	IC_{50} µg/mL MDA-MB-231 4TI MCF-7 12.5 12.5 11 1.2 10 8 NDAM reduced the 4 T1 tumor size and weight. Cease the tumor progression of 4 T1 cells *in vivo*. Induced apoptosis in MCF-7, MDA-MB231 and 4 T1 cells *in vitro* NDAM regulated several immune markers in tumor-bearing mice	[45]
Thymoquinone *Nigella sativa*		MTT assay EMT6/P MCF-7 T47D Vero-normal MRC-5 Neuro-2a Wound healing assay	IC_{50} µM. 393 55 85 45 IC_{50} µg/mL Non-covered plates 2.95 EVA capmat™ covered plates 1.72 IC_{50}, µM 24 h 48 h 20 40 Inhibitory effect on the migration of Neuro-2a cells was mediated through the suppression of MMP-2 and MMP-9 expression.	[46] [47] [48]

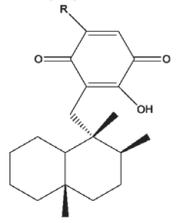
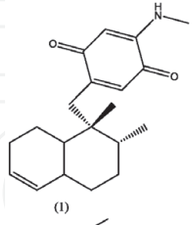
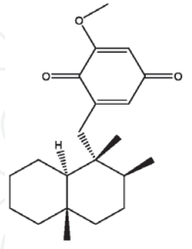
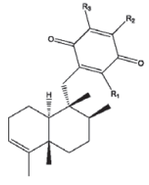
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Deoxyshikonin (1). Isobutyrylshikonin (2). α-methylbutyrylshikonin (3). β- hydroxyisovalerylshikonin (4). 5,8-*O*-dimethyl isobutyrylshikonin (5). 5,8-*O*-dimethyl deoxyshikonin (6). *Onosma visianii*	 R_1 R_2 R_3 (1) H H H (2)  H H (3)  H H (4)  H H (5)  CH_3 CH_3 (6) H CH_3 CH_3	MTT cell viability assay Cell cycle analysis	IC_{50} μg/mL 72 h MDA-MB-231 HCT-116 (1) 119 98 (2) 425 202 (3) 86 15 (4) 205 301 (5) 412 128 (6) 392 485 All compounds induce cell cycle arrest in tumor cell lines.	[20]
1-hydroxy-6,8-dimethoxy-3-methylanthracene-9, 10-dione (1). 8-hydroxy1,3-dimethoxy-6-methylanthraquinone (2). xanthopurpurin (3). 2-methyl-1,3,6-trihydroxy-9,10-anthraquinone (4). *Osmunda japonica*	 R_1 R_2 R_3 R_4 R_5 (1) OH CH_3 OCH_3 H OCH_3 (2) OCH_3 OCH_3 OH H CH_3 (3) H H OH H OH (4) H OH OH CH_3 OH	MTT assay Hela HepG2 A549	IC_{50} μg/mL Weak activity	[49]
Physcion *Osmunda japonica* *Rhamnus sphaerosperma*		MTT assay Hela, HepG2 A549 Cytomorphological Viability HaCaT SiHa C33A HSC-3 Annexin-V Cell Caspase-3 Activity Physcion using 12.5–50 μg/mL Western Blot DNA Damage Analysis	IC_{50} μg/mL Weak activity Showed higher cytotoxic effects Induced apoptosis and necrosis independent of the caspase-3 activation pathway decreased the activation of AKT in all tumor cells, induction of reversible damage (DNA). Changed the Levels of BAX and BCL-2 Inhibited AKT.	[49] [32]

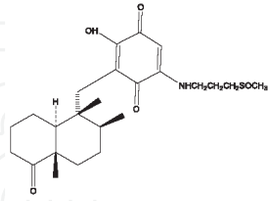
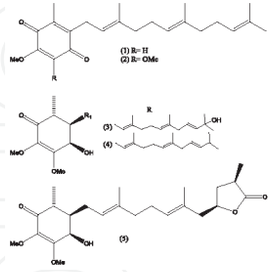
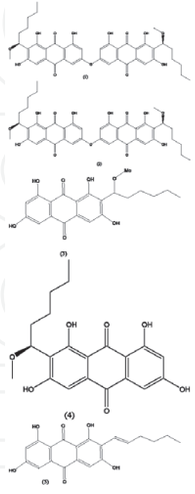
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
2,5-dihydroxy-3-heptyl-2,5-cyclohexadiene-1,4-dione (1) 2,5-dihydroxy-3-tridecyl-2,5-cyclohexadiene-1,4-dione or rapanone (2). 2,5-dihydroxy-3-pentadecyl-2,5-cyclohexadiene-1,4-dione (3). Adisiaquinone B (4) *Rumex dentatus, R. abyssinicus, R. usambarensis, R. bequaertii, R. ruwenzoriensis, R. crispus; Plumbago zeylanica,Myrsine Africana, Maesa lanceolata, Rapanea melanphloes, Aloe saponaria*	 R1 R2 R3 n (1) H H H 6 (2) H H H 12 (3) H H H 14  (4)	Neutral red uptake (NR) assay A549, SPC212, DLD-1, Caco-2, MCF-7, HepG2, CRL2120.	IC_{50} μM (1) 8.05 to 117.27 (2) 2.27 to 46.62 (3) 8.39 to 48.35 (4) 3.14 to 114.17	[29]
Alizarin (1). Xanthopurpurin (2) lucidin-ω-methyl ether (3). *Rubia philippinensis*	 R (1) OH (2) H (3) OCH_3	MTT assay	IC_{50} μM SK-MEL B16F10 MCF-7 MDA-MB231 (1) 53.08 98.79 49.17 48.64 (2) 21.35 23.71 15.75 14.65 (3) 42.79 10.51 8.59 7.95	[50]

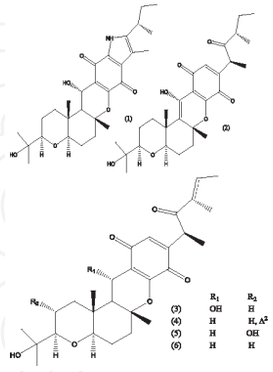
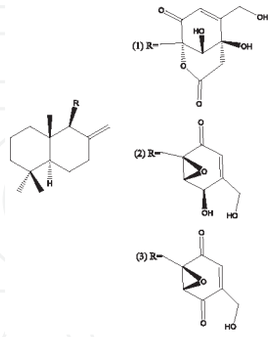
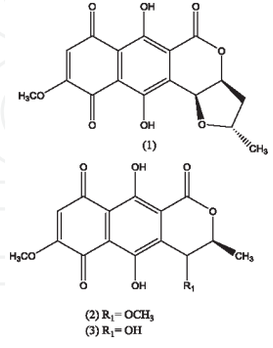
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Rhinacanthin-C *Rhinacanthus nasutus*		Sulforhodamide B assay KKU-M156 Vero Wound migration assay Chamber migration assay Chamber invasion assay. Gelatin zymography and uPA assay. Western blot analysis	IC_{50} μM 1.50 2.37 Inhibits the migration and invasion by decreasing MMP-2, uPA, FAK and MAPK pathways	[51]
Rhinacanthin S *Rhinacanthus nasutus*		RM assay KB MCF-7 NCI-H148	IC_{50} μM 11.66 20 15.86	[52]

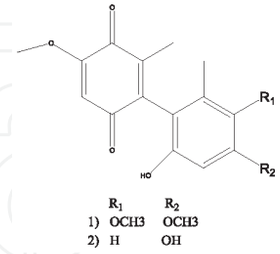
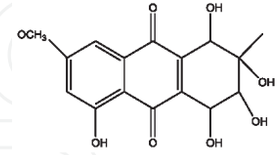
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
β-Lapachone *Tabebuia avellanedae* *Tabebula impetiginosa*		ABR assay HSC3, SCC4, SCC9, SCC15 SCC25 HepG2 HL-60 K562 AGP01 ACP-02 ACP-3 HT-29 HCT-116 FITC Annexin V Apoptosis qPCR array Westerm blot analysis	IC_{50} μM 1.02 16.22 0.16 0.06 2.78 0.99 0.09 1.35 20.33 48.94 15.49 25.03 5.62 Induce cell cycle arrest at G2/M phase and promote caspase- and ROS-mediated apoptosis In total, 44 genes were investigated in HSC3 cells treated with β-lapachone the pro-apoptotic genes BAX. Induced apoptotic cell death by NQO1-mediated ROS in a dose-dependent manner on MDA-MB-231 cells overexpressing NQO1 (231-NQO1+/+) MDA-MB-231 cells lacking NQO1 (231-NQO1−/−).	[53] [54]
3-diethylamino-5-methoxy-1, 2-benzoquinone (1) 3-ethylamino-5-methoxy-1, 2-benzoquinone (2) *Uncaria rhynchophylla*	 R (1) CH_2CH_3 (2) H	MTT assay	IC_{50} μM A549 HepG2 A2780 (1) 50.2 97.2 84.6 (2) 94.8 > 100.0 98.8	[55]

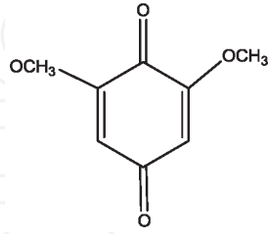
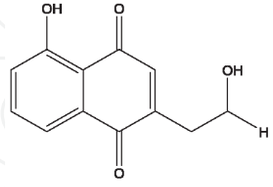
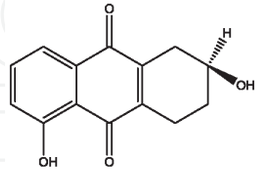
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Ventilanone A (1) Ventilanone B (2) Ventilanone C (3) Ventilanone D (4) Ventilanone E (5) *Ventilago harmandiana*	 R1 R2 R3 R4 (1) Me OH OMe OMe (2) Me OMe OMe OMe (3) Me OH OMe OH (4) H OH OMe OMe (5) H OMe OMe OMe	SRB assay	ED_{50} μM P-388 KB Col-2 (1) 9.33 > 50 > 50 (2) >20 > 50 > 50 (3) 13.82 > 50 > 50 (4) >20 > 50 > 50 (5) >20 37.31 38.81	[56]
Marine sponge				
Smenospongiarine (1) Smenospongorine (2) Smenospongimine (3) *Dactylospongia elegans*	 R (1) (2) (3) CH_3	CCK-8 method DU145 SW1990 Huh7 PANC-1	IC_{50} μM ranging from 2.33 to 37.85	[57]

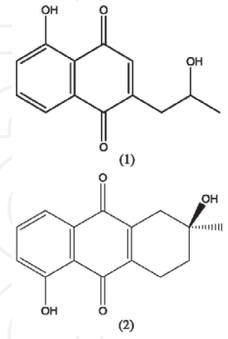
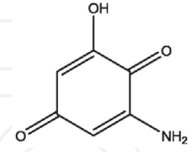
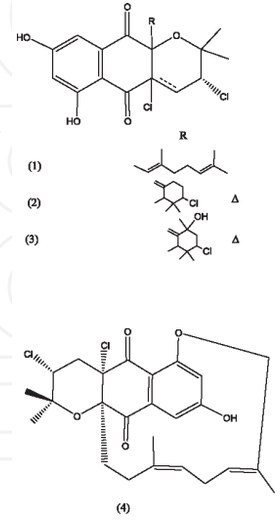
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Ilimaquinone (1) 5-epi-ilimaquinone (2) smenospongine (3) smenospongorine (4) smenospongiarine (5) smenospongidine (6) *Dactylospongia elegans*	 R (1) OMe (2) OMe C5 epimer (3) NH_2 (4) $NHCH_2CH(CH_3)_2$ (5) $NHCH_2CH_2CH(CH_3)_2$ (6) $NHCH_2CH_2Ph$	Commertial Kit C	CC_{50} µM U251MG Panc-1 (1) 19.3 20.4 (2) 19.4 16.2 (3) 2.4 —— (4) 19.4 22.6 (5) 4.5 15.1 (6) 4.0 12.6	[58]
(+)-19-methylaminoavarone(1) (−)-20-methoxyneoavarone(2) (+)-20-methoxyavarone(3) (+)-17,20-dimethoxyavarone(4) (+)-19-methoxyavaron(5) (−)-20-phenethylaminoavarone (6) (−)-20-methylaminoavarone(7) The different spices of *Dysidea sp*.	 (1)  (2)  R1 R2 R3 3) H H OCH_3 4) OCH_3 H OCH_3 5) H OCH_3 H 6) H H $NHCH_2CH_2Ph$ 7) H H $NHCH_3$	MTT assay A549 Hela HCT-116 Jukat K562 BEL-7402	IC_{50} µM Compound 2 showed the best cytotoxic activity with IC_{50} values ranging from 0.93 to 4.61 mM	[59]

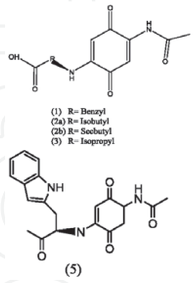
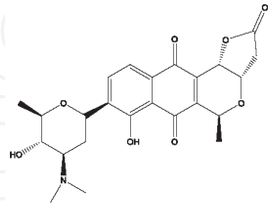
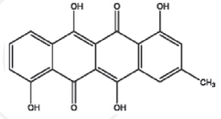
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Langcoquinones D The different genera *Dysidea*, *Spongia*, and *Dactylospongia*		WST-8 cell counting kit solution A549 MCF-7 HeLa	IC_{50} μM 8.9 5.9 8.6	[60]
Fugus				
Antrocinnamone (1) Quinone Q3 (2) Antrocamol LT3 (3) Antroquinonol (4) Antroquinonol B (5) *Antrodia cinnamomea*		The cell counting kit-8 assay	IC_{50} μM MDCK A549 HepG2 PC3 (1) >100 0.382 > 100 0.014 (2) >100 4.16 > 100 0.060 (3) >100 0.008 0.106 0.001 (4) 10.53 0.421 0.044 0.073 (5) >100 6.032 21.37 1.031	[61]
6,6′-oxybis(1,3,8-trihydroxy-2-((S)-1-methoxyhexyl)anthracene-9,10- dione) (1). 6,6′-oxybis(1,3,8-trihydroxy-2-((S)-1-hydroxyhexyl) anthracene9,10-dione) (2). 1′-O-methylaverantin (3). Averantin (4) Averythrin (5) *Aspergillus versicolor*		MTT assay SK-OV-3 SK-MEL-2 CNS XF498 HCT-15	IC_{50} μg/mL values ranging from 11.25–17.36	[62]

Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Cochlioquinones G (1) Cochlioquinones H (2) Cochlioquinone C (3) Cochlioquinone E (4) Cochlioquinone B (5) Cochlioquinone D (6) *Bipolaris sorokiniana*		SRB assay.	IC_{50} μM SF-268 HepG-2 MCF7 (1, 2, 3, 4, 5) IC_{50s} < 10 μM (6) 1.5 2.4 1.2	[63]
Purpurogemutantin (1). Macrophorin A (2). 4′-oxomacrophorin (3). *Gliomastix sp.* ZSDS1-F7		CCK-8 method K562, MCF-7, Hela, DU145, U937, H1975, SGC-7901, A549, MOLT-4 and HL60 cell lines	IC_{50} values ranging from 0.19 to 35.4 μM.	[64]
Ophioparmin (1). 4-methoxyhaemoventosins (2). 4-hydroxyhaemoventosin (3). *Ophioparma ventosa* lichen		MTT assay B16 HaCaT	IC_{50} μg/mL >10	[65]

Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Peniquinone A (1) Peniquinone B (2) *Penicillium* sp. L129		MTT assay	IC_{50} μM MCF-7 A549 U87 PC3 (1) 12.39 > 40 9.01 14.59 (2) 25.0 > 40 13.45 19.93	[66]
Altersolanol A *Phomopsis s*p. (PM0409092)		Monolayer assay propidium iodide (PI) BXF 1218 L BXF T24 CNXF 498NL CNXF SF268 CXF HCT116 CXF HT29 GXF 251 L LXF 1121 L LXF 289 L LXF 526 L LXF 529 L LXF 629 L LXF H460 MAXF 401NL MAXF MCF7 MEXF 394NL MEXF 462NL MEXF 514 L MEXF 520 L OVXF 1619 L OVXF 899 L OVXFOVCAR PAXF 1657 L PAXF PANC1 PRXF 22RV1	IC_{50} μg/mL 0.001 0.001 0.001 0.001 0.287 0.001 0.052 0.004 0.027 0.001 0.004 0.001 0.412 0.01 0.001 0.001 0.034 0.001 0.001 0.001 0.006 0.013 0.049 0.001 0.012	[67]

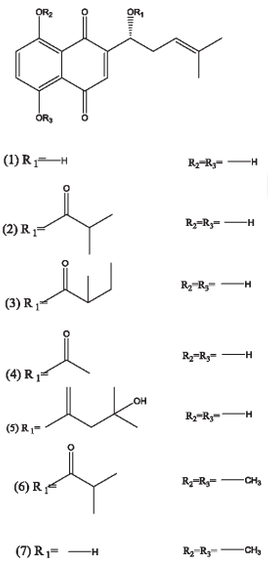
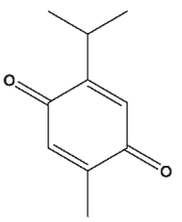
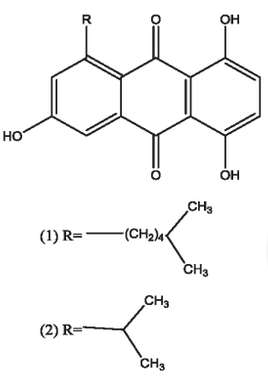
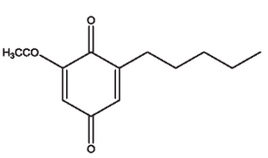
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
		PRXF DU145	0.001	
		PRXF LNCAP	0.01	
		PRXF PC3M	0.01	
		PXF 1752 L	0.05	
		RXF 1781 L	0.075	
		RXF 393NL	0.035	
		RXF 486 L	0.095	
		RXF 944 L	0.001	
		UXF 1138 L	0.061	
2,6-dimethoxy-1,4-benzoquinone *Saccharomyces cerevisiae*		CV assay	IC_{50} mg/mL	[68]
		MDA-MB-468	3.8	
		MDA-MB-231	5.5	
		BT-20	13.3	
		MCF-7	19.3	
		23132/87,	7.9	
		ASPC-1,	4.0	
		BxPC-3,	4.4	
		HT-29,	10.9	
		HRT-18b	15.8	
Auxarthrol D (1) Auxarthrol F (2) *Sporendonema casei* HDN16–802	 (1)  (2)	MTT assay HL-60; Hela; HCT-116; MGC-803; HO8910; MDA-MB-231; SH-SY5Y; PC-3; BEL-7402; K562; L-02.	IC_{50} μM values ranging from 4.5 to 22.9	[69]

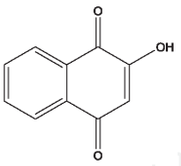
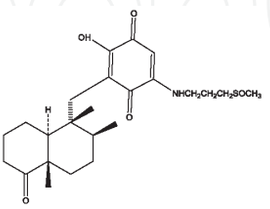
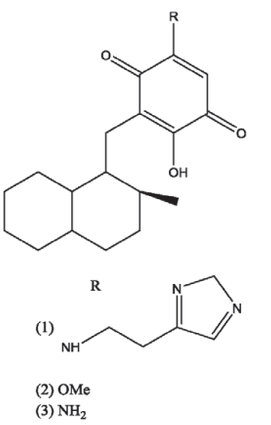
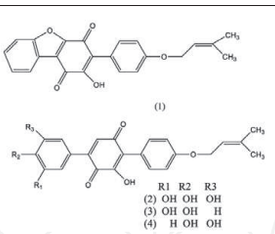
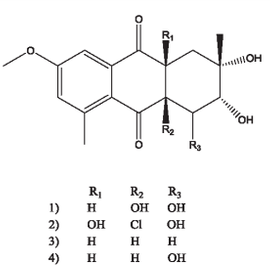
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
5- hydroxy-2-(2-hydroxypropyl)naphthalene-1,4-dione (1). (S)-2,5-dihydroxy-2-methyl1,2,3,4-tetrahydroanthracene-9,10-dione (2). *Micromonospora* sp. NEAU-gq13		CCK-8 colorimetric method	IC50 μg/ml HepG2 SF-268 ACHN (1) 1.01 3.04 10.08 (2) 12.98 5.66 11.43	[70]
Bacteria				
2-amino-6-hydroxy-[1,4]-benzoquinone *Geobacillus* sp. E263		Detection of apoptosis for fluorescence assay	The percentage of apoptotic cancer cells (MGC-803, HGC-27, MDA-MB-231,MDA-MB-435) at 10 or 100 μM was significantly increased	[71]
Napyradiomycin A3 (1) Napyradiomycin B7a (2) Napyradiomycin B7b (3) Napyradiomycin SC (4) *Streptomyces* sp. strain CA-271078		MTT assay HepG2	IC_{50} μM Values >50	[72]

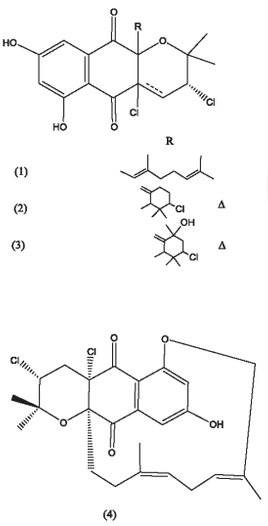
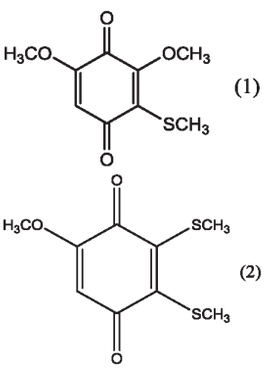
Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Ref.
Abenquine A (1) Abenquine B1 (2) Abenquine B2 (3) Abenquine C (4) Abenquine D (5) *Streptomyces sp.* strain DB634		SRB assay 518A2 A2780 HT29 MCF7 A549 FaDu NIH 3 T3	EC_{50} µM The compounds on the the 7 cell lines showed values >30	[73]
Medermycin *Streptomyces* sp. SS17A		MTT assay PC3 HCT-116	IC_{50} µM 0.02 0.04	[74]
Sharkquinone *Streptomyces sp.* EGY1		CAF AGS	IC_{50} µM 7.3	[75]

Celular lines: 23132/87, BGC-823, GXF 251 L and SGC-7901 human gastric carcinoma cells; ASPC-1, BxPC-3, PAXF 1657 L and PAXF PANC1 adenocarcinoma of the pancreas; DLD-1, Caco-2, HCT-15, CXF HCT116, CXF HT29, HCT116, HRT-18 and HT29 colon adenocarcinoma cells; PRXF 22RV1, PRXF DU145, PRXF LNCAP, PRXF PC3M and DU-145 human prostate carcinoma; MCF-7, MDA-MB 231, MDA-MB-468, BT-20 and BT-474 Human breast carcinoma cell line; A2780, OVXF 1619 L, OVXF 899 L, OVXF OVCAR3,CAOV-3 and SKOV-3 Human ovarian cancer cells; A549, H-1299, LXF 1121 L, LXF 289 L, LXF 526 L, LXF 529 L, LXF 629 L, LXF H460, NCI-H187, NCI-H1437, NCIH1655, NCI-H358, NCI-H460 and NSCLC cancer lung cells; CNXF 498NL and CNXF SF268 cancer of Central nervous System cells; RXF 1781 L, RXF 393NL, RXF 486 L, RXF 944 L and ACHN human renal cancer; BXF 1218 L and BXF T24 cancer Bladder cells; XF498 and SF-268 human central nervous system cancer; MEXF 394NL, MEXF 462NL, MEXF 514 L, MEXF 520 L, SK-MEL-5, 518A2, B16F10, C33A, HSC3, SCC4, SCC9, SCC15, SCC25 melanoma cells; CRL2120 and SK-MEL-2 human skin cancer; BEL-7402 and HepG2; SiHa, KB3.1 and HeLa human cervical adenocarcinoma cells; Jurkat lymphoblastic, HL-60 and K562 leukemia cells; MIAPaCa-2 and PANC-1 human pancreatic adenocarcinoma cancer; UXF 1138 L cancer Uterus cells; OC3-IV2 Human oral cancer; PXF 1752 L pleuramesothelioma; SPC212 human mesotelioma cell; SYF mouse embryonic fibroblast deficient in C-Src; U251MG human glioblastoma; FaDu hypopharyngeal carcinoma; KKU-M156 human cholangiocarcinoma cells. WI38 human normal lung, HaCaT immortalized human keratinocytes, nontumorigenic cell line, Vero kidney of a normal monkey cell, L929 nonmalignant mouse fibroblasts and NIH 3 T3 nonmalignant mouse fibroblasts. Inhibitory concentration of 50% (IC_{50}); Effective concentration of 50% (EC_{50}); Growth inhibition of 50% (IG_{50}); Assay of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MMT); Microscopy on a hemocytometer using trypan blue dye exclusion method (MHTBDE); Cytotoxicity Assay for fluorescence (CAF); Neutral red uptake assay (NR); Sulforhodamine B assay (SRB); Trypan Blue Exclusion assay (TBE); Alamar Blue reduction assay (ABR); Resazurin microplate assay (RM); Crystal violet assay (CV).

Table 1.
Anticancer activity of quinones isolated from different organism.

Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Reference
Plants				
Deoxyshikonin (***1***), isobutyrylshikonin (***2***), α-methylbutyrylshikonin (***3***), acetylshikonin (***4***), β-hydroxyisovalerylshikonin (***5***), 5,8-*O*-dimethyl isobutyrylshikonin (***6***) and 5,8-*O*-dimethyl deoxyshikonin (***7***). *Onosma visianii*		Micro-dilution antibacterial assay *B. megaterium* *E fecalis* *M. arborescens* *M. luteus* *S. epidermis* *C. Koseri* *H alvei* *P. proteolytica* *S. maltophilia* *Y. intermedia*	MIC 50 and 90 μg/mL For all compounds Range: 8–51/ 9–54.28 6–34/6–38 6–34/6–38 8–68/9–76 8–51/9–54 6–68/6–76 6–51/6–54 4–68/6–38 4–68/4–76 6–25/6–76	[20]
Thymoquinone *Nigella sativa*		Broth microdilution volatilization method *Haemophilus influenzae* *Staphylococcus aureus* *Streptococcus pneumoniae*	MIC (Broth/agar) μg/mL 8/8 16/16 16/32	[47]
1,4,6-Trihydroxy-8-isoheptanyl-9,10-anthraquinone (symploquinone A) (1) 1,4-Dihydroxy-6-methyl-8-isopropyl-9,10-anthraquinone (symploquinone C) (2) *Symplocos racemosa*		Microdilution assay *S. aureus* *P mirabilis*	MIC μg/mL (1) 160 (2) 83 (1) >160 (2) >160	[76]
Primin *Miconia willdenowii*		Mueller Hinton broth microdilution assay *C. albicans ATCC 10231* *C. krusei ATCC 6258* *C. tropicalis ATCC 750* *C. glabrata ATCC 90030* *C. parapsilosis ATCC 22019* *S. aureus (ATCC 6538)*	IC_{50} μM 72.08 36.04 72.08 72.08 72.08 8.94	[77]

Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Reference
Lawsone *Lawsonia inermis*		Microdilution assay *Saccharomyces cerevisiae*. Strain BY4741	MIC mM/L 229	[78]
Marine Sponge				
langcoquinones D *Dysidea*, *Spongia* and *Dactylospongia*		Microdilution assay *Bacillus subtilis* *Staphylococcus aureus*	MIC µM 12–5 25	[60]
Nakijiquinone V (1) Illimaquinone (2) Smenospongine (3) *Dactylospongia elegans*		Microdilution assay *Bacillus megaterium* DSM32 *Micrococcus luteus* ATCC4698 *Escherichia coli* K12	MIC µg/mL (**1**)32 (**1**) 32 (2) 32 (**3**) NA (**1**) 64 (**2**) 32 (**3**) NA	[79]
Fugus				
Cytosporaquinone A (1) Cytosporaquinone B (2) Cytosporaquinone C (3) Cytosporaquinone D (4) *Cytospora sp*. strain CCTU A309		Microdilution assay *Candida albicans* DSM 1665 *Micrococcus luteus* DSM 1790 *Mucor hiemalis* DSM2656 *Rhodoturulo glutinis* DMS 10134 *Bacillus subtilis* DMS 10 *Chromobacterium violaceum* DMS 30191 *Staphylococcua aureous* DMS 346	MIC µg/mL values from 16.66 to 66.66	[80]
Auxarthrol D (1) Auxarthrol G (2) 4-hydroxyaltersolanol A (3) Altersolanol B (4) *Sporendonema casei* HDN16–802		Microdilution assay *Mycobacterium phlei; Proteus sp; Bacillus subtilis; Vibrio parahemolyticus; Pseudomona aeruginosa*	MIC µM Values ranging from 12.5 to 100	[68]

Quinona/ Natural origin (plants, animals, microorganisms)	Structure	Activity or model where it was tested	Results	Reference
Bacteria				
Napyradiomycin A (1) Napyradiomycin B (2) napyradiomycin SC (3) napyradiomycin D1 (4) *Streptomyces* sp. strain CA-271078		Microdilution assay Methicillin-resistant Staphylococcus aureus MB5393; *Mycobacterium tuberculosis* H37Ra	MIC μg/mL Values ranging 3–48	[72]
Animal				
3,5- dimethoxy-2-(methylthio)cyclohexa-2,5-diene-1,4-dione (1) 5-methoxy-2,3- bis (methylthio)cyclohexa-2,5-diene-1,4-dione (2) Venom of *Diplocentrus melici*		Microdilution assay *S. aureus* *M. tuberculosis*	MIC μg/mL (1) 4 (2) 6 (1) > 160 (2) 4	[81]

Minimum inhibitory concentration (MIC).

Table 2.
Quinones with antimicrobial activity.

compound to obtain the results. There are different methods to carry out these tests. In this review, the activities were determined by the use of MTT, SRB, NR, IDO, iodide propidium, violet crystal, cell counting kits, resazurin reduction, sulforhodamine B, AGS, Trypan blue, immunophenotyping, Alamar blue, FITC Annexin V Apoptosis, the CCK-8 colorimetric method, and Annexin V/7-AAD.

The determination of antimicrobial activity was carried out by MIC, micro-dilution, and broth microdilution volatilization.

Quinones have good activity against numerous cell cancer lines; they also exhibit good antimicrobial activity. This situation, along with the wide variety of structures that these compounds exhibit, make them a very interesting topic to continue to explore for other mechanisms of action and the chemical modification of their structures, among other topics.

Conflict of interest

The authors declare no conflict of interest.

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