Chapter 2

# Phenolic Compounds from the Natural Sources and Their Cytotoxicity

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Additional information is available at the end of the chapter

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**Abstract**

Natural phenolic compounds are considered as one of the important secondary metabolites for their chemopreventive and chemotherapeutic effects in cancer. These compounds show potent activities for cancer prevention and its treatment. There are many phenolic compounds present in medicinal and edible plants such as, flavonoids, bioflavonoids, stilbenes, chalconoids, chromones, phenylpropanoids, curcuminoids, coumarins, tannins, lignans, neolignans, anthraquinones, quinones, xanthones, phenolic acids and their glycosides and many more. The antioxidant potential of phenolic compounds is almost bolded in the treatment and prevention of cancer. Mono phenolic, polyphenolic and phenolic acids compounds from a large variety of plants, foods, spices, insects, fungus, beverages, lichens, algae and mammals have been shown to inhibit or attenuate the initiation, progression and spread of cancers in cells in vitro and in animals in vivo. In this chapter, we try to cover general view and the recent literature to summarize structural information and cytotoxic effects of phenolic compounds on different cancer cell lines from medicinal herbs and plants.

**Keywords:** natural phenolic constituents, cytotoxic activities, cancer cell lines

## 1. Introduction

Natural products offer opportunities for innovation in drug discovery and play a major role for cancer cure. A considerable number of antitumor agents currently used in the clinic are of natural origin. For instance, over half of all anticancer prescription drugs approved internationally between the 1940s and 2006 were natural products or their derivatives. Among

them, plants have been the chief source of natural compounds used for medicine [1]. Many traditional and folk medicinal plants have been use for cancer therapy throughout the world and they work very well for the prevention of cancers. Phenolic compounds play very important role for the treatment and prevention on different types of cancers which are a major health problem around the world. These secondary metabolites associated with the health benefits of human derived from consuming high levels of fresh and dried fruits and vegetables. These compounds with hydroxyl bearing aromatic ring skeleton exhibit wide range of different biological activities including: anti-inflammatory, antioxidant, cytotoxicity, antimicrobial, anti-allergic. According to WHO, 8.2 million people die each year from cancer and it is estimated 13% of all deaths worldwide [2]. In this chapter, we discuss the most recent literature on phenolic constituents from natural sources and their anticancer activities on different cancer cell lines (**Table 1**).

| Source | Compound name | Class of compounds | Cytotoxic activity | Refernces |
|---|---|---|---|---|
| *Artocarpus heterophyllus* | Artocarpin (**1**), cudraflavone C (**2**), 6-prenylapigenin (**3**), kuwanon C (**4**), norartocarpin (**5**), albanin A (**6**), cudraflavone B (**7**) | Isoprenoid-substituted flavonoids | B16 melanoma cells | [3] |
| Apple, grapes, tomato green tea, pine and many other | Kaempferol (**8**) | Flavonoid | p53 or PLK-1, in MCF-7 breast cancer and HeLa cervical cancer cells, U-2 OS human osteosarcoma cell, A549 lung cancer cell, Miapaca-2, Panc-1 and SNU-213 human pancreatic cancer cells | [4] |
| *Dorstenia mannii* | Dorsmanin F (**9**) | Flavanone | LeukaemiaCCRF-CEM, MDA-MB-231-BCRP, CEM/ADR5000 cells | [5] |
| *Morus mesozygia* | Artocarpesin (**10**), cycloartocarpesin (**11**) | Flavonoid | Induced apoptosis in CCRF-CEM leukemia cells | [6] |
| Oriental tobacco, *Nicotiana tabacum* | 6,7-dimethoxy-4′hydroxy-8-formylflavon (**12**), 4′,7-dihydroxy-8-formyl-6-methoxyflavon (**13**) | Flavonoid | Human tumor (NB4, A549, SHSY5Y, PC3 and MCF7) cell lines | [7] |
| *Sophora flavescens* | Isoxanthohumol (**14**) | Flavonoid | Breast cancer (MCF-7), ovarian cancer (A-2780), prostate cancer (DU145 and PC-3) and colon cancer (HT-29 and SW620) cells, human cytochrome P450 (CYP1A2). | [8] |
| Kushen *Sophora flavescens* | Kushecarpin D (**15**) | Novel flavonoid | Human umbilical vein endothelial cell line (ECV304), antiangiogenic activity, together with its antiproliferative effect on endothelial cells without causing apoptosis | [9] |
| *Scutellaria barbata* | Luteolin (**16**) | Flavonoid | HepG2 and Bel7402 cells, human hepatocellular carcinoma cells, prostate cancer (PCa), assessing the PC3 and LNCaP cells, MCF-7 human breast cancer cells, PC12 cell line | [10–12] |

| Source | Compound name | Class of compounds | Cytotoxic activity | Refernces |
|---|---|---|---|---|
| Propolis and in honey | Chrysin (**17**) | Flavonoid | Oropharyngeal KB, mammary LM3, anaplastic thyroid KAT18, anaplastic thyroid HTh7, pancreatic PANC-1, liver H22, gastric SGC-7901, colon HT-29, cervical Hela, melanoma A375, oesophageal OE33, lung A549, colon DLD-1, rectal SW837, breast MDA-MB-231, glioma U87-MG, esophageal squamous KYSE-510, leukemia U937, prostate PC-3, hepatocellular HepG2, acute T-lymphoblastic leukemia CEM, neuroblastoma SH-SY5Y, squamous cell carcinoma FaDu, breast MCF-7, oral SCC-9, prostate DU-145, leukemia K562, cell line PC12 | [13] |
| *Macrothelypteris torresiana* | DICO (**18**) | Novel nonaromatic B-ring flavonoid | Human hepatoma HepG2 cells | [14] |
| Mulberry tree *Morus* species | Morusin (**19**) | Prenylated flavonoid | Human hepatoma SK-Hep1 cells | [15] |
| *Artocarpus communis* | Artocarpin (**20**) | Prenylated flavonoid | HepG2 and PLC/PRF/5 hepatoma cells, human cutaneous SCC cell line HSC-1, human T47D breast cancer cells | [16, 17] |
| *Daphne genkwa Sieb* | Genkwanin (**21**) | Flavonoid | HT-29 and SW-480 human colorectal cancer cells | [18] |
| Strawberries, apples, persimmons, grapes, onions and cucumbers | Fisetin (**22**) | Flavonoid | Human malignant melanoma cells A375 (CLR- 1619) and RPMI-7951 (HTB-66), SK-MEL-28 cells, A375 and SK-MEL-28 cells, RPMI-7951 cells | [19] |
| *Clerodendrum inerme* and various medicinal herbs | Hispidulin (**23**) | Flavonoid | Human HepG2 hepatocarcinoma cell line and the mouse L929 fibroblast cell line, human HEK293 fibroblast cell lines, human renal cancer cell (HRCC) lines 786-0 and Caki-1, PANC-1 cancer cells from human pancreas | [20, 21] |
| Fruits, vegetables, leaves and grains | Quercetin (**24**) | Flavonoid | HepG2 cells, Human GL-15 glioblastoma cells, breast cancer cells MCF-7 and MCF-7/dox | [22, 23] |
| All citrus fruits and *Cordia obliqua* | Hesperetin (**25**) | Flavonoid | Human esophageal squamous cell carcinoma Eca109 cells, human breast cancer MCF-7 cells, prostate cancer PC-3 cells, HT-29 human colon adenocarcinoma cell, human cervical cancer cell line HeLa cells | [24] |
| *Hypericum perforatum* | Apigenin (**26**) | Flavonoid | MCF-7 breast carcinoma cells, breast tumor cell line MDA-MB231, human cervical carcinoma HeLa cells, human colon carcinoma cell, human leukemia cells, A549 lung cancer cell, human ovarian carcinoma HO-8910PM cells, human prostate cancer PC-3 cell, thyroid carcinoma cell lines, UCLA NPA-87-1 (NPA), cell line PC12 | [25, 26] |

| Source | Compound name | Class of compounds | Cytotoxic activity | Refernces |
|---|---|---|---|---|
| *Azadirachta indica* | Quercetin-3-*O*-β-D-glucopyranoside (**27**) | Flavonoid | Protect cells from $H_2O_2$-induced cytotoxicity | [27] |
| *Polygonum amplexicaule* | Amplexicaule A (**28**) | Flavonoid glycoside | Human breast cancer cell lines MCF-7 and MDA-MB-435 | [28] |
| Wheat bran | Triticuside A (**29**) | Flavonoid glycoside | Human breast cancer cells (MCF-7 and MDA-MB-231) | [29] |
| Citrus fruits | Naringin (**30**) | Flavonoid diglycoside | Breast cancer (TNBC), MDA-MB-231, MDA-MB-468 and BT-549 cells, K562 (human leukemia cell line), Raji (human Burkitt's lymphoma cell line) and NK-92MI | [30, 31] |
| Filamentous bacterium streptomyces | Quercetin-3-*O*-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (**31**) | Flavonoid diglycoside | Human lung cancer A549 cells through p53 and cytochrome c | [32] |
| *Cirsium setidens, Aster scaber* | Pectolinarin (**32**) and astragalin (**33**) | Flavonoid glycoside | Human brain neuroblastoma SK-N-SH cells | [33] |
| *Sophora japonica* | Troxerutin (**34**) | Flavonoid diglycoside | Human prostate cancer radioresistant (DU145) and radiosensitive (PC3) cells | [34] |
| *Bupleurum flavum, Artemisia capillaris* | Vicenin (**35**) | Flavonoid glycoside | Hepatocellular carcinoma HEP-G2 cells, human prostate carcinoma LNCaP, PC- 3 & DU-145 | [35, 36] |
| Soybean | Genistein (**36**) | Isoflavone | CIP2A in MCF-7-C3 and T47D breast cancer cells, human prostate cancer cell PC3-M, PC3 and DU-145 human PCa cell lines, sarcomatoid mammary carcinoma cell line F3II, B16F0 melanoma cell line | [37, 38] |
| Soybean | Daidzein (**37**) | Isoflavone | LnCaP, DU145 and PC3 human prostate cancer cell lines, MCF-7 breast cancer cell | [39] |
| *Ateleia glazioviana* | Biochanin A (**38**) | Isoflavone | Pancreatic cancer cells (Panc1 and AsPC-1) | [40] |
| *Erythrina stricta, E. variegata* | Alpinum isoflavone (**39**) | Isoflavon | Leukemia CEM/ADR5000 cells, drug-resistant breast adenocarcinoma MDA-MB-231-*BCRP* cells, CEM/ADR5000 cells, colon carcinoma HCT116 | [41] |
| *Pueraria lobata* | Puerarin (**40**) | Isoflavone-*C*-glucoside | Myeloid leukemia cell lines, U937, Kasumi-1, HL-60 and NB4 cells, breast cancer MCF-7/adriamycin (MCF-7/adr) cells, colon cancer HT-29 cell | [42] |
| *Toxicodendron vernicifluum* | Butein (**41**) | Chalcone | Human colon adenocarcinoma cell line 220.1, human leukemia cells HL-60, $HER2^+$ HCC-1419, HCC-2218 and SKBR-3 breast cancer cells, human PCa (LNCaP, CWR22Rv1 and PC-3), human uveal melanoma cell lines (M17, SP6.5 and C918), HeLa human cervical cancer cell line | [43–47] |

| Source | Compound name | Class of compounds | Cytotoxic activity | Refernces |
|---|---|---|---|---|
| *Spatholobus suberectus* | Isoliquiritigenin (**42**) | Chalcone | Human leukemia cells HL-60 cell, human U373 glioblastoma cells, human hepatoma HepG2) cells, DU145 human prostate cancer cells | [48] |
| *Eugenia aquea* | 2′,4′-dihydroxy-6-methoxy-3,5-dimethylchalcone (**43**) | Chalcone | Human cell lines liver cancer SMMC-7721 cells, pancreas cancer 8898 cells, tumor of cervix uteri HeLa cells, lung cancer SPC-A-1 cells, high metastatic lung carcinoma 95-D cells and gall bladder carcinoma GBC-SD cells | [49, 50] |
| *Polygonum limbatum* | 4′-hydroxy-2′,6′-dimethoxychalcone (**44**) | Chalcone | MDA-MB-231-pcDNA3 breast cancer, HCT116 (p53+/+) colon cancer cells/−), the U87MG glioblastoma cells | [51] |
| *Humulus lupus* | Xanthohumol (**45**) | Prenylated Chalone | Human breast cancer (MCF-7), colon cancer (HT-29) and ovarian cancer (A-2780) cells | [52, 53] |
| *Piper methysticum* | Flavokawain B (**46**) | Chalcone | Breast cancer cell lines, MCF-7 and MDA-MB231, HCT116 human colon cancer | [54] |
| *Artocarpus communis* | Isolespeol (**47**) | Chalcone | Liver cell line Hep3B, PLC5, Huh7, human colon cancer HT-29, COLO205 cell, SW 872 human liposarcoma cell | [55] |
| *Ashitaba* (*Angelica keiskei*) | Xanthoangelol (**48**), 4-hydroxyderricin (**49**) | Chalcone | Human neuroblastoma (IMR-32) and leukemia (Jurkat) cells, SW 872, HT-29, COLO205, Hep3B, PLC5, Huh7, HepG2, KATO III, human tumor cell lines, HL60 (leukemia), CRL1579 (melanoma), A549 (lung) and AZ521 (stomach) | [56, 57] |
| *Dorstenia barteri, Psoralea corylifolia* | Isobavachalcone (**50**) | Chalcone | CCRF-CEM leukemia cells, human neuroblastoma cell lines (IMR-32 and NB-39), Induced apoptosis in CCRF-CEM leukemia cells | [58] |
| *Dorstenia poinsettifolia* | Poinsettifolin B (**51**) | Chalcone | Leukaemia CCRF-CEM, MDA-MB-231-BCRP, M/ADR5000 cells | [59] |
| Citrus kinokuni | 2′-hydroxy-3,4,4′, 5,6′-pentamethoxychalcone (**52**) | Chalcone | Human breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and melanoma (A375-C5) | [60] |
| *Rhuspyroides* | Rhuschalcones II–VI (**53, 54**) (**53**–**57**) | Bichalcone | HT29 and HCT-116 colon tumor cell lines | [61] |
| *Hibiscus syriacus* | Syriacusin A (**58**) | Naphthalene | Human skin fibrobrast cells (CRL-2076), human tumor cell lines UACC62, ACHN, SW620 and SF539 | [62] |
| *Rumex nepalensis* | Rumexneposide A (**59**) | Naphthalene acylglucoside | A549 (human non-small cell lung cancer), SKBR3, MCF-10A, MCF-7 and H522 cells (nonsmall-cell lung carcinoma) | [63] |
| *Pentas parvifolia and Pentas bussei* | Parvinaphthol B (**60**), parvinaphthols C (**61**) | Naphthalene | MDA-MB-231 human triple-negative breast cancer cell line | [64] |

| Source | Compound name | Class of compounds | Cytotoxic activity | Refernces |
|---|---|---|---|---|
| *Rumex dentatus* | Chrysophanol (**62**) | Anthraquinone | MCF-7 breast cancer cell line, gastric cancer 7901 cells, Melanoma A375 cells and oophoroma SKOV-3 cells | [65] |
| *Streptomyces* sp. ERINLG-26 | 9,10-anthraquinone (**63**), 2-hydroxy-9,10-anthraquinone (**64**), 2,3-dihydroxy-9,10-anthraquinone (**65**) | Anthraquinone | A549 lung adenocarcinoma and COLO320 cancer cell line | [66–68] |
| *Rheum palmatum* | Chrysophanol 8-*O*-beta-(6′-acetyl) glucopyranoside **(66)** | Anthraquinone glucoside | Human oral squamous cell carcinoma (HSC-2) and salivary gland tumor (HSG) cell lines than against normal human gingival fibroblasts (HGF) | [69] |
| *Cratoxylum maingayi* and *C. cochinchinense* | Formoxanthone C (**67**) | Xanthone | Human lung cancer (NCI-H187), MCF-7 (breast adenocarcinoma), KB (human oral cancer), HeLa (human cervical cancer) and HT-29 (colon cancer) | [70, 71] |
| Mangrove fungus *Phomopsis longicolla*, Fungus *Phomopsis longicolla, Rhizhopora mucronata* | Phomoxanthone A (**68**) | Xanthone | Tumour cell lines or of blood cancer cell lines | [72] |
| *Garcinia mangostana* | Garcinone C (**69**) | Xanthone | MCF-7, A549, Hep-G2 and CNE cell lines | [73] |
| *Garcinia nobilis* | Morusignin I (**70**), 8-hydroxycudraxanthone G (**71**), cudraxanthone I (**72**) | Xanthone | Breast cancer cells transduced with control vector (MDA-MB-231-pcDNA3), Human wild-type HCT116 (p53+/+) colon cancer cells, Human glioblastoma multiforme U87MG cells, Human HepG2 hepatocellular carcinoma cells and normal AML12 | [74] |
| *Securidaca longepedunculata* | 1,6,8-trihydroxy-2,3,4,5-tetramethoxyxanthone (**73**), 1,6-dihydroxy-2,3,4,5,8-pentamethoxyxanthone (**74**) | Xanthone | Human pancreatic cancer cell line, PANC-1 | [75] |
| *Garcinia hunburyi* | Desoxymorellin (**75**) | Xanthone | HEL (human embryonic lung fibroblasts) and HeLa (Henrietta Lacks cervical cancer) | [76] |
| *Garcinia cantleyana* | Cantleyanone (**76**) | Xanthone | Breast cancer (MDA-MB-231 and MCF-7), ovarian cancer (CaOV-3) and HeLa cells | [77] |
| *Garcinia lateriflora* | Lateriflorone (**77**) | Xanthone | P388 cancer cell line | [78] |
| *Garcinia morella* | Gambogic acid (**78**) | Xanthone | T47D and DLD-1 breast cancer cells | [79] |
| *Garcinia gaudichaudii* | Gaudichaudione (**79**) | Xanthone | Parental murine leukemia P388 and P388/doxorubicin-resistant cell lines | [80] |
| *Garcinia cowa* | Cowaxanthones G (**80**) | Xanthone | Human cancer cell lines (HeLa, PANC-1 and A549) | [81] |

| Source | Compound name | Class of compounds | Cytotoxic activity | Refernces |
|---|---|---|---|---|
| *Oncidium baueri* | Batatasin III (**81**) | Stilbenoid | U251 (glioma, CNS), MCF-7 (breast), NCI-ADR/RES (ovarian expressing phenotype multiple drugs resistance), 786-0 (renal), NCI-H460 (lung, non-small cell), HT29 (colon), HaCat (human keratinocytes, immortalized non-tumoral cell) | [82] |
| *Scirpus yagara* | Sciryagarol I (**82**) and II (**83**) | *Cis*-stilbenoid | HeLa Cell Line human epitheloid cervix carcinoma | [83] |
| *Gnetum macrostachyum* | Macrostachyols D (**84**) | Oligostilbenoid | Human cervical carcinoma (HeLa) and human mouth epidermal carcinoma (KB) cell lines | |
| *Cajanus cajan* | Cajanotone (**85**), cajaninstilbene acid (**86**), pinosylvin monomethyl ether (**87**), longistylin A (**88**), longistylin C(**89**) | Stilbenoid | Human hepatoma cell line HepG2, human breast adenocarcinoma MCF-7 and human lung cancer cell line A549 | [84] |
| Peanuts | Arachidin-1 (**90**) | Peanut Stilbenoid | Human leukemia HL-60 cells | [85] |
| *Combretum caffrum* | Combretastatin A-4 (**91**) | Stilbenoid | Human hepatocellular carcinoma HepG2, SMMC-7721, gastric carcinoma BGC-803 cells, breast carcinoma MDA-MB-435 | [86] |
| *Macaranga siamensis* | Macasiamenenes A (**92**), macasiamenene K (**93**), Macasiamenene L (**94**), acasiamenenes M (**95**) | Prenylated stilbenoid | MOLT-3 (acute lymphoblastic leukemia) | [87] |
| *Monomeria barbata* | 1,4,7-trihydroxy-2-methoxy-9,10-dihydrophenanthrene (**96**), 1,3,8-tri (phydroxybenzyl)-4-methoxy-phenanthrene-2,7-diol (**97**) | Phenanthrene | HepG-2, promyelocytic leukaemia HL-60, ovarian carcinoma Skov-3 | [88] |
| *Bulbophyllum odoratissimum* | Bulbophythrins A (**98**) and B (**99**) | Dimeric phenanthrene | Human leukemia cell lines K562 and HL-60, human lung adenocarcinoma A549, human hepatoma BEL-7402 and human stomach cancer SGC-7901 | [89] |
| *Helicteres hirsuta* | Pinoresinol (**100**), boehmenan (**101**) and boehmenan H (**102**) | Lignan | LNCaP, Lu1 (human lung cancer), MCF-7 (human breast cancer) and HUVEC (human umbilical vein endothelial) cell lines, | [90] |
| *Sambucus williamsii* | Sambucasinol A (**103**), B (**104**), C (**105**) | Lignan | Human cell lines A549, SK-OV-3, SK-MEL-2 and XF498 | [91] |
| *Pycnanthus angolensis* | Pycnanthulignene A (**106**) | Lignan | CCRF-CEM leukemia cell line, CEM/ADR50 0 0 cells | [41] |
| *Phyllanthus glaucus* | Phyllanthusmin C (**107**) | Lignan glycoside | HL-60, MCF-7 and SW480 cells | [92] |

**Table 1.** Cytotoxic phenolics from different natural source.

## 2. Natural phenolics with anticancer properties

### 2.1. Flavonoids and their cytotoxic activities

Flavonoids and their glycosides are the main phenolic constituents isolate form many natural sources in a reasonable amount. These phenolic compounds are very well-known for their cytotoxic activity and gave very promising results against different types of tumors. The basic structures of flavonoids are based on a $C_6$-$C_3$-$C_6$ skeleton derived from 1,3-diphenylpropane. Flavonoids are further divided into three subclasses on the basis of their little structural changes, substitutions and degree of hydroxylation and polymerization, such as, flavonoids (2-phenylchromen-4-one), isoflavonoids (3-phenylchromen-4-one) and neoflavonoids (4-phenylchromen with no hydroxyl group substitution at position 2). More than ten thousand flavonoids have been identified from natural sources and it exhibit a number of human health benefits due to their interactions with different cellular targets including antioxidant, anti-inflammatory, antiviral and anticancer properties. Isoprenylated flavonoids isolated from Moraceae family has many cytotoxic activity in different cancer cell lines including MCF-7 human breast cancer, TK-10 human renal cancer and UACC-62 human melanoma cells, A549 human lung cancer, Hep3B human hepatocellular cancer, HT-29 human colorectal cancer cells.

The cell viability of B16 melanoma cells after 3 days culture with compounds Artocarpin, cudraflavone C, prenylapigenin, kuwanon C, norartocarpin, albanin A and cudraflavone B at different concentrations was determined using 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide MTT colorimetric assays. These compounds 1–7 exhibit potent cytotoxicity in a concentration-dependent manner. The $IC_{50}$ values are 10.3, 9.2, 32.5, 14.2, 7.8, 84.7 and 12.5 μM [3].

Kaempferol is a dietary flavonoid and it has many protective effects for human health, was treated with human breast cancer cell line, MCF-7 and it regulated down the expression of polo-like kinase PLK-1, which has reported to regulate mitotic progression and to be upregulated in several human tumors. This polyphenolic compound significantly reduces cell viabilities of U-2 OS, HOB and 143B cells, but exerts low cytotoxicity on human fetal osteoblast progenitor hFOB cells. It has anticancer effects on Miapaca-2, Panc-1 and SNU-213 human pancreatic cancer cells. In a dose-dependent manner, its decreased viability of pancreatic cancer cells by increasing apoptosis. The anticancer effect of kaempferol mediated by inhibition of EGFR-related Src, ERK1/2 and AKT pathways and it could act as potent pancreatic cancer cells inhibitor [4]. The $IC_{50}$ value of Dorsmanin F is a prenylated flavonoid and it ranged from 5.34 to 1.94 μM towards leukemia CCRF-CEM cells to 33.30–28.92 μM towards MDA-MB-231-BCRP cells, respectively and from 0.20 to 195.12 μM against CCRF-CEM. This compound induced apoptosis in CCRF-CEM leukemia cells, mediated by MMP disruption and increased reactive oxygen spp (ROS) production [5]. Artocarpesin, cycloartocarpesin (unique flavonoid structures) displayed cytotoxic effect on four cell lines with $IC_{50}$ values, respectively, below 106, 50 and 25 μM. The $IC_{50}$ values of these compounds ranged from 23.95 μM for hepatocarcinoma HepG2 cell, 105 μM towards colon carcinoma HCT116 (p53−/−) cells for artocarpesin, from 15.51 μM for leukemia CCRF-CEM cells and 49.83 μM for glioblastoma U87MG.EGFR cells for cycloartocarpesin [6]. 6,7-dimethoxy-4′-hydroxy-8-formylflavon and 4′,7-dihydroxy-

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8-formyl-6-methoxyflavon are formylated flavonoid and showed significant cytotoxicity against PC3 and A549 cell lines with $IC_{50}$ values of 2.6 and 1.6 μM, respectively [7]. Isoxanthohumol is known as hops and wines flavonoid and it exhibits antiproliferative activity against human breast cancer MCF-7 cell lines, A-2780 ovarian cancer cell lines, prostate cancer PC-3 and DU145 and colon cancer SW620 and HT-29 cells lines. It inhibits the activation of carcinogens: 2-amino-3-methylimidazol-[4, 5-f]quinoline and aflatoxin B1, AFB1 via human cytochrome P450 CYP1A2 [8]. Kushecarpin D is a Chinese traditional herbal medicine and exhibits antiangiogenic activity demonstrated by its effects on migration, adhesion, tube formation of an endothelial cell line. The antiangiogenic activity, together with its antiproliferative effects on endothelial cells, indicates that kushecarpin D is an excellent candidate for development as chemo preventive molecule to be used in combating tumor development [9]. Luteolin is one of the very important flavonoid found in many foods with lot of health benefits and it prevent cancers strongly, it induce cell cycle arrest and apoptosis in various human cancer cells and it synergize antitumor effects of 5-FU on Bel7402 and HepG2 cells, which can related with apoptosis and regulation of 5-FU metabolism. The $IC_{50}$ value of luteolin on $PC_3$ and LNCaP cells was 31.44 and 32.05 μM, respectively. It resulted in a marked reduction in cell proliferation in a dose-dependent manner and enhanced the paclitaxel-induced apoptosis in human breast cancer MDA-MB-231 cells by blocking STAT3 [10–12]. Chrysin is found in many flowers and honey and it has preventive effect on cancer induced chemically on xenograft tumor by inducing activity of antioxidant and detoxification enzyme, reducing the activities of cytochrome P450 (CytP450)-dependent monooxygenases, inhibiting cellular proliferation and inducing apoptosis. Chrysin has induced breast cancer resistance protein (BCRP) in Caco-2 cells. Chrysin and many other flavonoids such as fisetin, kaempferol, galangin, myricetin and apigenin reported as potent inhibitors of P-form phenol sulfo transferase mediated sulfation induced carcinogenesis in human hepatoma cell line HepG2. Chrysin kill several histotype cancer cells, including hematological, cervical, liver, colon, lung, breast, nasopharyngeal, glioblastoma, prostate, thyroid and pancreatic cancer [13]. DICO is a nonaromatic B ring flavonoid having potent antitumor activity and inhibited growth of HepG2 cells in different dose/time dependent manners. It induced G2/M cell cycle arrest and apoptosis via a ROS-mediated mitochondrial pathway. It has significant antitumor effect through G2/M cell cycle arrest and apoptosis induction, which suggested DICO has therapeutic potential against tumors [14]. Morusin belongs to the prenylated class of flavonoids and it suppressed signal transducer and activator of transcription 3 STAT3 and nuclear factor-kB/NFkB signaling pathway, which modulate protein expression involved in invasion process. Morusin decreased lung colonization of SK-Hep1 cells in mice. It indicates that morusin possesses antitumor progression potential by suppressing STAT3 and NFkB [15]. Artocarpin showed significant anticancer activities on breast cancer cells (T47D cells) with $IC_{50}$ value on T47D cells was 12.6 μM on concentration-dependent manner. Anticancer effect of artocarpin in HepG2 and PLC/PRF/5 hepatoma cells is mediated through autophagic cell death mechanism and it showed dose-dependent reduction on cancer cell viability after 24 h of treatment and $IC_{50}$ value was calculated to be approximately 15 μM in both cell lines [16, 17]. Genkwanin a methoxy flavonoid, significantly inhibited HT-29 and SW-480 human colorectal cancer cells proliferation and inflammatory cytokine IL-8 secretion. It has a better antitumor activity via enhancing host immunity and decreasing inflammatory cytokine levels [18]. Fisetin is a

tetrahydroxy flavonoid having many health benefits and it effects on short- and long-term growth of BRAF-mutated A375, SK-MEL-28 and RPMI-7951 melanoma cancer cells. Results of MTT assay demonstrated that fisetin (10–60 μM) treatment significantly decreased the growth of A375 8.64–61.75%, SK-MEL-28, 6.94–59.79% and RPMI-7951, 11.60–64.11% cells in a concentration-dependent manner [19]. Hispidulin is found in many herbs and significantly inhibited HepG2 cell growth in a time and dose-dependent manner. Hispidulin (at 200 μM) inhibited the growth of HepG2 cells by nearly 50, 70 and 90% after 24, 48 and 72 h of treatment, respectively, which suggest that hispidulin promotes HepG2 cell death through apoptosis. It inhibited cell growth in a dose-dependent manner in (HRCC) lines 786-0 and Caki-1 cell lines, whereas Caki-1 cells were found to be more resistant to hispidulin treatment [20, 21]. Quercetin is a dietary flavonoid (berries flavonoid) showed strong cytotoxicity as 1.49-fold in MCF-7 cells and 1.98-fold in MCF-7/dox cells. It suppressed proliferation and survival of HepG2 cancer cells and induced apoptosis by enhancing the expression of p53 and BAX through downregulation of ROS, PKC, PI3K and COX-2 [22, 23]. Hesperetin a citrus flavonoid exhibited inhibition of cell growth in a concentration and time-dependent manner with $IC_{50}$ at 72 h 200 μM. It could significantly promote apoptosis of Eca109 cells in a dose-/time-dependent manner [24]. Apigenin a trihydroxy flavonoid with potential health benefits exhibited strong growth inhibitory activity in HER2/neu breast cancer cells but was much less effective in inhibiting growth of cells expressing basal levels of HER2/neu. It induces apoptosis in MDA-MB-453 breast cancer cells with involving intrinsic and extrinsic apoptotic pathways. It has shown to downregulate levels of cyclin D1, D3 and cdk4 and increases p27 protein levels in breast cancer cells. Apigenin inhibited human cervical carcinoma HeLa cells growth through an apoptotic pathway. In various human colon carcinoma cells, it resulted cell growth inhibition and G2/M cell cycle arrest. The effects of apigenin on lung cancer cells were evaluated and it inhibited A549 lung cancer cell. It has capability to significantly reduce cell number and induce apoptosis in PWR-1E, LNCaP, PC-3 and DU145 cells [25, 27]. Quercetin-3-*O*-β-D-glucopyranoside also known as isoquercetin and found in mangoes in high amount and it is an interesting dietary compound worth further investigation as a cytoprotective agent. Pretreatment of PC12 cells with nontoxic concentrations of this compound protect cells from $H_2O_2$ induced cytotoxicity with decrease in generation of reactive oxygen species (ROS). These observations qualify it as cytoprotective dietary compound [27]. Amplexicaule A is found in many herbs and it increased levels of cleaved caspase-3,-8,-9 and PARP, resulted from suppression of MCL-1 and BCL-2 expression in cells. This compound inactivated the Akt/mTOR pathway of breast cancer cells. It influenced strongly on breast cancer cells, most likely by induction of apoptosis [28]. Triticuside A a dietary flavonoid found in wheat and induced apoptosis accompanied by a significant decrease in Mcl-1 and Bcl-2 proteins and by increase in cleavage of caspases-3, -7, -9 and PARP. It suppressed the level of phospho-Akt and its downstream targets, mTOR and P70 S6 kinase. LY294002, a specific inhibitor of PI3K, significantly enhanced the triticuside A induced apoptosis. It may a potentially useful wheat bran component and can used for treatment of breast cancer [29].

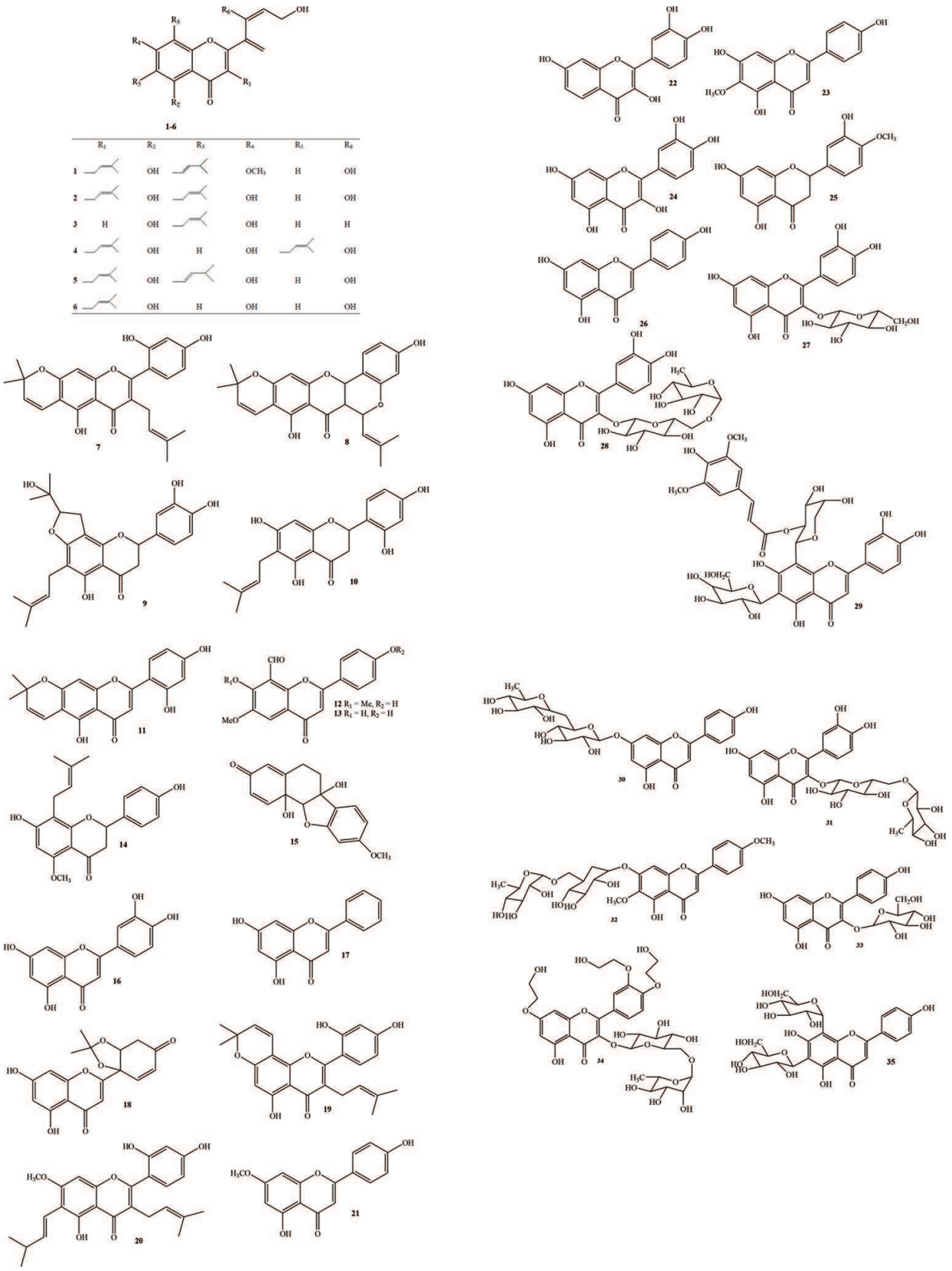
Naringin is a diglycoside flavonoid and found in many citrus fruits and it inhibited cell proliferation and promoted cell apoptosis and G1 cycle arrest, accompanied by increased p21 and decreased surviving. Significant inhibitory effects of naringin on the cell proliferation of TNBC cells were observed. MDA-MB-231 and BT-549 cells treatment with naringin (50, 100

and 200 M) for 48 h, significantly increased apoptosis in breast cancer cells. It exerts significant effects on inhibition of breast cancer cells growth in through mediating-catenin pathway. Treatment of Raji with naringin showed maximum sensitivity towards NK cell lysis and the activity was 2.5-fold with naringin treatment [30–32]. Quercetin-3-*O*-*α*-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside induces apoptosis in A549 cancer cells via caspase activation through cytochrome release from mitochondria. It tested against A549 lung cancer cell line, COLO320DM cancer cell line and Vero cell line and it showed prominent cytotoxic activity against A549 lung cancer cell. This compound showed 87.41% activity at dose of 164 μM with $IC_{50}$ value of 82 μM. COLO320DM cancer cell line was maintained in complete tissue culture medium [32]. Pectolinarin and astragalin isolated from edible plants against $H_2O_2$-induced cell death of human brain neuroblastoma SK-N-SH cells. These compounds showed protective effects against $H_2O_2$-induced cell death and inhibited ROS generation by oxidative stress [33]. Troxerutin showed strong binding with calf thymus DNA in vitro and DNA interaction was confirmed by CD spectropolarimetry. The mode of binding of troxerutin to DNA was assessed by competing with EtBr or DAPI, known DNA intercalator and minor groove binder, respectively. It induced cytotoxicity in radioresistant DU145 and sensitive PC3 prostate cancer cells. When troxerutin was pretreated with DU145 and PC3 cells and it were exposed to gamma-radiation, the cytotoxicity induced in PC3 and DU145 prostate cancer cells and it was monitored by MTT assay. The toxicity induced by troxerutin 5 μM was more than 40% over control at 24 h, but more than 50% increase was observed at 48 h. Radiation per se induced around 18% cell death in PC3 cells [34]. Vicenin gave $IC_{50}$ values 141.7 μM, 195.7 μM and 369.3 μg $mL^{-1}$ on treatment with PC-3, DU-145 and LNCaP cells. Curcumin was used as positive control with $IC_{50}$ 17.90 μM. It is an active constituent of the medicinal herbs (Tulsi) and it effectively induced antiproliferative, antiangiogenic and proapoptotic effect in CaP cells (PC-3, DU-145 and LNCaP) [35, 36] (**Figure 1**).

### 2.2. Isoflavonoids and their cytotoxic activities

Isoflavonoids play very important role in human health-promoting natural chemicals. They belong to plants secondary metabolites, mediate diverse biological functions through numerous pathways. Isoflavonoids are phenolic compounds and possess a 3-phenylchroman skeleton that biogenetically derived from 2-phenyl chroman skeleton of flavonoids. Some studies reported that anticarcinogenic activities of dietary soy isoflavonoids play important role for preventing colorectal cancer. Isoflavonoids have shown to possess many biological properties that can account for cancer prevention. Isoflavones exert their effects through numerous pathways with respect to the cancer prevention; and it use mechanisms of action which appear to be various, complementary and overlapping.

Genistein is a soybeans isoflavones and it decrease the risk of breast cancer and induced downregulation of CIP2A in breast cancer cells MCF-7-C3 and T47D, which correlates with its growth inhibition and apoptotic activities. In a model of human prostate carcinoma, treatment with genistein, decreased the metastatic burden, without changing the size of primary tumor and cell detachment were also decreased. According to studies, patients with PCa effectively tolerate genistein and therapeutic modulation of metastasis, specifically MMP-2 (matrix metallopeptidase 2) is possible [39, 40]. Inhibitory effect of daidzein investigated by




| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ |
|---|---|---|---|---|---|---|
| 1 | | OH | | $OCH_3$ | H | OH |
| 2 | | OH | | OH | H | OH |
| 3 | H | OH | | OH | H | H |
| 4 | | OH | H | OH | | OH |
| 5 | | OH | | OH | H | OH |
| 6 | | OH | H | OH | H | OH |

**Figure 1.** Structures of flavonoids **1–35**.

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bacterial flora in intestines, on DU145, LnCaP and PC3 human prostate cancer cell. The results provide a better understanding of the biomolecular mechanisms of this compound as natural anticancer agent and provide base for development of daidzein and its analogs as potent anticancer molecules [39]. Biochanin A is found in nuts and beers and it effects on pancreatic cancer progression and it induced dose-dependent toxicity on pancreatic cancer cells Panc1 and AsPC-1. It reduced colony formation ability of Panc1 cells and induced dose-dependent apoptosis [40]. The $IC_{50}$ value of Alpinum isoflavone ranged from 5.91 μM towards leukemia CEM/ADR5000 cell and to 65.65 μM towards drug-resistant breast adenocarcinoma MDA-MB-231-*BCRP* cells. This sioflavone induced apoptosis of CCRF-CEM cells, mediated by the loss of MMP and increase the ROS production [41]. Puerarin prevents the proliferation of breast cancer cells (MDA-MB-231, HS578T and MCF-7) at 50% of cell growth inhibition with concentration of 46, 71 and 69 μM, respectively. Puerarin was further preventing three different types of breast cancer in the G0/G1 phase of the cell cycle and stimulated apoptosis in these cells [42] (**Figure 2**).

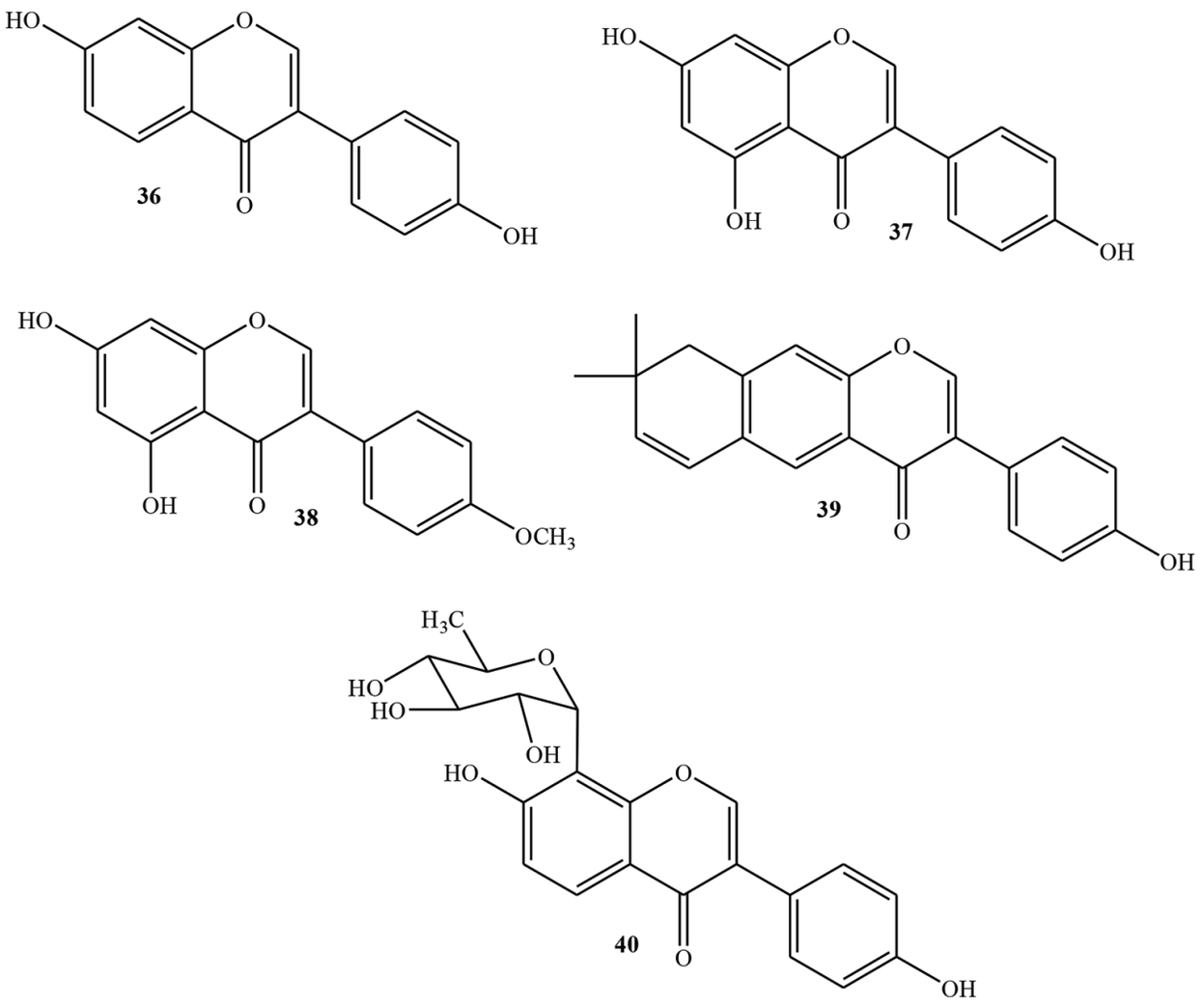


**Figure 2.** Structure of isoflavonoids **36–40**.

### 2.3. Chalcone and their cytotoxic activities

Chalcones mainly belongs to flavonoids family and known as open chain flavonoid in which two aromatic rings A and B structurally joined by $\alpha,\beta$-unsaturated carbonyl system. Plants containing chalcones have been used traditionally as anti-inflammatory, antioxidant, antimalarial, antimicrobial, antifungal, antitubercular, cytotoxic, antiviral, antitumor and chemopreventive agent. These are very common phenolics specially founds in Leguminosae, Moraceae and Asteraceae families.

Butein is a natural dietary chalcone has many traditional uses and a herbal medicine. It reduced the cell viability of cultured human uveal melanoma cells in a dose-dependent manner with $IC_{50}$ at 13.3 and 15.8 μM in SP6.5 and M17 cell lines, respectively. Similar effects were also found in a highly aggressive and metastatic C918 cell line ($IC_{50}$ 16.7 μM). At 2 μM concentration, it inhibited the incorporation of 14C-labelled thymidine, uridine and leucine into the colon cancer cells whilst 5-fluorouracil (5-FU, a chemotherapeutic drug) at 50 μM concentration. The cytotoxic action of butein was different from 5-FU but may be similar to colchicine, a known HeLa cell inhibitor. Butein inhibit telomerase activity by downregulating hTERT gene expression in human leukemia cells and it causes apoptosis of breast cancer cells, while luminal $HER2^+$ HCC-1419, HCC-2218 and SKBR-3 breast cancer cells. Treatment with butein (10–30 μM) decreased cell viability in LNCaP (29, 42 and 52%), CWR22Rv1 (20, 31 and 42%) and PC-3 (11, 22 and 35%) cells. It inhibited colony formation, cell viability, migration, invasion, induced cell cycle at G2/M stage, cell apoptosis and enhanced caspase-3, -8 and -9 activity in HeLa cells in a dose-dependent manner [43–47]. Isoliquiritigenin is a natural chalcone and used for the treatment of cancer, it is cytostatic and able to overcome the intrinsic resistance of U373 cancer cells to proapoptotic stimuli. After 72 h treatment with 10 μg $mL^{-1}$ of isoliquiritigenin, a typical differentiated morphology observed in HL-60 cancer cells, including the decrease in karyoplasmic ratio and the increase in kidney-shape nuclear cells. This compound is able to induce the monocytic differentiation in leukemia cells. It has potential as a drug for leukemia. HepG2 cells are significantly more resistant to isoliquiritigenin when the activity of p53 was blocked. Isoliquiritigenin inducible p53 plays a key apoptotic role and may do so by regulating the expression of specific target molecules that promotes efficient apoptotic cell death following G2/M-cell cycle arrest. It inhibits the proliferation of prostate cancer cells, via inhibition of ErbB3 signaling and PI3K/Akt pathway [48]. 2′,4′-dihydroxy-6-methoxy-3,5-dimethylchalcone tested on human cell lines including liver cancer SMMC-7721 cells, pancreas cancer 8898 cells, tumor of cervix uteri HeLa cells, lung cancer SPC-A-1 cells, high metastatic lung carcinoma 95-D cells and gall bladder carcinoma GBC-SD cell lines was dose-dependent. It observed that different cells had a different sensitivity for inhibition effect of this chalcone. The $IC_{50}$ values on cytotoxicity were 32.3, 37.2, 37.7, 81.3, 84.6 and 84.8 μM for SMMC-7721, 8898, HeLa, GBC-SD SPC-A-1 and 95-D cells, respectively [49, 50]. 4′-hydroxy-2′,6′-dimethoxychalcone showed $IC_{50}$ values in a range of 2.54 μM against CEM/ADR5000 leukemia cells to 58.63 μM towards hepatocarcinoma HepG2 cells. This compound arrested cell cycle between Go/G1 phase and induced apoptosis via disrupted mitochondrial membrane potential MMP and increased production of reactive oxygen species (ROS) in the studied leukemia cell line [51]. Xanthohumol is a prenylated chalcone found in beers; it caused dose dependent (0.1–100 μM) decrease in growth of MCF-7, HT-29 and A-2780 cancer

cell lines. After two-day treatment, the concentrations at which growth of MCF-7 cells was inhibited by 50% ($IC_{50}$) were 13.3 μM for xanthohumol. After four-day treatment, $IC_{50}$ for xanthohumol was 3.47 μM [52, 53]. Flavokawain B is known as kava chalcone and it induced caspase and mitochondria-dependent apoptosis which characterized by cytochrome c release and Bak translocation to mitochondria. It induces G2/M accumulation, autophagy and apoptosis, leading to HCT116 colon cancer cell growth inhibition. It further induced both MCF-7 and MDA-MB231 and significant G2/M arrest was seen in MDA-MB231 cells [54]. Isolespeol is a geranyl chalcone and it showed inhibitory activity against human liposarcoma cells SW 872 with $IC_{50}$ values of 3.8 μM. Treatment of SW 872 human liposarcoma cells with this compound stimulated increase protein expression of Fas, FasL and p53 [55]. Xanthoangelol and 4-hydroxyderricin inhibit adipocytes differentiation through AMPK and mitogen-activated protein kinase pathways, resulting in the down-expression of adipocyte-specific transcription factors. Xanthoangelol induce apoptotic cell death by activation of caspase-3 in neuroblastoma and leukemia cells through a mechanism that does not involve Bax/Bcl-2 signal transduction. Therefore, this compound may effective drug for the treatment of neuroblastoma and leukemia. 4-Hydroxyderricin showed significant cytotoxicity in four human tumor cell with $IC_{50}$ values 4.8 μM (CRL1579), 5.5 μM (HL60), 4.2 μM (AZ521) and 10.2 μM (A549). 4-Hydroxyderricin induced further the early apoptosis of HL60 cells and it observed as membrane lipid exposure in the flow cytometry [56, 57]. The $IC_{50}$ values for Isobavachalcone is a prenylated chalcone and having wide range of biological activities including anticancer, it ranged from 0.20 μM (towards CCRF-CEMcells) to 195.12 μM (towards leukemia CEM/ADR 5000 cells) for doxorubicin. It induces apoptosis in CCRF-CEM leukemia cells, mediated by caspase activation and the disruption of MMP [58]. Cytotoxicity of Poinsettifolin B assessed against different sensitive and multidrug-resistant cancer cell lines. The $IC_{50}$ values for this compound ranged from 5.34 to 1.94 μM towards CCRF-CEM leukemia cells, to 33.30 and 28.92 μM towards human breast cells MDA-MB-231-BCRP, respectively and from 0.20 μM against human leukemia cell CCRF-CEM, to 195.12 μM against CEM/ADR5000 cells [59]. *2′-hydroxy-3,4,4′,5,6′-pentamethoxychalcone is very potent in inhibiting* breast adenocarcinoma (MCF-7), lung cancer (NCI-H460) and melanoma (A375-C5) cell lines [60]. Rhuschalcones II−VI showed potent cytotoxic activities against HCT-116 and HT29 human colon cancer cells [61] (**Figure 3**).

### 2.4. Naphthalenes and their cytotoxic activities

Naphthalenes are simplest and most important member of arenas, in which two benzene rings are fused with each other and it based on a $C_6$-$C_4$ skeleton. Many naphthalene-based natural products have been isolated from different sources and showed significant biological activities.

Syriacusin A inhibit activity of human neutrophil elastase HNE, a serine protease to degrade extracellular matrix ECM proteins including elastin, with $IC_{50}$ values 8.0, 5.2 and 6.1 μM, respectively [62]. Rumexneposide A showed against broad spectrum activity against human cancer cells lines, including lung and breast cancer cells (A549, H522, MCF-7, MCF-10A, SKBR3) with $IC_{50}$ value 31.0, 15.7, 21.8, 22.8 and 20.7 μM [63]. Parvinaphthol B, parvinaphthols C showed marginal cytotoxicity against the MDA-MB-231 human triple-negative breast cancer cell line with $IC_{50}$ values ranging from 62.3 to 129.6 μM [64].

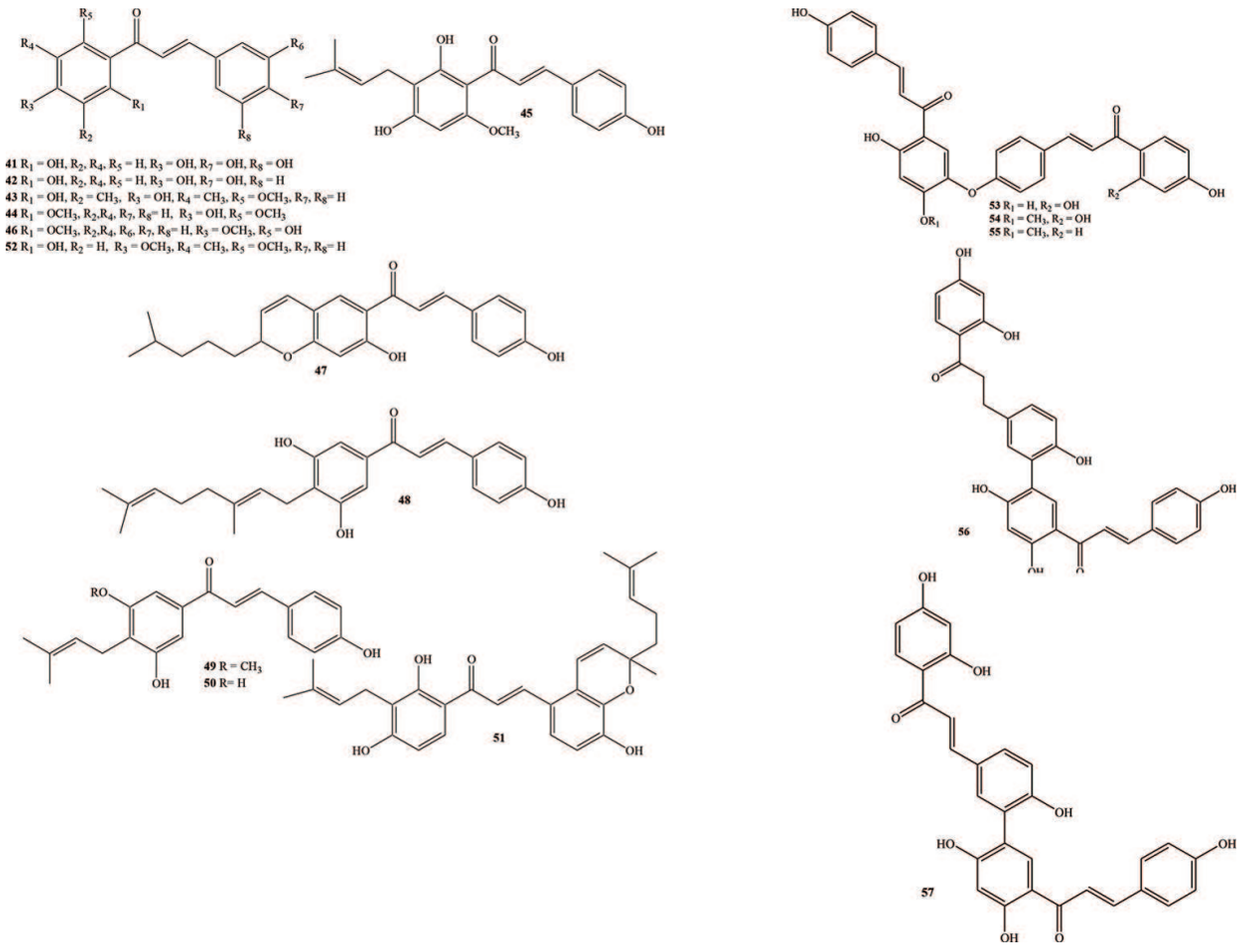


**Figure 3.** Structure of chalcones **41–57**.

## 2.5. Anthraquinone and their cytotoxic activities

Anthraquinones are the active constituents of many herbs with a tricyclic C6-C2-C6-based skeleton. They are widely distributed in the *Fabaceae, Liliaceae, Labiate, Polygonaceae* and *Rhamnaceae* families. Anthraquinone found in herbs (*Polgyonum*) in vegetable (cabbage, lettuce and beans).

Chrysophanol was active in the oophoroma SKOV-3 cell line, where the $IC_{50}$ value was 5.62 μM and with $IC_{50}$ value 20.4 μM for MCF-7 breast cancer cell line [65]. 9,10-anthraquinone showed strong cytotoxic activity against COLO320 human colon carcinoma cell line. It gave 79.7% cytotoxicity at 300 μg $mL^{-1}$ concentration of compound with 75 μg $mL^{-1}$ $IC_{50}$ value. The treatment of human colon carcinoma cell line COLO320 with 9,10-anthraquinone significantly decreased the proliferation of cells and enhanced the formation of apoptotic bodies and fragmented DNA. The expressions of p53 and caspase-3 was upregulated from 9,10-anthraquinone in colon adenocarcinoma cells [66]. 2-hydroxy-9,10-anthraquinone showed cytotoxic activity against A549 lung and COLO320 cells lines and it showed 62.7% activity at the dose of 500 μg $mL^{-1}$ with $IC_{50}$ value of 400 μg $mL^{-1}$ against COLO320 cells [67]. 2,3-dihydroxy-9,10-anthraquinone inhibits PI3K/AKT activity after treatment. Also, COX-2 enzyme plays a major role in colorectal cancer and significantly reduced COX-2 enzyme in COLO320 cells.

It involves in apoptotic pathway, mitochondrial function, cell cycle checkpoint and control the over expression gene during the colorectal cancer [66]. Chrysophanol 8-O-beta-(6′-acetyl) glucopyranoside exhibited relatively higher cytotoxic activities against human oral squamous cell carcinoma HSC-2 and salivary gland tumor HSG cell lines than against normal human gingival fibroblasts HGF cells lines [69] (**Figure 4**).

### 2.6. Xanthone and their cytotoxic activities

Xanthones are three-membered ring compounds with (C6-C1-C6) skeleton and are mainly found in higher plants and microorganisms. Now days, they gained great importance due to their significant pharmacological and biological properties. These types of natural compounds have broad biological profile, such as, antihypertensive, anti-inflammatory, antioxidant antithrombiol, anticancer and antiviral activities. Xanthones are commonly found in Gentianaceae, Moraceae, Guttiferae, Clusiaceae, Polygalaceae in citrus fruits and mangosteen.

Formoxanthone C has $\alpha,\alpha,\beta$-trimethylfuran ring and it showed potent cytotoxic activity against NCI-H187 with $IC_{50}$, 0.22 μg $mL^{-1}$, which is stronger than elliptecine, a standard drug with $IC_{50}$, 0.45 μg $mL^{-1}$ [70, 71]. Phomoxanthone A displayed strong anticancer activity, on the treatment against cisplatin resistant (CisR) cancer cell lines or blood cancer cell lines with an $IC_{50}$ values in sub-micromolar concentration and it was up to 100-folds less active against PBMC peripheral blood cells from a healthy donors [72]. Garcinone C was tested for cytotoxicity against MCF-7, A549, Hep-G2 and CNE cell lines by 3-(4,5-dimethylthiazol2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay, while doxorubicin used as positive control. Garcinone C showed strong cytotoxicity against all cell lines with $IC_{50}$ values from 4.3 ± 0.1 to 7.1 ± 0.5 μM [73]. Morusignin I 70 and cudraxanthone I inhibited proliferation of all cancer cell lines including sensitive and drug-resistant phenotype. 8-hydroxycudraxanthone G showed activity on many cell lines with $IC_{50}$ values ranged from 16.65 μM against CCRF-CEM leukemia cells to 70.38 μM against HepG2 hepatocarcinoma cells. The $IC_{50}$ values of different cells ranged from 7.15 μM against CCRF-CEM human leukemic cells to 53.85 μM against U87MG.Δ*EGFR* human glioblastoma cells for morusignin I and 2.78 μM against MDA-MB231 BCRP breast cancer cells to 22.49 μM against U87MG human glioblastoma *cell* line for cudraxanthone I [74]. 1,6,8-trihydroxy-2,3,4,5-tetramethoxyxanthone, 1,6-dihydroxy-2,3,4,5,8-pentamethoxyxanthone were tested for preferential cytotoxic activity against human pancreatic cancer cells PANC-1 under nutrient deprived condition. These compound displayed potent cytotoxicity with $PC_{50}$ of 22.8 and 17.4 μM, respectively. They triggered apoptosis-like PANC-1 cell death in NDM with glucose sensitive mode [75]. Desoxymorellin inhibited the growth of HEL human embryonic lung fibroblasts and HeLa Henrietta Lacks cervical cancer cell with a minimum inhibitory concentration MIC of 0.39 mg $mL^{-1}$ [76]. Cantleyanone displayed significant cytotoxicity against breast cancer MDA-MB-231 and MCF-7, ovarian cancer CaOV-3 and HeLa cells with $EC_{50}$ values ranging from 0.22 to 17.17 mg $mL^{-1}$ [77]. Lateriflorone was cytotoxic against P388 cancer cell line with an $ED_{50}$ value 5.4 mg $mL^{-1}$ [78]. Gambogic acid inhibited proliferation of T47D and DLD-1 breast cancer cells with $GI_{50}$ values of 0.04 and 0.03 mm, respectively [79]. Gaudichaudione displayed strong growth inhibitory activity against parental murine leukemia P388 and P388/doxorubicin resistant cell lines at low μM concentrations [80]. Cowaxanthones G showed potent inhibition on cell viability $IC_{50} < 10$ μM, while etoposide was used as positive control [81] (**Figure 5**).

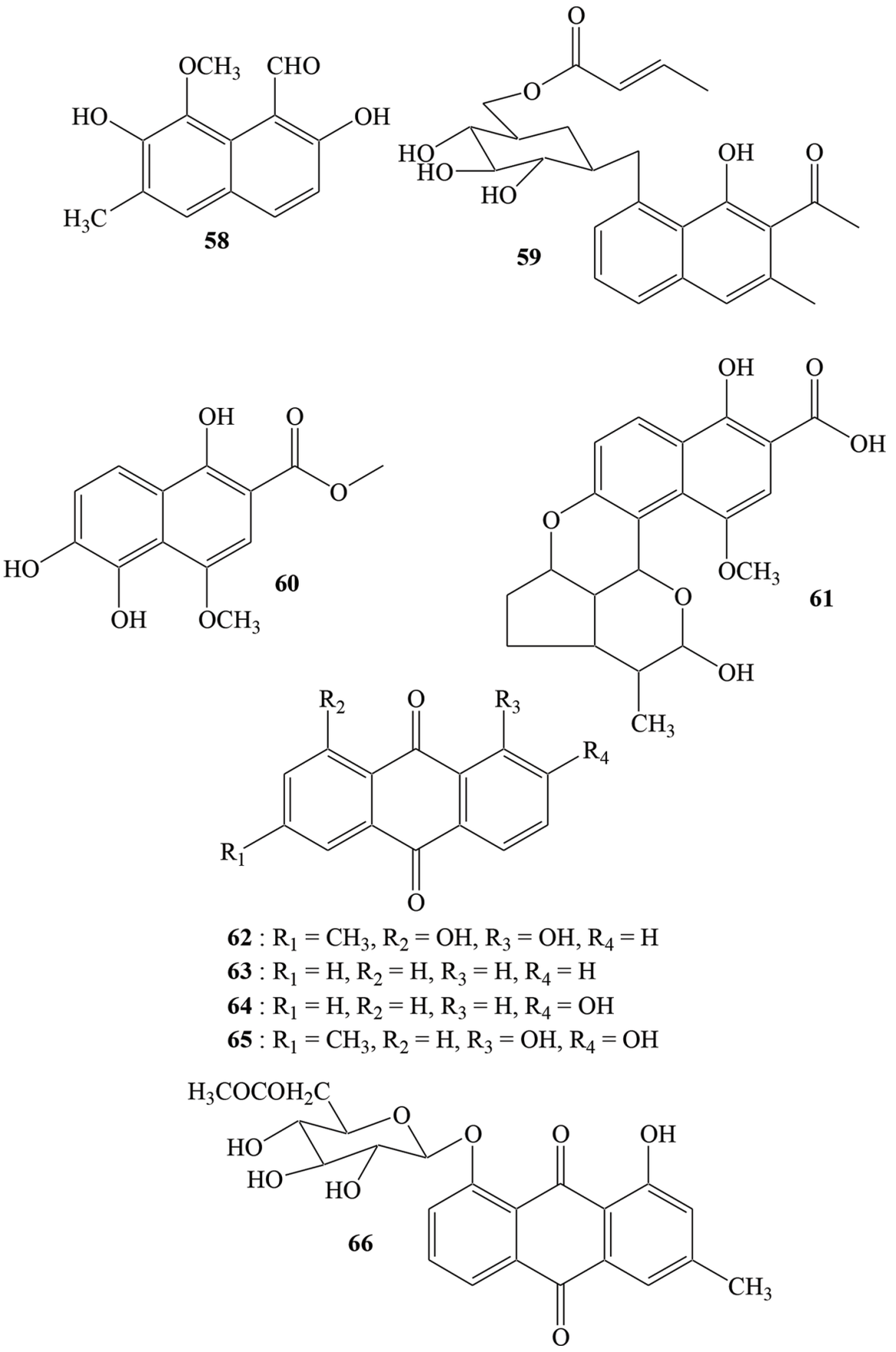


**Figure 4.** Structure of naphthalenes **58–61** and Anthraquinones 62–66.

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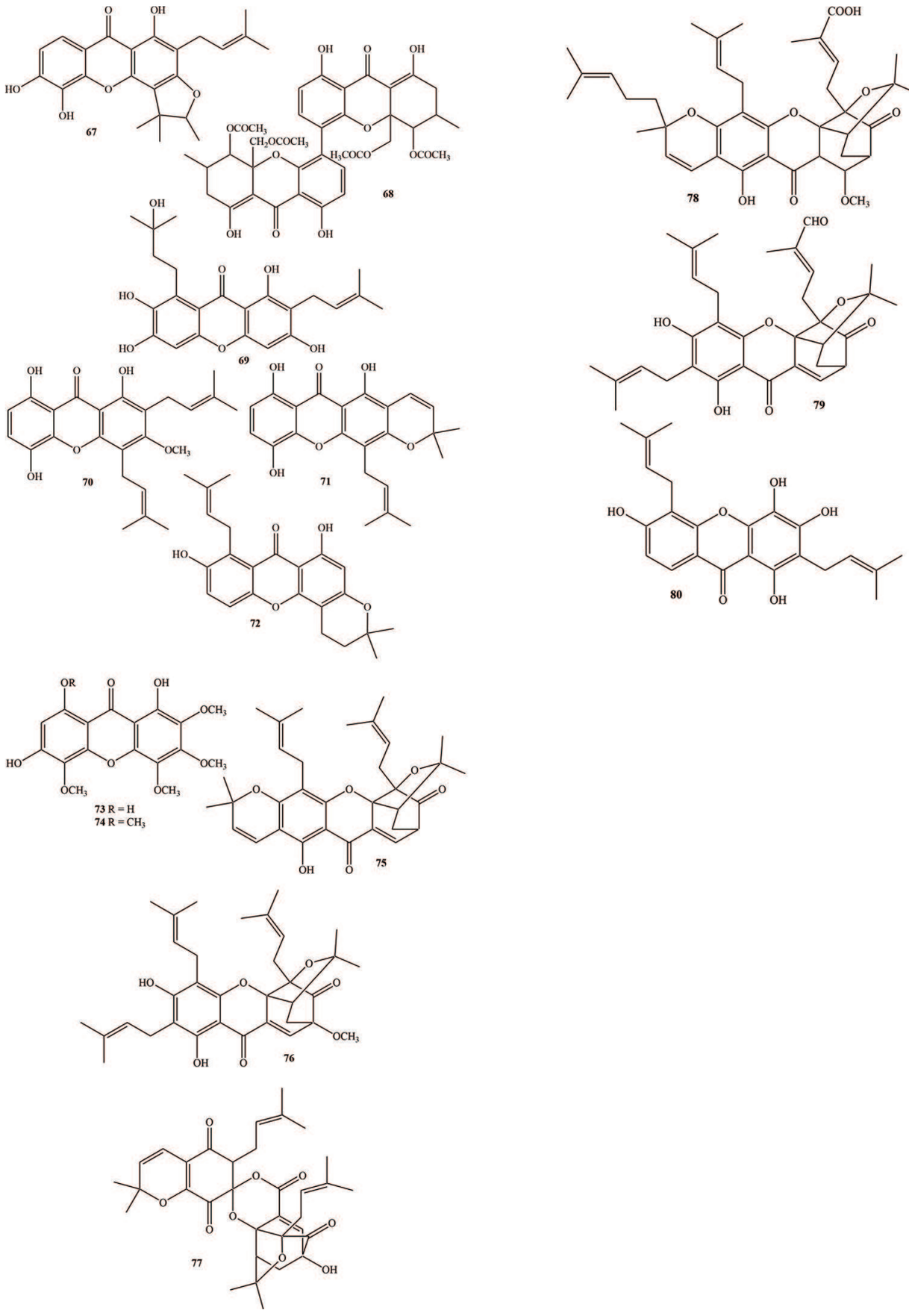


**Figure 5.** Structure of structure of xanthones **67–80**.

### 2.7. Stilbene and their cytotoxic activities

Stilbenoids are formed by flavonoid biosynthesis pathway and it consists on C6-C2-C6-based skeleton and usually found in peanuts, grapes and wines. Stilbenoid have a great interest on account due to their promising pharmacological activities including anticancer, antimicrobial, antioxidant and anti-inflammatory. Stilbenoid play important role of phytoalexin in plants. They play very important role in the defense of different pathogen.

Batatasin III inhibited growth of all cell lines including U251 glioma, CNS, MCF-7 breast, NCI-ADR/RES (ovarian expressing phenotype multiple drugs resistance), 786-0 renal NCI-H460 lung, non-small cell, HT29 colon, HaCat human keratinocytes, immortalized non-tumoral cell with $GI_{50}$ values close to 30 mg $mL^{-1}$ [82]. The cytotoxicity of Sciryagarol I and II was evaluate by MTT assay against human tumor cell lines MGC803, SMMC7721 and Hela and it showed significant cytotoxicity against Hela cell lines with $IC_{50}$ values 61.21 and 7.21 μM, respectively [83]. Oligostilbene macrostachyol D showed significant cytotoxicity to HeLa cells with $IC_{50}$ value of 4.13 μM. Cajanotone, cajaninstilbene acid, pinosylvin monomethyl ether, longistylin A and longistylin C showed strong cytotoxicities against human hepatoma HepG2, human breast adenocarcinoma MCF-7 and human lung cancer A549 cell lines with $IC_{50}$ values in the range of 3.5–15.5 μM, while doxorubicin used as a positive control [84]. Arachidin-1 induced human leukemia HL-60 cells death with $EC_{50}$ value 4.2 μM and it was more potent than resveratrol and induces cell death in HL-60 cells through only the intrinsic apoptotic pathway [85]. Combretastatin A-4 showed strong cytotoxity against human cancer cell lines: HepG2 with $IC_{50}$ value 9.2, SMMC-7721 with $IC_{50}$ value 12.8, BGC-803 with $IC_{50}$ value 12.2, MDA-MB-231 with $IC_{50}$ value 17.6 μM [86]. Macasiamenenes A2, macasiamenene K, Macasiamenene L, acasiamenenes M exhibited significant cytotoxicity against MOLT-3 cancer cell line with the $IC_{50}$ values in the range of 0.66–9.78 μM, etoposide used as Positive control standard [87] (**Figure 6**).

### 2.8. Phenanthrene and their cytotoxic activities

Phenanthrenes consist on three fused aromatic rings and found in *Dendrobium* and *Dioscorea* spp.

Cytotoxicities of 1,4,7-trihydroxy-2-methoxy-9,10-dihydrophenanthrene, 1,3,8-tri (phydroxybenzyl)-4-methoxy-phenanthrene-2,7-diol towards liver carcinoma HepG-2, promyelocytic leukaemia HL-60, ovarian carcinoma Skov-3 and epidermoid carcinoma A431 cancer cell lines were determined by MTT method. 1,4,7-trihydroxy-2-methoxy-9,10-dihydrophenanthrene is the strongest one to HepG-2 and Skov-3 with $IC_{50}$ of 15.9 and 124.0 mmol $L^{-1}$, respectively; 1,3,8-tri (phydroxybenzyl)-4-methoxy-phenanthrene-2,7-diol is the strongest one to HL-60 and A431 with $IC_{50}$ of 34.9 and 46.4 mmol $L^{-1}$, respectively [88]. Biphenanthrenes bulbophythrins A and B were evaluated in vitro for their inhibitory ability against human leukemia cell lines K562 and HL-60, human lung adenocarcinoma A549, human hepatoma BEL-7402 and human stomach cancer SGC-7901, using cisplatin as a positive control. Bulbophythrins A exhibited some selectivity against HL-60 and BEL-7402 with $IC_{50}$ values of $1.27 \times 10^{-3}$ and $1.22 \times 10^{-3}$ μmol $mL^{-1}$, respectively, whereas bulbophythrins B was most active against A549 with $IC_{50}$ value of $1.18 \times 10^{-3}$ μmol $mL^{-1}$ [89] (**Figure 7**).

http://dx.doi.org/10.5772/66898

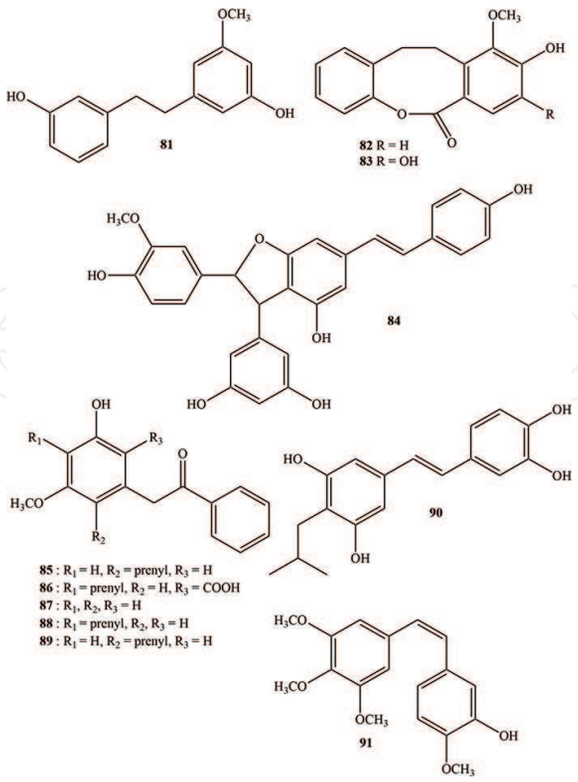


**Figure 6.** Structure of structure of stilbenoids **81–95**.

## 2.9. Lignan and their cytotoxic activities

Lignans based on (C6-C3)2 biphenolic skeleton and they consists on a large group of plant phenolic produced by the oxidative dimerization of two phenyl propanoid moieties. They are found in black berries, strawbwerries, raspberries, blue berries, broccoli, apricot, cabbage and many seeds. The antiestrogenic effects of lignans could help to reduce the risk of hormone-associated breast, uterine, ovarian and prostate cancers.

Pinoresinol, boehmenan and boehmenan H were found the most cytotoxic against human cancer cell lines Lu1, LNCaP and MCF-7 and a normal cell line HUVEC with $ED_{50}$ values for Lu1 cell line was 0.8, 10.4 and 5.3 g $mL^{-1}$, for LNCaP cell line was 0.5, 9.5 and 7.7 g $mL^{-1}$, while the $ED_{50}$ values for MCF-7 cell line was 1.7, 10.0 and 10.2 g $mL^{-1}$, $ED_{50}$ values for HUVEC 1.1, 9.0 and 6.2 g $mL^{-1}$ were observed for these lignans. The cytotoxic activity of pinoresinol against various cancer cell lines has been mentioned in the literature. It exhibited cytotoxicity against the KB cell line with an $IC_{50}$ value of 2.2 μg $mL^{-1}$ [90]. The cytotoxic activity of Sambucasinol A, B and C was evaluated by determining their inhibitory effects on human tumor cell lines A549, SK-OV-3, SK-MEL-2 and XF498 using the SRB bioassay. These compounds showed cytotoxicity against all cell lines, with $IC_{50}$ values in the range of 11.07–19.62 μM [89]. The $IC_{50}$ values for the pycnanthulignene A ranged from 0.20 μM (towards CCRF-CEM cells) for pycnanthulignene A to 195.12 μM (towards CEM/ADR5000 cells) for doxorubicin [41]. Phyllanthusmin C showed significant cytotoxicity against human leukemia HL-60 cells, human breast MCF-7 cells and human colon SW480 cell lines with $IC_{50}$ values of 9.2, 19.2 and 20.5 μM, compared with the cisplatin with $IC_{50}$ values of 1.7, 10.9 and 9.9 μM, respectively [92] (**Figure 8**).

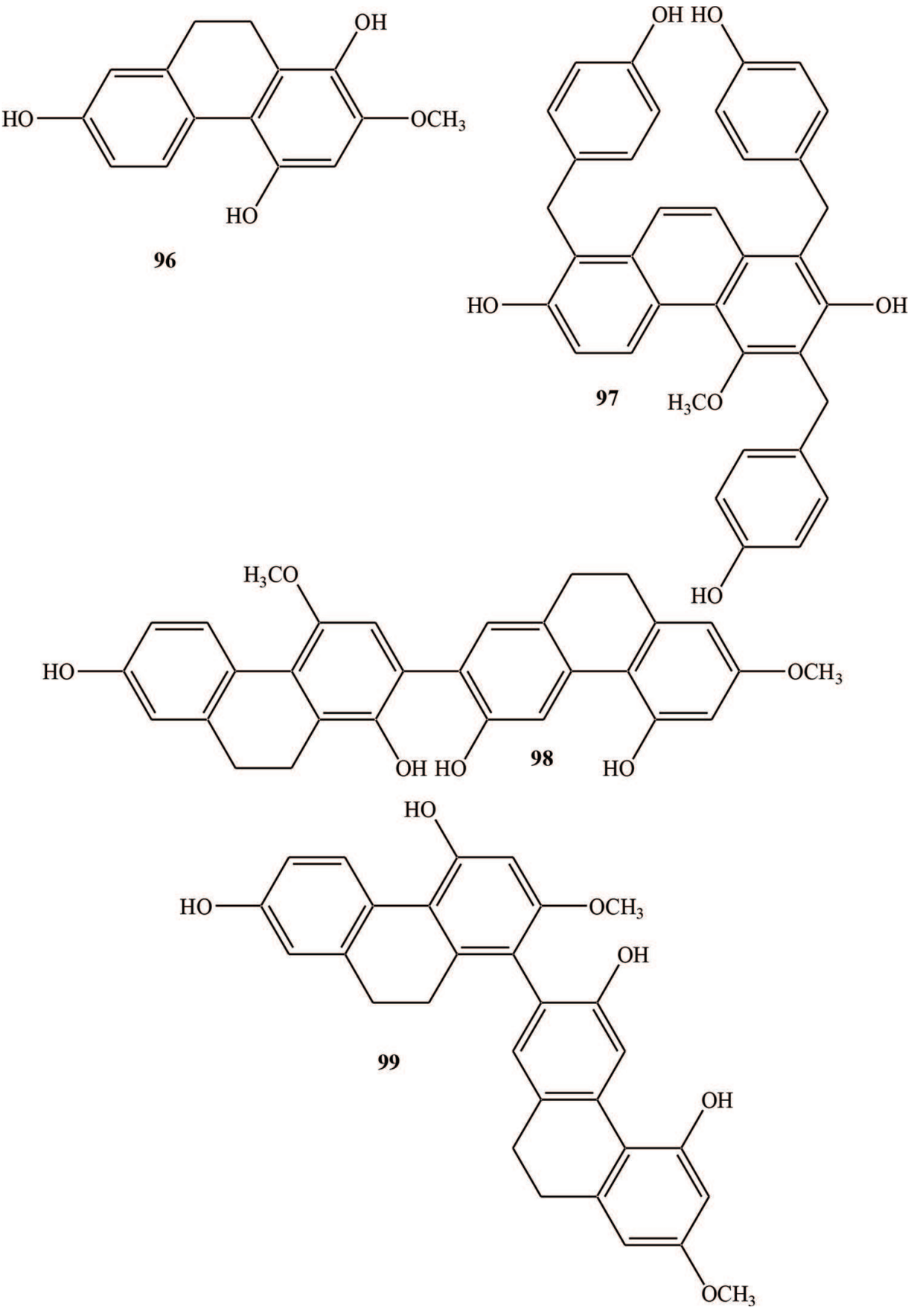


**Figure 7.** Structure of phenanthrenes **96–99**.

http://dx.doi.org/10.5772/66898

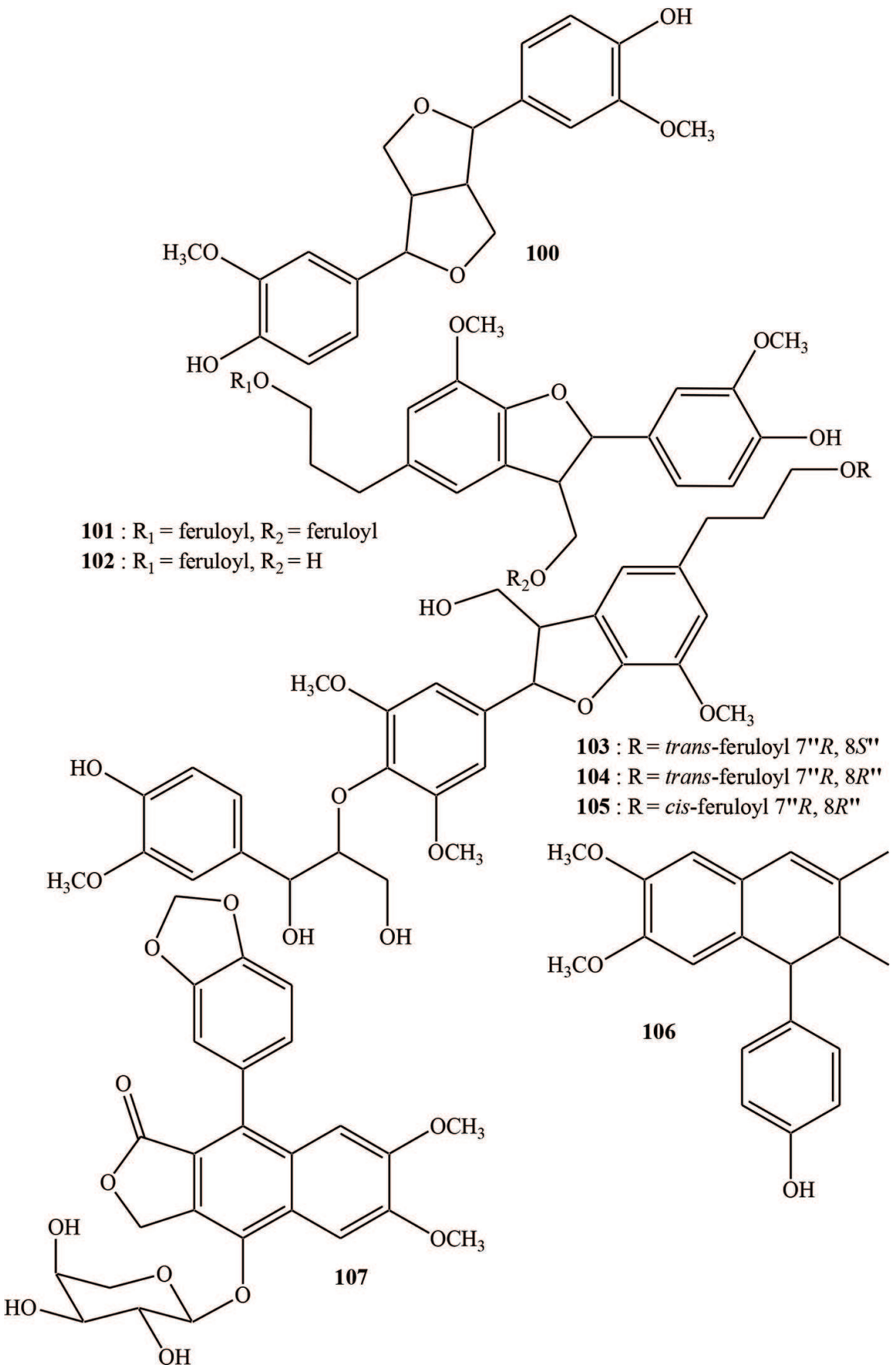


**Figure 8.** Structure of lignans **100–107**.

## 3. Conclusion

Phenolic plays an important role in human nutrition and health benefit and chemoprevention is one of the most realistic and promising approaches for the prevention of malignant disorders. The results of this chapter may help to identify the phenolic compounds from natural sources with optimized cytotoxic activity to be tested for the treatment of different types of tumors. Phenolic compounds are incorporated into them and the order of their incorporation efficiency is similar to its cytotoxic activity. The cytotoxic data of phenolic compounds compiled in this chapter and relationships presented here cannot only be useful in chemoprevention to choose the correct source of these compounds containing most active natural polyphenols, considering the individual genetic cancer risks and familial anamnesis but also in the selection of parent compounds to design and synthesize novel chemotherapy drugs starting from the valuable material given to us by the nature.

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