# Pro-Oxidant Natural Products as Anticancer Agents

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**Abstract:** Cancer cells produce high levels of reactive oxygen species (ROS) that lead to a state of increased basal oxidative stress. Since this state of oxidative stress makes cancer cells vulnerable to agents that further augment ROS levels, the use of pro-oxidant agents is emerging as an exciting strategy to selectively target tumor cells. Natural products have provided a significant contribution to the development of several drugs currently used in cancer chemotherapy. Although many natural products are known to affect the redox state of the cell, most studies on these compounds have focused on their antioxidant activity instead of on their pro-oxidant properties. This article provides an overview of natural products with pro-oxidant and anticancer activities, with special focus on plant secondary metabolites, and discusses their possible use as cancer chemotherapeutic agents.

**Keywords:** Alkaloids, cancer, hydrogen peroxide, phenolic compounds, plant secondary metabolites, prooxidant, reactive oxygen species, terpenoids.

## INTRODUCTION

Cancer kills over seven million people worldwide every year [1]. The mortality rate of this disease has not changed much in the past few decades even in developed countries as the United States [2]. Although cancer therapy in the form of surgery or radiotherapy is effective when the disease is early detected, many cancers are still diagnosed when cells from a primary tumor have already metastasized to other parts of the body. The main form of treatment at this point is chemotherapy, which consists of delivering drugs systemically so that they can reach and kill the tumor cells. But most of these drugs cause severe side effects in patients and, therefore, need to be used at suboptimal levels. The low efficacy of chemotherapy in patients with advanced cancers is reflected in the low 5-year survival rates observed in these patients [2]. For example, cancer statistics show that the most commonly diagnosed cancer in the world is lung cancer [1], that approximately 50% of patients diagnosed with this type of cancer have distant metastasis [2] and that only 3% of these patients manage to survive more than 5 years [2]. The low efficacy of cancer therapy for the treatment of patients with metastasis makes the development of novel chemotherapeutic agents necessary.

Despite the recent interest by pharmaceutical companies in molecular modeling, combinatorial chemistry and other synthetic chemistry techniques, natural products and medicinal plants continue to be an important source of new drugs. Natural products are not only used as therapeutic agents, but are also a source of lead compounds that have provided the basis for the semisynthesis or total synthesis of new drugs. An analysis of the sources of drugs approved from January 1981 to the middle of October 2008 revealed that 6% of the 1024 new chemical entities were unmodified natural products and that only 37% were drugs not related to natural products [3, 4]. The role these latter in drug discovery is particularly relevant in oncology. It is estimated that over the time frame from around the 1940s to 2006, of the 155 small molecules approved for cancer therapy, only 27% were not related to natural products [3]. The first plant-derived anticancer agents to advance into clinical use were the *Vinca* alkaloids vinblastine and vincristine. Other important plant-derived anticancer compounds include paclitaxel (taxol), the epipodophyllotoxin derivative etoposide, and the camptothecin derivatives topotecan and irinotecan [5]. The mechanism of action of these drugs is considered to consist in the inhibition of microtubule assembly (*Vinca* alkaloids and paclitaxel), inhibition of DNA topoisomerase II (etoposide) and inhibition of DNA topoisomerase I (campothecin derivatives). Recent evidence suggests that the formation of reactive oxygen species (ROS) may also contribute to the anticancer effects of these drugs [6-8]. The induction of oxidative stress by pro-oxidant agents is indeed emerging as an attractive anticancer strategy that may be used to target cancer cells selectively [9-13]. After discussing the role of oxidative stress in cancer and the possible use of pro-oxidant agents in cancer therapy, this article provides an overview of pro-oxidant natural products with anticancer activity and examines their potential as cancer chemotherapeutic agents.

## OXIDATIVE STRESS IN CANCER CELLS

Oxidative stress is an imbalance between the generation and elimination of reactive oxygen species in favor of the former, causing excessive oxidative damage to macromolecules, cells and tissues. Reactive oxygen species (ROS) is the collective term used to name oxygen radicals (including hydroxyl radical and superoxide radical) and some other non-radical derivatives of oxygen, such as hydrogen peroxide

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($H_2O_2$). ROS can easily generate free radicals (any species containing one or more unpaired electrons) and/or cause oxidative damage [14]. ROS are generated by all aerobic organisms and their production seems to be needed for signal-transduction pathways that regulate several different physiological processes. Excessive amounts of ROS, however, can start toxic and lethal chain reactions, which oxidize and disable structures that are required for cellular integrity and survival. ROS are generated in multiple compartments and by multiple enzymes within the cell. Important contributions include proteins within the plasma membrane, such as the growing family of NADPH oxidases; lipid metabolism within the peroxisomes; as well as the activity of various cytosolic enzymes such as cyclooxygenases. Although all these sources contribute to the overall ROS production, the vast majority of cellular ROS can be traced back to the mitochondria [15, 16].

Accumulating evidence indicates that cancer cells generate excessive levels of ROS and have a state of oxidative stress. Many malignant cells produce high levels of ROS in culture. For instance, Szatrowski and Nathan reported that several tumor cell lines, representing a variety of tissue types, constitutively produced large amounts of $H_2O_2$. They observed that the cumulative amount of $H_2O_2$ produced after 4 h by these tumor cells was comparable to the amount of $H_2O_2$ produced by similar numbers of phorbol ester-triggered neutrophils [17]. The increased production of ROS by cancer cells observed *in vitro* has also been found *in vivo*. For example, chronic lymphocytic leukemia cells freshly taken from patients showed increased ROS production compared with normal lymphocytes. This was also observed with B-cell lines from patients with Burkitt's lymphoma associated with Epstein–Barr virus infection and malignant B-cells from patients with hairy cell leukemia (see [18] and references therein). For solid tumors, however, demonstrating increased ROS production *in vivo* is difficult to achieve owing to methodological inadequacies, so most researchers have studied oxidative damage levels rather than ROS production. Such studies have shown increased levels of oxidative damage (e.g. 8OHdG) in human cancers and in animal cancers induced by a wide range of carcinogens (reviewed in [18]). Interestingly, the most important carcinogenic agents and behaviors induce oxidative stress, including most chemical carcinogens (e.g. *N*-nitrosamines, asbestos, arsenic), ultraviolet radiation, cancer-associated viruses or bacteria, inflammation, alcohol, tobacco smoke and obesity. It is also recognized that age is the principal risk factor for most cancers and that oxidative stress may be the most important causal factor in aging (see [19, 20] and references therein).

The increased levels of ROS of cancer cells seem to play a key role in cancer development [12, 18, 21]. ROS such as $H_2O_2$ can induce cell malignant transformation, and the malignant phenotype of tumor cells can be reversed by decreasing the levels of ROS [12, 22-24]. For instance, expression of the ROS generation system Nox1 in normal NIH3T3 fibroblasts resulted in cells with malignant characteristics that produced tumors in athymic mice. These transformed cells showed a 10-fold increase in $H_2O_2$ levels. When human catalase was expressed in these transformed cells, $H_2O_2$ concentration decreased, and the cells reverted to a normal appearance, the growth rate normalized, and cells no longer produced tumors in athymic mice [24]. In addition, ROS have been shown to participate in the most relevant aspects of carcinogenesis. Most researchers consider that cancer is a genetic disease caused by the acquisition of multiple mutations in genes that control cell proliferation, cell death and genomic instability [25]. It is also accepted that cells must develop several acquired capabilities in order to become a malignant cancer: increased cell proliferation (caused, in part, by resistance to growth inhibition and independence from mitogenic stimulation), apoptosis resistance, cellular immortalization, increased angiogenesis, invasion and metastasis. In addition, genetic instability is considered to be a key event that enables the acquisition of these capabilities [26, 27]. Accumulating experimental data indicate that an increase in the cellular concentrations of ROS such as $H_2O_2$ can explain all these hallmarks of cancer. It is known that an increase in the levels of $H_2O_2$ can lead to DNA damage, mutations, and genetic instability [26-31]; $H_2O_2$-induced DNA damage seems to be mediated by hydroxyl radical generated from $H_2O_2$ by the Fenton reaction [28-30]. Several studies have also demonstrated that ROS can induce cell proliferation [31], apoptosis resistance [32, 33], increased angiogenesis [34, 35], and invasion and metastasis [36-38]. Indeed, these studies showed that an increase in the levels of $H_2O_2$-detoxifying enzymes could reduce cell proliferation, promote apoptosis, and inhibit invasion, metastasis and angiogenesis. In short, cancer cells produce high levels of ROS that lead to a state of increased basal oxidative stress. Such state of oxidative stress is induced by the most important human carcinogens and plays an important role in cancer development.

## SELECTIVE ANTICANCER ACTIVITY OF PRO-OXIDANT AGENTS

Since cancer cells have increased levels of ROS that play an important role in carcinogenesis, agents with antioxidant activity may induce cancer preventive effects by reducing and/or preventing such increase in the cellular levels of ROS. Because pro-oxidant agents increase the cellular levels of ROS, it is recognized that these agents can induce carcinogenic effects. But when pro-oxidant agents increase the cellular levels of ROS to cytotoxic levels, these agents may induce selective killing of cancer cells and be therapeutically useful. It is important to mention that all these effects can be achieved by agents with both antioxidant and pro-oxidant properties (e.g. curcumin), which can act as cancer chemopreventive, carcinogenic, and chemotherapeutic agents mainly depending on the concentration by which they are used [12, 39].

The role of ROS in cancer therapy is increasingly being acknowledged and the induction of oxidative stress by pro-oxidant agents is emerging as an attractive anticancer strategy [9-12, 40-43]. Recent data suggests that ROS participate in the anticancer activity of many chemotherapeutic agents commonly used in the clinic, including paclitaxel, docetaxel, cisplatin, doxorubicin, arsenic trioxide, bortezomib, procarbazine and etoposide [6-8, 10, 40, 44-54]. For instance, although it has been known for many years that the microtubule protein tubulin is the therapeutic target for paclitaxel (taxol), recent experiments have shown that the accumulation of $H_2O_2$ is a crucial step for paclitaxel-induced cancer cell death both *in vitro* and *in vivo* [6, 8]. $H_2O_2$ seems to be a

key player in oxidative stress-induced cancer cell death. Many anticancer agents increase the levels of $H_2O_2$ [6, 45, 47], and $H_2O_2$ is known to be an efficient inducer of cell death in cancer cells [12, 48, 55]. Interestingly, cancer cells are more susceptible to $H_2O_2$-induced cell death than non-malignant cells [56-58]. Using several cancer and normal cell lines, Chen *et al*. [56] observed that high concentrations of ascorbic acid selectively killed a variety of cancer cells and that this effect was mediated by $H_2O_2$. They showed, for instance, that a concentration of 50 μM $H_2O_2$ induced more percentage of cell death in Burkitt's lymphoma cells than 250 μM in normal lymphocytes and normal monocytes [56]. This selective effect of $H_2O_2$ has also been observed in cells derived from solid tumors. Using lung cancer cells and non-malignant lung fibroblasts under the same experimental conditions, we recently found that specific concentrations of $H_2O_2$ and of the $H_2O_2$-generating agent pyrogallol induced selective killing of the cancer cells [59].

It is not clear why specific concentrations of $H_2O_2$ (and of pro-oxidant agents) can kill cancer cells selectively. *In vitro* and *in vivo* data indicate that tumor cells produce higher concentrations of $H_2O_2$ than their normal counterparts [17, 18, 31, 60-62]. This, and the fact that there is a threshold of $H_2O_2$ above which cells cannot survive, may explain why specific concentrations of $H_2O_2$ induce selective killing of cancer cells [12]. Excessive cellular accumulation of $H_2O_2$ may cause cell death through the induction of DNA damage, which seems to be mediated by hydroxyl radical generated from $H_2O_2$ in the presence of iron or copper (Fenton reaction) [28-30]. Unlike non-malignant cells, cancer cells have mutations in DNA repair genes and cannot properly repair specific types of DNA damage [25, 63]. It is possible that some cancers may have a reduced capacity to repair ROS-induced DNA damage and be more vulnerable than normal cells to the cytotoxic activity of ROS. It has also been proposed that the increased levels of copper found in various malignancies may explain why some pro-oxidant agents (e.g. plant polyphenols) can induce selective killing of cancer cells [64]. The increased levels of copper of cancer cells would favor the formation of higher levels of hydroxyl radical through the Fenton reaction.

## PRO-OXIDANT NATURAL PRODUCTS WITH ANTICANCER ACTIVITY

An overview of natural products with both pro-oxidant and anticancer activities is presented in Table **1**. The name of the natural product, the type of compound, the natural source (representative species) and the references are provided. The first part of the table comprises plant compounds of primary metabolism and their derivatives. Then, plant secondary metabolites, including phenolic compounds, terpenoids and alkaloids, are compiled. The last section includes other natural products from different natural sources (compounds of animal, microorganism, or marine origin, vitamins, etc). The mechanism involved in the generation of ROS is not available for most compounds and is not included. The general mechanisms involved in ROS generation by a variety of pro-oxidant agents (from natural and synthetic origin) have been discussed extensively elsewhere [42].

Some natural products reported in Table **1** are drugs currently used in cancer chemotherapy (e.g. paclitaxel, vincristine, vinblastine, bleomycin, mitomycin, doxorubicin, idarubicin, aclarubicin and actinomycin D). Others have entered clinical trials for the treatment of specific types of cancer (e.g. curcumin, epigallocatechin-3-gallate, genistein, resveratrol, camptothecin, perillil alcohol, licopene, phenylethyl isothiocyanate, sulforaphane, aplidin, eicosapentaenoic acid, linoleic acid, ursodeoxycholic acid, vitamin C, vitamin $D_2$ and vitamin $D_3$; see http://clinicaltrials.gov/). The chemical structures of these compounds are represented in Fig. (**1**) and Fig. (**2**). The anticancer activity of most compounds compiled in Table **1** has only been evaluated in pre-clinical models.

It is important to mention that, although the pro-oxidant effect of a specific natural product may not be the most important cytotoxic mechanism of action, this pro-oxidant effect may be responsible for the selective anticancer activity of the compound. For instance, it is known that the main mechanism of action of paclitaxel consists in the inhibition of microtubule assembly. A drug that only inhibits microtubule assembly would be equally cytotoxic in cells with the same proliferating rate, as microtubules are necessary for cell proliferation. Because it is known that cancer cells are more vulnerable to paclitaxel than highly proliferating non-malignant cells, it has been enigmatic for many years why this drug has certain selectivity for cancer cells [25]. Recently, it was observed that the accumulation of $H_2O_2$ is crucial for paclitaxel-induced cancer cell death both *in vitro* and *in vivo* [6, 8]. Being well known that $H_2O_2$ can induce selective killing of cancer cells, it seems possible that paclitaxel-induced $H_2O_2$ production plays a role in the selective anticancer effects of this natural product.

Since the redox state of the cell is important for many cellular processes, it has been discussed that pro-oxidant agents may act as "dirty" drugs (agents that modulate multiple molecular targets through pleiotropic interactions). However, recent research suggests that this pleiotropic mode of action may be an advantage to overcome cancer cell drug resistance typical of drugs acting on just one target [42]. Although pro-oxidant agents could be used as stand-alone drugs, evidence suggests that they could also be used in combination [42]. Indeed, although ROS induce cancer cell death, tumor cells are known to develop mechanisms that prevent ROS from reaching cytotoxic levels. The glutathione and thioredoxin antioxidant systems are crucial for detoxifying ROS. These antioxidant systems are activated in cancer cells and play an important role in the development of resistance to many anticancer agents [65-71]. The possible drug resistance induced by pro-oxidant agents could be reduced with glycolysis inhibitors [13]. Evidence indicates that pro-oxidant agents can increase the cellular levels of $H_2O_2$ and that glycolysis inhibitors can reduce the capacity of cells to detoxify $H_2O_2$. Experimental data have shown that malignant cells are more susceptible to glucose deprivation than non-transformed cells, and that an increase in the levels of $H_2O_2$ may mediate the cytotoxic effect induced by glucose deprivation [62, 72-74]. Two possible mechanisms may explain why the activation of glycolysis plays an important function in protecting tumor cells from $H_2O_2$-induced cell death. First, the activation of glycolysis increases the formation of pyru-

**Table 1. Natural Products with Pro-Oxidant and Anticancer Activities**

| Compound | Type of Compound | Natural Source | References |
|---|---|---|---|
| **Compounds of Primary Metabolism and derivatives** | | | |
| Abrin | Aminoacid | *Abrus precatorius* (Fabaceae) | [81, 82] |
| Ajoene | Organosulfur | *Allium sativum* (Alliaceae) | [83, 84] |
| Allicin | Organosulfur | *Allium sativum* (Alliaceae) | [85-87] |
| Benzyl isothiocyanate | Organosulfur | *Brassica* spp. (Brassicaceae) | [88, 89] |
| Diallyl disulfide | Organosulfur | *Allium* spp. (Alliaceae) | [90, 91] |
| Dimethyl disulfide | Organosulfur | *Allium* spp. (Alliaceae) | [92] |
| Jasmonic acid | Fatty acid | *Jasminum* spp. (Oleaceae), widespread | [93] |
| Linoleic acid | Fatty acid | *Carthamus tinctorius* (Asteraceae) | [94, 95] |
| Linolenic acid | Fatty acid | *Perilla frutescens* (Lamiaceae) | [95-97] |
| L-Mimosine | Aminoacid | *Mimosa* spp., *Leucaena* spp. (Fabaceae) | [98, 99] |
| Melatonin | Aminoacid | *Prunus cerasus* (Rosaceae) | [100, 101] |
| Methyl jasmonate | Fatty acid | *Jasminum* spp. (Oleaceae), widespread | [93, 102] |
| Phenylethylisothiocyanate | Organosulfur | *Brassica* spp. (Brassicaceae) | [89, 103, 104] |
| Sorbitol | Sugar alcohol | *Malus* spp. (Rosaceae) | [105] |
| Sulforaphane | Organosulfur | *Brassica* spp. (Brassicaceae) | [106, 107] |
| **Phenolic Compounds** | | | |
| 2'-Hydroxycinnamaldehyde | Phenolic acid | *Cinnamomum* spp. (Lauraceae) | [108, 109] |
| 3,7,4'-trihydroxyflavone | Flavone | *Rhus chinensis* (Anacardiaceae) | [110, 111] |
| 4'-Hydroxycinnamaldehyde | 4'-Hydroxycinnamaldehyde | *Alpinia galanga* (Zingiberaceae) | [112] |
| 4-Hydroxycinnamic acid | Hydroxycinnamic acid | *Erythrina fusca* (Fabaceae), widespread | [113, 114] |
| 6- Dehydrogingerdione | Aryl alkanones | *Zingiber officinale* (Zingiberaceae) | [115, 116] |
| 6-Gingerol | Aryl alkanones | *Zingiber officinale* (Zingiberaceae) | [117, 118] |
| 6-Shogaol | Aryl alkanones | *Zingiber officinale* (Zingiberaceae) | [119] |
| 8-Shogaol | Aryl alkanones | *Zingiber officinale* (Zingiberaceae) | [120] |
| Acacetin | Flavone | *Robinia pseudoacacia* (Fabaceae) | [121, 122] |
| Aesculetin | Coumarin | *Aesculus hippocastanum* (Hippocastanaceae) | [123] |
| Aloe-emodin | Anthraquinone | *Rheum* spp. (Polygonaceae), *Cassia* spp. (Fabaceae) | [124, 125] |
| Apigenin | Flavone | *Petroselinum crispum* (Apiaceae), widespread | [126, 127] |
| Baicalein | Flavone | *Scutellaria baicalensis* (Lamiaceae), *Oroxylum indicum* (Bignoniaceae) | [128, 129] |
| Baicalin | Flavone | *Scutellaria* spp. (Lamiaceae) | [130, 131] |
| Benzaldehyde | Aromatic aldehyde | *Prunus* spp. (Rosaceae), widespread | [132, 133] |
| Betuletol 3-methyl ether | Flavonol | *Allagopappus viscosissimus* (Asteraceae) | [134] |
| Butein | Chalcone | *Rhus verniciflua* (Anacardiaceae) | [135] |
| Caffeic acid | Phenolic acid | *Coffea* spp.(Rubiaceae), widespread | [136, 137] |

**(Table 1) contd….**

| Compound | Type of Compound | Natural Source | References |
|---|---|---|---|
| Cajanol | Isoflavanone | *Cajanus cajan* (Fabaceae) | [138] |
| Catechin | Flavan-3-ol | *Acacia catechu* (Fabaceae), widespread | [139, 140] |
| Catechol | Simple phenol | *Cola* spp. (Malvaceae), *Gaultheria* spp. (Ericaceae) | [141-143] |
| Chebulinic acid | Hydrolyzable tannin | *Terminalia chebula* (Combretaceae) | [144, 145] |
| Chlorogenic acid | Phenolic acid | *Coffea* spp. (Rubiaceae), widespread | [146-148] |
| Chrysin | Flavone | *Prunus* spp. (Rosaceae), | [149-151] |
| Chrysoeriol | Flavone | *Medicago sativa* (Fabaceae), widespread | [152] |
| Chrysophanol | Anthraquinone | *Rhamnus* spp. (Rhamnaceae), *Rheum* spp. (Polygonaceae) | [153] |
| Curcumin | Diarylheptanoid | *Curcuma longa* (Zingiberaceae) | [39, 154, 155] |
| Cyanidin | Anthocyanidin | *Vaccinium* spp. (Ericaceae), *Prunus* spp. (Rosaceae) | [156, 157] |
| Cyanidin 3-glucoside | Anthocyanin | *Vaccinium* spp. (Ericaceae), *Prunus* spp. (Rosaceae) | [157, 158] |
| Cyanidin-3-rutinoside | Anthocyanin | *Vaccinium* spp. (Ericaceae), *Prunus* spp. (Rosaceae) | [157, 159] |
| Daidzein | Isoflavone | *Glycine max* (Fabaceae), widespread | [160] |
| Dantron | Anthraquinone | *Xyris semifuscata* (Xyridaceae) | [161, 162] |
| Daphnetin | Coumarin | *Daphne* spp. (Thymelaeaceae) | [163] |
| Delphinidin | Anthocyanidin | *Delphinium* spp. (Ranunculaceae) | [157, 164] |
| Delphinidin 3-sambubioside | Anthocyanin | *Hibiscus* spp. (Malvaceae) | [165] |
| Diospyrin | Naphthoquinone | *Diospyros montana* (Ebenaceae) | [166] |
| Ellagic acid | Phenolic acid | *Vaccinium* spp. (Ericaceae), widespread | [167] |
| Emodin | Anthraquinone | *Rheum* spp. (Polygonaceae) | [168] |
| Epicatechin | Flavan-3-ol | *Acacia catechu* (Fabaceae), widespread | [139, 169] |
| Epicatechin-gallate | Flavan-3-ol | *Camellia sinensis* (Theaceae) | [170] |
| Epigallocatechin | Flavan-3-ol | *Camellia sinensis* (Theaceae) | [170] |
| Epigallocatechin-3-gallate | Flavan-3-ol | *Camellia sinensis* (Theaceae) | [170, 171] |
| Eriodictyol | Flavanone | *Eriodictyon californicum* (Boraginaceae) | [172] |
| Esculetin (Aesculetin) | Coumarin | *Aesculus hippocastanum* (Hippocastanaceae) | [163, 173] |
| Eugenol | Phenylpropanoid | *Eugenia caryophyllata* (Myrtaceae) | [174] |
| Eupafolin | Flavone | *Eupatorium perfoliatum* (Asteraceae), *Artemisia princeps* (Asteraceae) | [175-177] |
| Ferulic acid | Phenolic acid | *Ferula communis* (Apiaceae), widespread | [136] |
| Fisetin | Flavonol | *Fragaria* spp. (Rosaceae), widespread | [178, 179] |
| Flavokawain B | Chalcone | *Piper methysticum* (Piperaceae) | [180] |
| Fraxetin | Coumarin | *Fraxinus* spp. (Oleaceae) | [173, 181] |
| Gallic acid | Phenolic acid | *Kalanchoe* spp. (Crassulaceae), widespread | [182, 183] |
| Gambogic acid | Xanthone | *Garcinia hanburyi* (Clusiaceae) | [184, 185] |

**(Table 1) contd….**

| Compound | Type of Compound | Natural Source | References |
|---|---|---|---|
| Genistein | Isoflavone | *Genista* spp. (Fabaceae), widespread | [186] |
| Gentiacaulein | Xanthone | *Gentiana kochiana* (Gentianaceae) | [187] |
| Gentiakochianin | Xanthone | *Gentiana kochiana* (Gentianaceae) | [187] |
| Guttiferone-A | Benzophenone | *Garcinia livingstonei* (Clusiaceae) | [188] |
| Hesperetin | Flavanone | *Citrus* spp. (Rutaceae) | [189, 190] |
| Hydroxytyrosol | Simple Phenol | *Olea europaea* (Oleaceae) | [191] |
| Icariin | Flavonol glycoside | *Epimedium* spp. (Berberidaceae) | [192] |
| Isoeugenol | Phenylpropanoid | *Eugenia caryophyllata* (Myrtaceae) | [193, 194] |
| Isoliquiritigenin | Chalcone | *Glycyrrhiza glabra* (Fabaceae) | [178, 195] |
| Juglone | Naphtoquinone | *Juglans regia* (Juglandaceae) | [196, 197] |
| Kaempferol | Flavonol | *Kaempferia galanga* (Zingiberaceae), widespread | [198, 199] |
| Liquiritigenin | Flavanone | *Glycyrrhiza glabra* (Fabaceae) | [200] |
| Luteolin | Flavone | *Reseda luteola* (Resedaceae), widespread | [201, 202] |
| Malvidin | Anthocyanidin | *Althaea rosea* (Malvaceae) | [157, 203] |
| Malvidin 3-glucoside | Anthocyanin | *Vitis* spp. (Vitaceae) | [157, 204] |
| Methyl gallate | Phenolic acid | *Camellia sinensis* (Theaceae) | [205] |
| Morin | Flavone | *Maclura* spp. (Moraceae) | [206] |
| Myricetin | Flavonol | *Myrica rubra* (Myricaceae), widespread | [59, 207] |
| Naringenin | Flavanone | *Citrus* spp. (Rutaceae), widespread | [208, 209] |
| Nordihydroguaiaretic acid | Phenolic acid | *Larrea* spp. (Zygophyllaceae) | [210-212] |
| Norwogonin | Flavone | *Scutellaria* spp.(Lamiaceae) | [213] |
| Pelargonidin | Anthocyanidin | *Pelargonium* spp. (Geraniaceae) | [157, 203] |
| Pelargonidin 3-glucoside | Anthocyanin | *Vaccinium* spp. (Ericaceae) | [157, 214] |
| Pentagalloyl glucose | Hydrolyzable tannin | *Quercus infectoria* (Fagaceae) | [215, 216] |
| Peonidin | Anthocyanidin | *Paeonia* spp. (Ranunculaceae) | [157, 203] |
| Peonidin 3-glucoside | Anthocyanin | *Vaccinium* spp. (Ericaceae) | [157, 217] |
| Phloretin | Chalcone | *Malus* spp. (Rosaceae) | [178, 218] |
| Plumbagin | Naphthoquinone | *Drosera* spp. (Droseraceae) | [219, 220] |
| Procyanidin B2 | Proanthocyanidin | *Cinnamomum cassia* (Lauraceae), *Vaccinium* spp. (Ericaceae) | [221, 222] |
| Protoapigenone | Flavone | *Thelypteris torresiana* (Thelypteridaceae) | [223] |
| Psoralen | Furanocoumarin | *Psoralea corylifolia* (Fabaceae) | [224, 225] |
| Pterostilbene | Stilbenoid | *Vitis* spp. (Vitaceae) | [226] |
| Quercetin | Flavonol | *Citrus* spp. (Rutaceae), widespread | [207] |
| Resveratrol | Stilbenoid | *Vitis* spp. (Vitaceae) | [227, 228] |
| Rhein | Anthraquinone | *Rheum* spp. (Polygonaceae) | [229, 230] |
| Rosmarinic acid | Hydroxycinnamic acid | *Rosmarinus officinalis* (Lamiaceae), widespread | [231, 232] |

**(Table 1) contd….**

| Compound | Type of Compound | Natural Source | References |
|---|---|---|---|
| Rottlerin | Phloroglucinol | *Mallotus philippinensis* (Euphorbiaceae) | [233, 234] |
| Rutin | Flavonol | *Ruta* spp. (Rutaceae), widespread | [235-238] |
| Salicylic acid | Phenolic acid | Salix spp. (Salicaceae) | [239-241] |
| Shikonin | Naphthoquinone | *Lithospermum erythrorhizon* (Boraginaceae) | [242, 243] |
| Sinapic acid | Phenolic acid | *Brassica* spp.(Brassicaceae), widespread | [113, 114] |
| Sophoranone | Flavanone | *Sophora subprostrata* (Fabaceae) | [244] |
| Tannic acid | Tannin | *Quercus* spp. (Fagaceae), widespread | [245, 246] |
| Taxifolin | Flavanonol | *Silybum marianum* (Asteraceae) | [111, 149, 247] |
| Tricetin | Flavone | *Oryza sativa* (Poaceae) | [248] |
| Usnic acid | Dibenzofuran | *Usnea* spp. (Parmeliaceae) | [249, 250] |
| Vanillin | Phenolic acid | *Vanilla* spp. (Orchidaceae) | [251-253] |
| Wogonin | Flavone | *Scutellaria baicalensis* (Lamiaceae) | [254, 255] |
| Xanthohumol | Chalcone | *Humulus lupulus* (Cannabaceae) | [256, 257] |
| Xanthotoxin | Furanocoumarin | *Ammi majus* (Apiaceae) | [258, 259] |
| **Terpenoids** | | | |
| 18β-Glycyrrhetinic acid | Triterpenoid | *Glycyrrhiza glabra* (Fabaceae) | [260, 261] |
| Andrographolide | Diterpenoid | *Andrographis paniculata* (Acanthaceae) | [262] |
| Artemisinin | Lactone sesquiterpenoid | *Artemisia annua* (Asteraceae) | [263-265] |
| Asiatic acid | Triterpenoid | *Centella asiatica* (Mackinlayaceae) | [266] |
| Astilbotriterpenic acid | Triterpenoid | *Astilbe chinensis* (Saxifragaceae) | [267] |
| Betulinic acid | Triterpenoid | *Betula* spp. (Betulaceae) | [268] |
| Bixin | Apocarotenoid | *Bixa orellana* (Bixaceae) | [269] |
| Bufalin | Cardiac glycoside | *Bufo bufo* (Bufonidae) | [270] |
| Cannabidiol | Cannabinoid | *Cannabis sativa* (Cannabaceae) | [271-273] |
| Costunolide | Sesquiterpenoid | *Laurus nobilis* (Lauraceae) | [274, 275] |
| Cucurbitacin B | Triterpenoid | *Iberis amara* (Brassicaceae) | [276] |
| Dioscin | Steroidal saponin | *Dioscorea* spp. (Dioscoreaceae) | [277] |
| Diosgenin | Steroidal sapogenin | *Dioscorea* spp. (Dioscoreaceae) | [278] |
| Erythrodiol | Triterpenoid | *Olea europaea* (Oleaceae) | [279, 280] |
| Farnesol | Sesquiterpenoid | *Vachellia farnesiana* (Fabaceae), widespread | [281-283] |
| Ginkgolide B | Diterpenoid | *Ginkgo biloba* (Ginkgoaceae) | [284, 285] |
| Ginsenoside RH-2 | Triterpenoid saponin | *Ginkgo biloba* (Ginkgoaceae) | [286, 287] |
| Glaucocalyxin A | Diterpenoid | *Rabdosia japonica* var. glaucocalyx (Lamiaceae) | [288] |
| Guggulsterone | Triterpenoid | *Commiphora mukul* (Burseraceae) | [289, 290] |
| Gypenosides | Triterpenoid | *Gynostemma pentaphyllum* (Cucurbitaceae) | [291, 292] |
| Helenalin | Sesquiterpenoid | *Arnica* spp. (Asteraceae) | [293] |
| Linalool | Monoterpenoid | *Coriandrum sativum* (Apiaceae), widespread | [294] |

**(Table 1) contd….**

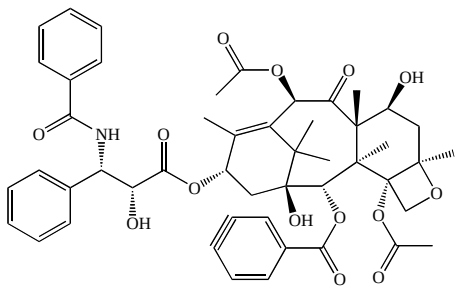
| Compound | Type of Compound | Natural Source | References |
|---|---|---|---|
| Lupeol | Triterpenoid | *Mangifera* spp. (Anacardiaceae), widespread | [295] |
| Lycopene | Carotenoid | *Solanum lycopersicum* (Solanaceae) | [296-298] |
| Oleandrin | Cardiac glycoside | *Nerium oleander* (Apocynaceae) | [299] |
| Oleanolic acid | Triterpenoid | *Olea europaea* (Oleaceae), widespread | [300, 301] |
| Oleuropein | Iridoid | *Olea europaea* (Oleaceae) | [302-304] |
| Oridonin | Diterpenoid | *Rabdosia rubescens* (Lamiaceae) | [305] |
| Ouabain | Cardiac glycoside | *Strophanthus gratus, S. kombe* (Apocynaceae) | [306] |
| Ovatodiolide | Diterpenoid | *Anisomeles indica* (Lamiaceae) | [307] |
| Taxol | Diterpenoid | *Taxus brevifolia* (Taxaceae) | [6, 308, 309] |
| Parthenolide | Sesquiterpenoid | *Chrysanthemum parthenium* (Asteraceae) | [310, 311] |
| Perillyl alcohol | Monoterpenoid | *Perilla frutescens* (Lamiaceae) | [312, 313] |
| Polygodial | Sesquiterpenoid | *Tasmannia* spp. (Winteraceae) | [314, 315] |
| Pristimerin | Triterpenoid | *Maytenus heterophylla* (Celastraceae) | [316, 317] |
| Protopanaxadiol | Triterpenoid saponin | *Panax ginseng* (Araliaceae) | [318, 319] |
| Sarsasapogenin | Steroidal sapogenin | *Smilax* spp. (Smilacaceae) | [320] |
| Tetrahydrocannabinol | Cannabinoid | *Cannabis sativa* (Cannabaceae) | [321] |
| Thymol | Monoterpenoid | *Thymus* spp. (Lamiaceae), widespread | [322] |
| Triptolide | Diterpenoid | *Tripterygium wilfordii* (Celastraceae) | [323, 324] |
| Ursolic acid | Triterpenoid | *Arctostaphylos uva-ursi* (Ericaceae), widespread | [325] |
| Uvaol | Triterpenoid | *Olea europaea* (Oleaceae) | [280] |
| Withaferin | Withasteroid | *Withania somnifera* (Solanaceae) | [326, 327] |
| α-Hederin | Triterpenoid saponin | *Hedera helix* (Araliaceae) | [328] |
| α-humulene | Sesquiterpenoid | *Humulus lupulus* (Cannabaceae) | [329] |
| β-Amyrin | Triterpenoid | *Medicago sativa* (Fabaceae), widespread | [330] |
| β-carotene | Carotenoid | *Daucus carota* (Apiaceae), widespread | [331-333] |
| β-Escin (aescin) | Triterpenoid saponin | *Aesculus hippocastanum* (Hippocastanaceae) | [334] |
| Atractyloside | Diterpenoid | *Atractylis* spp. (Asteraceae) | [335, 336] |
| β-Sitosterol | Phytosterol | *Serenoa repens* (Arecaceae), widespread | [337] |
| Vernolepin | Lactone sesquiterpenoid | *Vernonia hymenolepis* (Compositae) | [338] |
| **Alkaloids** | | | |
| 6-Methoxydihydrosanguinarine | Benzophenanthridine | *Hylomecon hylomeconoides* (Papaveraceae) | [339, 340] |
| Berberine | Isoquinoline | *Berberis* spp. (Berberidaceae) | [341, 342] |
| Boldine | Aporphine | *Peumus boldus* (Monimiaceae) | [343, 344] |
| Caffeine | Xanthine | *Coffea* spp. (Rubiaceae), *Camellia sinensis* (Theaceae) | [345-347] |
| Camptothecin | Quinoline | *Camptotheca acuminata* (Nyssaceae) | [7, 348] |
| Cepharanthine | Isoquinoline | *Stephania cepharantha* (Menispermaceae) | [349, 350] |

**(Table 1) contd….**

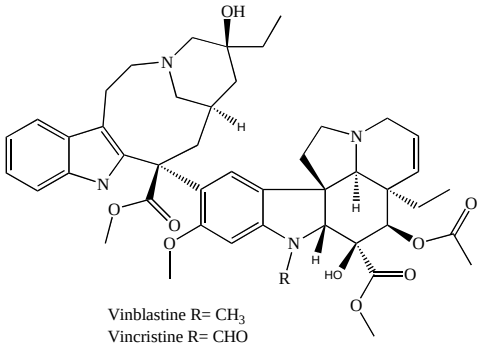
| Compound | Type of Compound | Natural Source | References |
|---|---|---|---|
| Chelerythrine | Phenanthridine | *Chelidonium majus* (Papaveraceae) | [351-353] |
| Ellipticine | Pyridocarbazole | *Ochrosia elliptica* (Apocynaceae) | [354-356] |
| Homoharringtonine | Cephalotaxine | *Cephalotaxus harringtonia* (Cephalotaxaceae) | [357] |
| Indole acetic acid | Indole | *Arabidopsis thaliana* (Brassicaceae) | [358, 359] |
| Indole-3-carbinol | Indole | *Brassica* spp. (Brassicaceae) | [360] |
| Lycopodine | Quinolizidine | *Lycopodium clavatum* (Lycopodiaceae) | [361] |
| Morphine | Phenanthrene | *Papaver somniferum* (Papaveraceae) | [362, 363] |
| Oxymatrine | Quinolizidine | *Sophora flavescens* (Fabaceae) | [364] |
| Pancratistatin | Phenanthridine | *Hymenocallis* spp. (Amaryllidaceae) | [365, 366] |
| Piperine | Piperidine | *Piper* spp. (Piperaceae) | [367, 368] |
| Sampangine | Aporphine | *Cananga odorata* (Annonaceae) | [369] |
| Sanguinarine | Benzylisoquinoline | *Sanguinaria canadensis* (Papaveraceae) | [353, 370] |
| Tetrandrine | Bis-benzylisoquinoline | *Stephania tetrandra* (Menispermaceae) | [371, 372] |
| Tomatine | Steroidal | *Solanum lycopersicum* (Solanaceae) | [373, 374] |
| Vinblastine | Bis-indole | *Catharanthus roseus* (Apocynaceae) | [375, 376] |
| Vincristine | Bis-indole | *Catharanthus roseus* (Apocynaceae) | [377, 378] |
| **Other Natural Products** | | | |
| 4-Acetyl-12,13-epoxyl-9-trichothecene-3,15-diol | Macrocyclic Trichocenes | *Isaria japonica* (Onygenaceae) | [379] |
| Aclarubicin | anthracycline | *Streptomyces galilaeus* (Streptomycetaceae) | [380] |
| Actinomycin-D | Polypeptide | *Streptomyces* spp. (Streptomycetaceae) | [381, 382] |
| Aplidin | Depsipeptide | *Aplidium albicans* (Clavelinidae) | [383-385] |
| Arachidonic acid | Fatty acid | Widespread in vertebrates | [96, 386, 387] |
| Asciddemin | Pyridoacridine | *Cystodytes dellechiajei* (Polycitoridae) | [388, 389] |
| Bleomycin | Glucopeptide | *Streptomyces verticillus* (Streptomycetaceae) | [390, 391] |
| Boningmycin | Glucopeptide | *Streptomyces verticillus var. pingyangensis* (Streptomycetaceae) | [392] |
| Butenolide | Lactone | Angelica spp. (Apiaceae) | [393] |
| Capsaicin | Capsaicinoid | *Capsicum spp*. (Solanaceae) | [394, 395] |
| Chenodeoxycholic acid | Bile acid | Liver of animals | [396-398] |
| Cholic acid | Bile acid | Liver of animals | [399, 400] |
| C-phycocyanin | Phycobiliprotein | *Aphanizomenon flos-aquae* (Nostocaceae) | [401] |
| Cribrostatin 6 | Quinone | *Cribrochalina* spp. (Haliclonidae) | [402] |
| Daunomycin | anthracycline | *Streptomyces peucetius* (Streptomycetaceae) | [403] |
| Deoxycholic acid | Bile acid | Liver of animals | [397, 398, 404] |
| Deoxynivalenol (Vomitoxin) | Epoxy-sesquiterpenoid | *Fusarium* spp. (Nectriaceae) | [405, 406] |
| Docosahexaenoic acid (DHA) | Fatty acid | *Crypthecodinium cohnii* , *Schizochytrium* spp. | [407] |

**(Table 1) contd….**

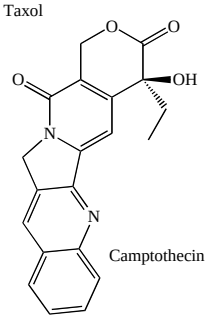
| Compound | Type of Compound | Natural Source | References |
|---|---|---|---|
| Doxorubicin | Anthracycline | *Streptomyces* spp. (Streptomycetaceae) | [377, 408, 409] |
| Eicosapentaenoic acid (EPA) | Fatty acid | *Crypthecodinium cohnii, Parietochloris incise* | [96, 410, 411] |
| F-2 Mycotoxin (Zearalenone) | Trichothecene | *Gibberella* spp. (Nectriaceae) | [412, 413] |
| Fucoxanthin | Carotenoid | *Undaria pinnatifida* (Alariaceae) | [414] |
| Isoobtusilactone A | Butanolide | *Cinnamomum kotoense* (Lauraceae) | [415, 416] |
| Kotomolide A | Butyrolactone | *Cinnamomum kotoense* (Lauraceae) | [417] |
| Mitomycin C | Aziridine | *Streptomyces caespitosus* (Streptomycetaceae) | [418-420] |
| Neocarzinostatin | chromoprotein enediyne | *Streptomyces carzinostaticus* (Streptomycetaceae) | [421] |
| Norharman | β-carboline alkaloid | *Passiflora incarnata* (Passifloraceae) | [422, 423] |
| Ochratoxin A | Pentaketide | *Aspergillus ochraceus* (Trichocomaceae) | [424-426] |
| Patulin | Furopyranone | *Penicillium* spp. (Trichocomaceae) | [427-429] |
| Putrescine-1,4-dicinnamide | Phenylpropanoid | *Pholiota spumosa* (Strophariaceae) | [430] |
| Secotenuifolide | Butanolide | *Cinnamomum tenuifolium* (Lauraceae) | [431] |
| T-2 mycotoxin | Trichothecene | *Fusarium* spp. (Nectriaceae) | [432, 433] |
| Ursodeoxycholic acid | Bile acid | Liver of animals | [434] |
| Vitamin A (retinol) | Carotenoid | *Daucus carota* (Apiaceae) | [435-437] |
| Vitamin C (Ascorbic acid) | Butenolide | *Citrus* spp. (Rutaceae), widespread | [56, 438, 439] |
| Vitamin D2 (Ergocalciferol) | Steroid | *Lentinus edodes* (Marasmiaceae) | [440] |
| Vitamin D3 (Cholecalciferol) | Steroid | Animal origin | [441, 442] |
| Vitamin K2 | Naftoquinone | *Brassica* spp. (Brassicaceae), widespread | [443, 444] |
| Vitamin K3 | Naftoquinone | *Brassica* spp. (Brassicaceae) , widespread | [445, 446] |



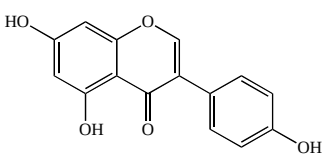
Taxol



Vinblastine R= $CH_3$
Vincristine R= CHO



Camptothecin



Genistein

**(Fig. 1) contd…**

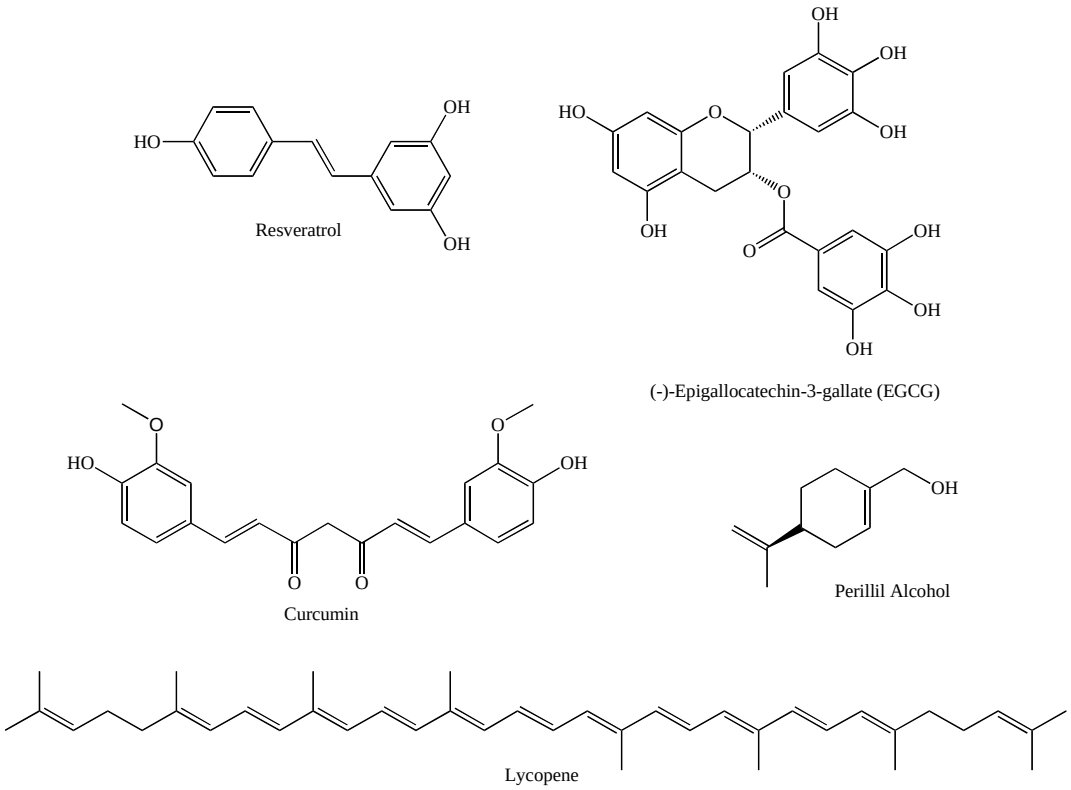
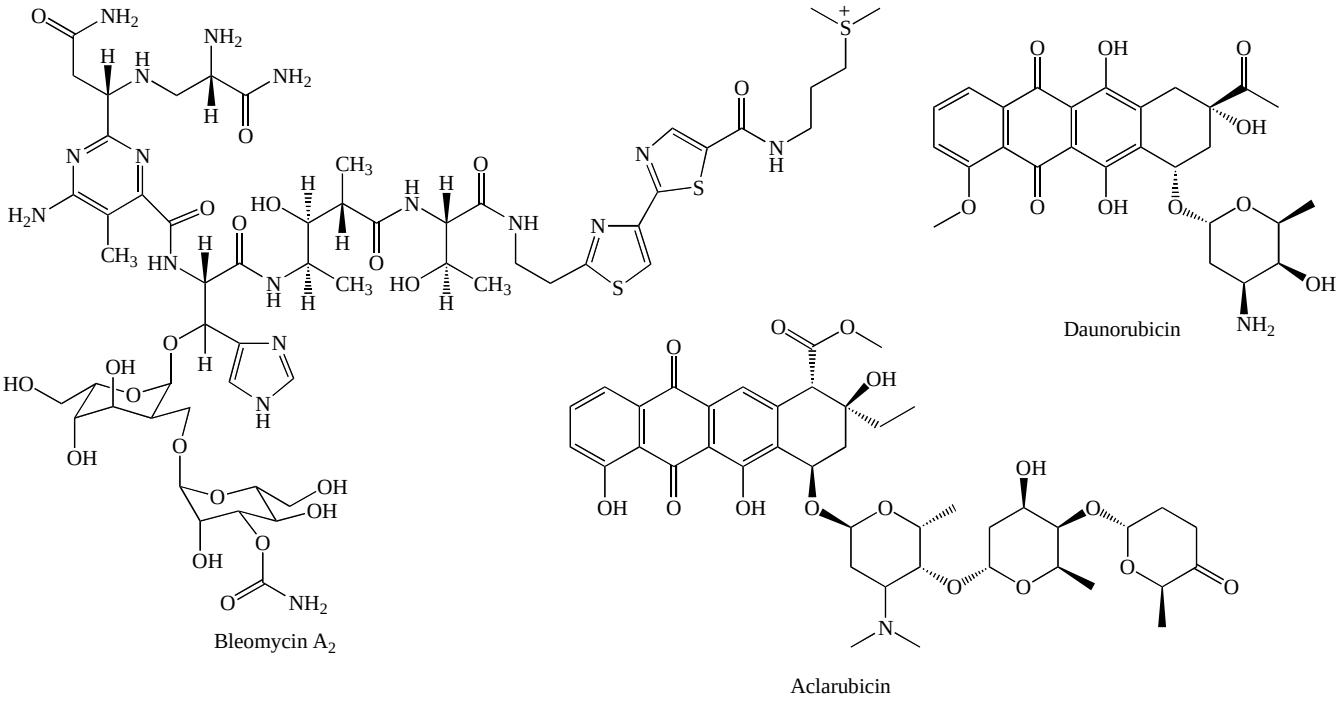



**Fig. (1).** Selected plant secondary metabolites with pro-oxidant and anticancer activities.



**(Fig. 2) contd…**

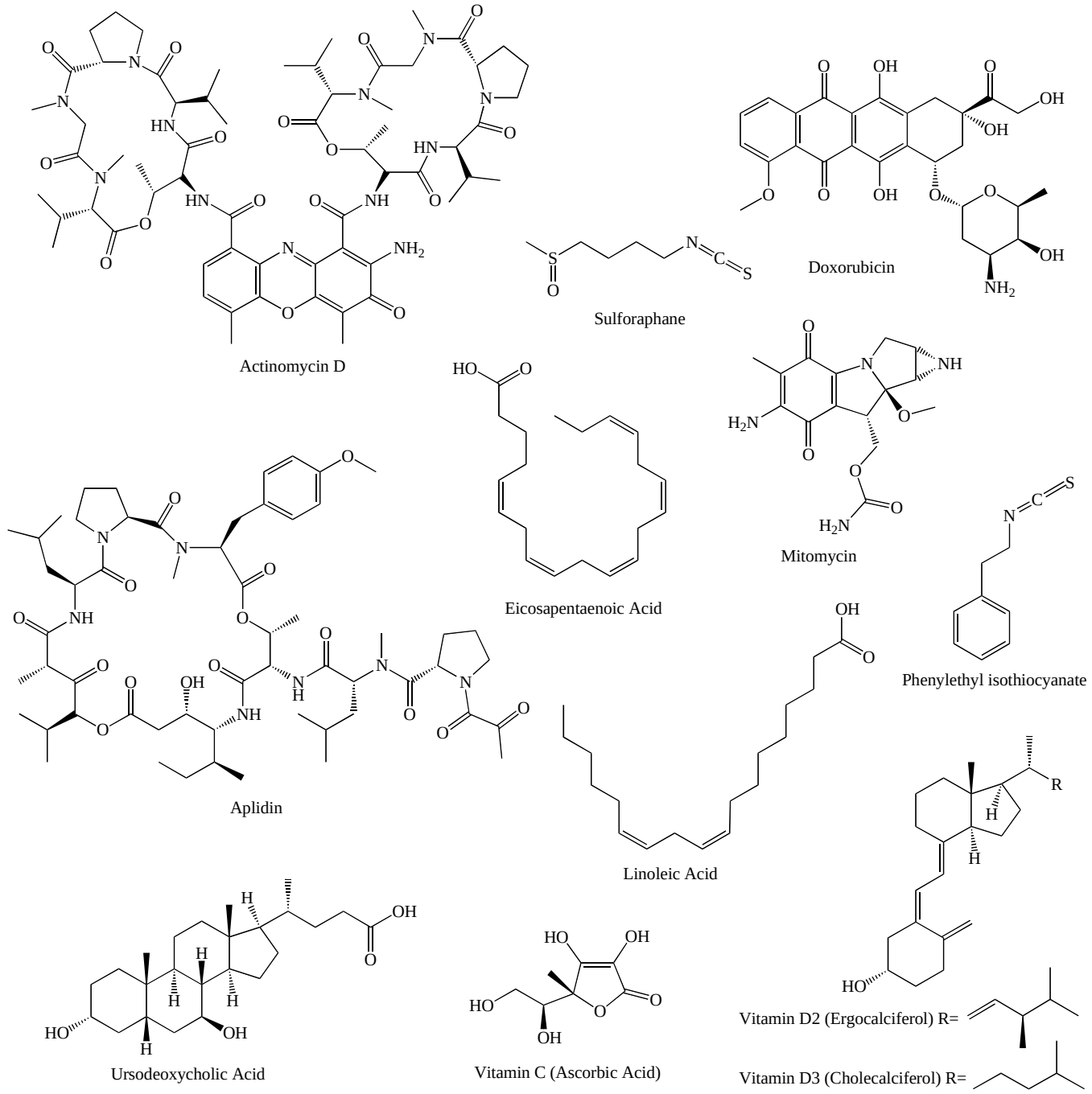



**Fig. (2).** Selected natural products, excluding plant secondary metabolites, with pro-oxidant and anticancer activities.

vate, which is an efficient scavenger of $H_2O_2$ [75-78]. Second, glucose metabolism through the pentose phosphate pathway regenerates NADPH from $NADP^+$ in a reaction in which glucose-6-phosphate is converted into 6-phosphogluconolactone by the enzyme glucose-6-phosphate dehydrogenase. The regeneration of NADPH is required for $H_2O_2$ detoxification through the glutathione peroxidase/glutathione reductase system and through the thioredoxin peroxidase/thioredoxin reductase system [73, 79, 80] (reviewed in [13]). Therefore, the anticancer potential of pro-oxidant natural products could be maximized in combination with glycolysis inhibitors.

In conclusion, natural products have made a significant contribution to the development of many anticancer drugs currently used in chemotherapy. Recent observations suggest that pro-oxidant agents may represent a new class of anticancer drugs with capacity to target tumor cells selectively. In this article, we have provided an overview of pro-oxidant natural products with anticancer activity and discussed their anticancer potential.

## CONFLICT OF INTEREST

Declared none.

## ACKNOWLEDGEMENT

Declared none.

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