Natural phenolics: a source of anticancer agents

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Cancer is a worldwide scourge, which affects people of all ages, and is rapidly becoming a global pandemic. It is one of the main leading causes of death especially in developing countries. Mankind has been trying hard to find better and cheaper treatments with fewer side effects to reduce the incidence of the disease and its consequent mortality. Natural phenolics play an important role in cancer prevention and treatment. Phenolics from medicinal plants are responsible for their chemopreventive properties and also contribute to their activity as apoptosis inducers. For many years, phenolic compounds have been intensely studied, *in vitro* and *in vivo*, for their antitumor effects. In recent years, the use of these compounds has increased considerably. In this regard, this article provides an overview of some natural phenolic compounds with approved anticancer activities.

Keywords:
anticancer activity, medicinal plants, natural phenolics

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Phenolic compounds comprise a broad class of natural products formed mainly by plants, as well as microorganisms and marine organisms. Nowadays the interest in these compounds has increased mainly due to their diverse chemical structure and various biological activities, which is valuable in the prevention of some chronic or degenerative diseases. Phenolic compounds are widely dispersed throughout the plant kingdom representing about 9000 different phenolic structures. As secondary metabolites they also display defensive growth and development effects. They have at least one aromatic ring with one or more hydroxyl groups attached, being able to range from low molecular weight molecules to high molecular weight complex ones. Phenolic compounds generally appear as esters and glycosides rather than as free compounds due to the conferred stability of these molecules. This family of compounds is one of the most widely studied families and had been published in numerous reports due to their beneficial effects in various aspects of human health and well-being [1–3].

Since ancient times, plants have been used as remedies to treat different types of illnesses showing satisfying results. Today, more than 60% of anticancer drugs originate either from natural compounds or are derived from them, making these bioactive molecules increasingly promising for drug companies, even as prototypes of final formulations for anticancer drugs [4,5].

The antioxidant activity of the phenolic compounds depends on their structure, in particular the number, positions of the hydroxyl groups, and the nature of substitutions on the aromatic rings. Table 1 outlines the most important groups of plant phenolics [6].

Plant phenolics with anticancer activity

Cancer is a growing public crisis. The estimated worldwide new incidences are about six million cases per year. It is the second major cause of death after cardiovascular diseases. A large number of plants have been tested for their anticancer activities, and plenty of compounds have survived to be potential leads.

The therapeutic effect of some isolated natural phenolics on malignant tumors are tabulated in Table 2. The name of the natural phenolic compound, the natural source (representative species and family) and the references are provided. Structures of some selected phenolic compounds are shown in Fig. 1.

Conclusion

Plants have been a prime source of highly effective conventional drugs for the treatment of many types of cancer. In many instances, the actual compounds isolated from the plants may not serve as a drug, but lead to the development of potential novel agents. With the development of new technologies, some of

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Table 1 Groups of phenolic compounds

Number of carbon atoms	Basic skeleton	Class	Examples
6	C6	Simple phenols, benzoquinones	Catechol, hydroquinone, 2,6-dimethoxybenzo-quinone
7	C6–C1	Phenolic acids	Gallic acid, salicylic acid
8	C6–C2	Acetophenones, tyrosine derivatives, phenylacetic acids	3-Acetyl-6-methoxy-benzaldehyde tyrosol, p-hydroxyphenylacetic acid
9	C6–C3	Hydroxycinnamic acids, phenylpropenes, coumarins, isocoumarins, chromones	Caffeic acid, ferulic acid, myristicin, eugenol umbelliferone, aesculetin, bergenon, eugenin
10	C6–C4	Naphthoquinones	Juglone, plumbagin
13	C6–C1–C6	Xanthones	mangiferin
14	C6–C2–C6	Stilbenes, anthraquinones	Resveratrol, emodin
15	C6–C3–C6	Flavonoids, isoflavonoids	Quercetin, cyaniding, genistein
18	$(C6–C3)_2$	Lignans, neolignans	Pinoresinol, eusiderin
30	(C6–C3–C6)2	Biflavonoids	Amentoflavone
N	(C6–C3)*n*, (C6)*n*, (C6–C3–C6)*n*	Lignins, condensed tannins	Proanthocyanidins, phlobaphenes

Table 2 Phenolic compounds with reported anticancer activity

No.	Compound	Type of tumor	Natural source	References
1	Quercetin	Leukemia, gastric adenocarcinoma, hepatocellular carcinoma, lung adenocarcinoma, prostate carcinoma, colon carcinoma, breast carcinoma	*Citrus* spp. (Rutaceae)	Wei and colleagues [7–9]
2	Kaempferol	Hepatocarcinoma, pancreatic carcinoma, osteosarcoma	*Kaempferia galangal* (Zingiberaceae)	Mylonis and colleagues [10–12]
3	Gallic acid	Leukemia, lung carcinoma	*Kalanchoe* spp. (Crassulaceae)	Lu and colleagues [13,14]
4	Ellagic acid	Colon carcinoma	*Vaccinium* spp. (Ericaceae)	[15]
5	Ferulic acid	Skin carcinoma, mammary carcinoma	*Ferula communis* (Apiaceae)	Alias and colleagues [16,17]
6	7-Hydroxycoumarin (umbelliferone)	Lung carcinoma	*Hieracium pilosella* (Asteraceae)	Lopez-Gonzalez *et al.* [18]
7	Psoralidin	Cervical carcinoma	*Psoralea corylifolia* (Fabaceae)	Bronikowska *et al.* [19]
8	(–)-Syringaresinol	Leukemia	*Castela emoryi* (Simaroubaceae)	Park *et al.* [20]
9	7-Hydroxymatairesinol	Prostate carcinoma	*Picea abies* (Pinaceae)	Bylund *et al.* [21]
10	Chrysin	Leukemia, hepatocellular carcinoma	*Prunus* spp. (Rosaceae)	Woo and colleagues [22,23]
11	Linariin	Large lung cell carcinoma	*Linaria vulgaris* (Plantaginaceae)	Tundis *et al.* [24]
12	Pectolinariin	Hepatocellular carcinoma		
13	Isolinariin A	Renal adenocarcinoma		
14	Isolinariin B			
15	Catechin	Melanoma, cervical carcinoma, bladder carcinoma, prostate carcinoma, colorectal carcinoma	*Acacia catechu* (Fabaceae)	Kevan and colleagues [25–29]
16	Dicoumarol	Bladder carcinoma, prostate carcinoma	*Dipteryx odorata* (Fabaceae)	Watanabe and colleagues [30,31]
17	Aesculetin	Cervical carcinoma	*Aesculus hippocastanum* (Hippocastanaceae)	Yang *et al.* [32]
18	Garcinone E	Hepatocellular carcinoma		Ho *et al.* [33]

(*Continued*)

Table2 (*Continued*)

No.	Compound	Type of tumor	Natural source	References
			Garcinia mangostana (Clusiaceae)	
19	α-Mangostin	Colon carcinoma	*Garcinia mangostana* (Clusiaceae)	Matsumoto and colleagues [34–40]
20	β-Mangostin	Leukemia		
21	γ-Mangostin	Melanoma, neck carcinoma		
22	Phloretin	Melanoma, hepatoma	*Malus* spp. (Rosaceae)	Korobi and colleagues [41,42]
23	Arbutin	Melanoma	*Arctostaphylos* spp. (Ericaceae)	Cheng *et al.* [43]
24	Resveratrol	Leukemia, skin carcinoma, breast carcinoma, kidney carcinoma, pancreatic carcinoma, breast carcinoma, prostate carcinoma	*Vitis* spp. (Vitaceae)	Jang and colleagues [44–46]
25	Rhaponticin	Leukemia	*Rheum rhabarbarum* (Polygonaceae)	Chowdhury *et al.* [47]
26	Epigallocatechin-3-gallate	Leukemia, hepatoma, melanoma, breast carcinoma, lung carcinoma	*Camellia sinensis* (Theaceae)	Lung and colleagues [48–52]
27	Genistein	Prostate carcinoma, ovarian carcinoma, cervical carcinoma, bladder carcinoma, breast carcinoma	*Genista* spp. (Fabaceae)	Suzuki and colleagues [53–57]
28	Daidzein	Breast carcinoma, prostate carcinoma, colon carcinoma	*Glycine max* (Fabaceae)	Choi and colleagues [58–60]
29	6-Hydroxyflavonone	Colon carcinoma	*Barleria prionitis* (Acanthaceae)	Shen and colleagues [61,62]
30	7-Hydroxyflavonone	Lung carcinoma		
31	2′-Hydroxyflavonone			
32	4′-Hydroxyflavonone			
33	Naringenin	Colon carcinoma	*Citrus* spp. (Rutaceae)	Hun *et al.* [63]
34	Delphinidin	Colorectal carcinoma, prostate carcinoma, leukemia	*Delphinium* spp. (Ranunculaceae)	Cvorovic and colleagues [64–66]
35	Cyanidin	Colorectal carcinoma	*Vaccinium* spp. (Ericaceae)	Cvorovic *et al.* [64]
36	Hesperidin	Nasopharyngeal carcinoma	*Citrus aurantium* (Rutaceae)	Li and colleagues [67,68]
37	Toxifolin	Colon carcinoma	*Cedrus deodara* (Pinaceae)	Shen and colleagues [61,62]
38	Naringin	Lung carcinoma, gastric carcinoma, hepatocellular carcinoma	*Citrus aurantium* (Rutaceae)	Hsiao *et al.* [62]
39	Epicatechin	Breast carcinoma	*Acacia catechu* (Fabaceae)	Damianaki and colleagues [69,70]
40	Peonidin-3-glucoside	Lung carcinoma	*Vitis vinifera* (Vitaceae)	Ho *et al.* [71]
41	Cyanidin-3-glucoside	Lung carcinoma	*Vaccinium* spp. (Ericaceae)	Ding *et al.* [72]
42	Cyanidin-3-rutnoside	Lung carcinoma	*Vaccinium* spp. (Ericaceae)	Chen *et al.* [73]
43	Cuphiin D1	Leukemia, epidermoid carcinoma, hepatocellular carcinoma, prostate carcinoma, cervical carcinoma	*Cuphea hyssopifolia* (Lythraceae)	Wang and colleagues [74,75]
44	Oenothein B	Leukemia, epidermoid carcinoma, hepatocellular carcinoma, prostate carcinoma, cervical carcinoma	*Epilobium angustifolium* (Onagraceae)	Wang and colleagues [75,76]

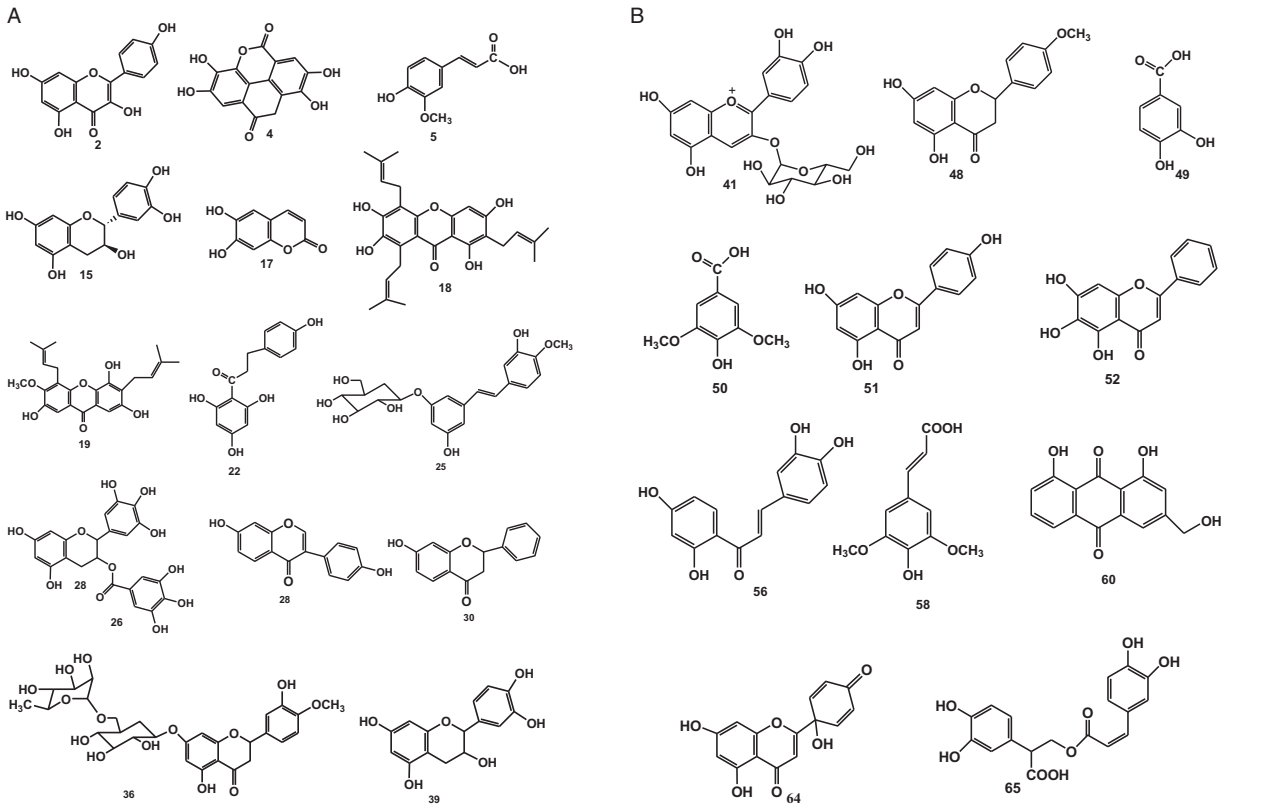
(*Continued*)

Table2 (*Continued*)

No.	Compound	Type of tumor	Natural source	References
45	α-Viniferin	Leukemia, submandibular gland carcinoma	*Bulbophyllum odoratissimum* (Orchidaceae)	Yegao *et al.* [77]
46	Densiflorol B	Leukemia, lung adenocarcinoma, hepatoma, stomach cancer	*Bulbophyllum odoratissimum* (Orchidaceae)	Yegao *et al.* [77]
47	Vanillic acid	Colon carcinoma, cervical carcinoma	*Angelica sinensis* (Apiaceae)	Thanaset *et al.* [78]
48	Acacetin	Gastric carcinoma, breast cancer	*Robinia pseudoacacia* (Fabaceae)	Pan and colleagues [79,80]
49	Protocatechuic acid	Colon carcinoma, cervical cancer	*Houttuynia cordata* (Saururaceae)	Thanaset *et al.* [78]
50	Syringic acid	Colon carcinoma, cervical carcinoma	*Ardisia elliptica* (Primulaceae)	Pan *et al.* [79]
51	Apigenin	Cervical carcinoma	*Petroselinum crispum* (Apiaceae)	Pei-Wen *et al.* [81]
52	Baicalein	Prostate carcinoma, gastric carcinoma	*Scutellaria baicalensis* (Lamiaceae)	Pidgeon and colleagues [82,83]
53	p-Hydroxybenzoic acid	Colon carcinoma, cervical carcinoma	*Hypericum perforatum* (Hypericaceae)	Thanaset *et al.* [78]
54	Hesperetin	Breast cancer	*Citrus* spp. (Rutaceae)	So *et al.* [84]
55	7,9,2′,4′-Tetrahydroxy-8-isopentenyl-5-methoxy-chalcone	Leukemia	*Sophora flavescens* (Fabaceae)	Lee *et al.* [85]
56	Butein	Melanoma	*Rhus verniciflua* (Anacardiaceae)	Iwashita *et al.* [86]
57	Caffeic acid	Colon carcinoma	*Cinnamomum verum* (Lauraceae)	Murad *et al.* [87]
58	Sinapic acid	Colon carcinoma, cervical carcinoma	*Brassica* spp. (Brassicaceae)	Thanaset *et al.* [78]
59	Cajanol	Breast cancer	*Cajanus cajan* (Fabaceae)	Luo *et al.* [88]
60	Aloe emodin	Lung carcinoma, nasopharyngeal carcinoma	*Rheum* spp. (Polygonaceae)	Lee and colleagues [89,90]
61	Icariin	Hepatoma	*Epimedium* spp. (Berberidaceae)	Li *et al.* [91]
62	Isoliquiritigenin	Melanoma	*Glycyrrhiza glabra* (Fabaceae)	Murad *et al.* [87]
63	Wogonin	Leukemia	*Scutellaria* spp. (Lamiaceae)	Chow *et al.* [92]
64	Protoapigenone	Breast carcinoma	*Thelypteris torresiana* (Thelypteridaceae)	Chen *et al.* [93]
65	Rosmarinic acid	Colorectal carcinoma	*Rosmarinus officinalis* (Lamiaceae)	Xavier *et al.* [94]

the natural tested compounds which have failed in earlier clinical studies are now stimulating renewed interest. The ability to attach agents to carrier molecules directed to specific tumors holds promising results for the effective targeting of highly cytotoxic natural products against tumors, while avoiding their toxic side effects on normal healthy tissues. With the urgent need for the detection of new proteins having significant regulatory effects on tumor cell cycle progression, and their conversion into valuable natural targets, molecules isolated from plants and other natural organisms are proving to be an important source of novel inhibitors of the action of these key proteins and have the potential for development into selective anticancer agents.

Figure 1



Structure of some selected phenolics.

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Conflicts of interest

There are no conflicts of interest.

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