Natural Polyphenols that Display Anticancer Activity through Inhibition of Kinase Activity

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Abstract: Over eleven hundred publications reporting anticancer activities of polyphenols have appeared in the peer-reviewed literature. In addition, a search of the PubMed database using "polyphenols – cancer – review" as keywords produced over 320 hits for review articles (July 2009). Polyphenol anticancer activities include, among others, anti-oxidative, pro-apoptotic, DNA damaging, anti-angiogenic, and immunostimulatory effects. Targeting specific protein kinases to combat cancer represents a major focus of oncology research within the so-called targeted therapy approach. An exhaustive search of the PubMed database (July 2009) using "polyphenols – cancer - kinases" as keywords resulted in more than 130 hits, half of them having been published within the past five years. Furthermore, the PubMed database contains 25 reviews on the subject of anti-kinase activity of some specific polyphenols, including mainly curcumin and the green tea polyphenol (-)-epigallocatechin 3-gallate (EGCG). However, no attempt has been made yet to review this area of research in a comprehensive, general manner. The current review therefore aims to highlight those anticancer polyphenols that target specific kinases in various types of cancer. The present review also provides an in-depth analysis of polyphenol structure-activity relationships in relation to their anticancer activities and specific kinase targeting. Lastly, a number of polyphenols are identified as potential antitumor agents that could be used to combat biologically aggressive cancers, including metastasizing cancers, through the targeting of specific kinases.

INTRODUCTION

Natural polyphenols constitute one of the most widespread groups of plant secondary metabolites and their distribution is almost ubiquitous. Somewhere between 100,000 and 200,000 of polyphenolic metabolites are believed to exist in nature and their function in plants is protection from photosynthetic stress, UV radiation, reactive oxygen species, wounds and herbivores. Although polyphenolics are extremely structurally diverse, most of these metabolites arise from amino acids phenylalanine and tyrosine, which undergo deamination to cinnamic acids, incorporating the C6-C3 phenylpropanoid unit. Cinnamic acids enter the phenylpropanoid pathway leading to the biosynthesis of a large variety of plant polyphenols, such as cinnamic acids (C6-C3), stilbenes (C6-C2-C6), flavonoids (C6-C3-C6), coumarins (C6-C3) and anthocyanidines (C6-C3-C6, Tables **1-4**). Polyphenols are an important part of human diet and the original interest in these compounds was due to their antinutritional effects, specifically due to their ability to decrease absorption and digestability of food by binding to proteins and minerals. Indeed, the astringency of many fruits can be explained by precipitation of salivary proteins upon binding to polyphenols. More recently, however, polyphenols have received a great deal of attention due to their anti-inflammatory, anti-oxidative and anticancer activities. Their conjugated structures give rise to superb electron delocalization properties, conferring the ability to quench free radicals. Indeed, polyphenols react with a large number of reactive oxygen species (ROS), including superoxide radical, singlet oxygen, peroxyl radical, nitric oxide, hydroxyl radical, nitrogen dioxide and peroxynitrite. In addition, polyphenols strongly chelate a range of metal ions leading to reduced formation of ROS from auto-oxidation of organic compounds. The presence of several hydroxyl groups in their structures makes polyphenols excellent hydrogen bond donors. These hydrogen bonding properties are believed to be responsible for their high affinity for proteins and nucleic acids. Therefore, in addition to their anti-oxidative and chemopreventive potential, this group of structurally diverse natural products has provided a wide variety of bioactive agents for specific protein targeting. In this context, polyphenols are investigated as promising medicinal agents for the treatment of bacterial infections, ulcer, hypertension, vascular fragility, allergies, hypercholesterolemia and, most notably, various types of cancer. While a number of literature reviews have addressed the anticancer properties of natural polyphenols (see references [1-4]), targeting protein kinases with these compounds has not received its due attention in the review literature despite a large amount of original research reports indicating that this strategy holds an immense potential for the development of novel cancer therapies. Therefore, the aim of the present review is to fill this gap in the literature by focusing on polyphenols whose anticancer properties are mediated through specific kinase activity inhibition.

KINASES AND CANCER

Protein kinase inhibitors are a well-established class of clinically useful drugs, particularly for the treatment of cancer [5]. Indeed, several families of protein kinases orchestrate the complex events that drive the cell cycle, and their activity is frequently deregulated in hyperproliferative cancer cells [6]. In addition, recent genetic and biochemical studies have provided information about the requirement for certain

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cell cycle kinases by specific tumours and specialized tissue types [6]. Development and design of specific inhibitors for protein kinases has become a major strategy in many drug discovery programs [7]. Inhibition of protein kinase activity may be achieved by blocking the phosphorylation activity or by disrupting protein-protein interactions [7]. Peptides that can mimic most truly these regulatory modes are a common choice for protein kinase-targeting [7]. With a target in hand, medicinal chemists can generate low molecular weight compounds that bind the target with high affinity and alter cancer cell biological behavior [7]. In many cases, however, drugs fail as they lack appropriate pharmaceutical properties and are of limited specificity resulting in unfavorable side effects, as described in the next section. Novel information on kinase biology is opening up novel avenues for the design of selective inhibitors that may provide more subtle modulation of these drug discovery targets [8]. The identification of such modulators requires adoption of a new generation of high-throughput screening techniques [8]. These approaches will allow measurement of conformational changes in kinases as well as protein-protein interactions *via* assessment of functional responses such as cellular translocation [8]. Therefore, a range of novel techniques, together with the understanding that numerous "orphan" kinases will provide targets for therapeutics, suggest that a new era of kinase therapies is rapidly emerging [8].

Tyrosine kinase inhibitors (TKI) are effective in the targeted treatment of various malignancies [9]. Imatinib (Gleevec) was the first to be introduced into clinical oncology and it was followed by such drugs as gefitinib, erlotinib, sorafenib, sunitinib, and dasatinib [9]. Although they share the same mechanism of action, namely competitive inhibition at the catalytic ATP binding site of a tyrosine kinase, they differ from each other in the spectrum of targeted kinases, their pharmacokinetics as well as substance-specific adverse effects [9].

Aurora kinases represent one of the emerging targets for drug discovery in oncology [10]. These kinases play important roles in centrosome maturation, chromosome separation and cytokinesis [10]. They are overexpressed in a broad range of tumor cell lines and human primary tumors; thus, their inhibition may open up new opportunities to develop novel anticancer agents [10]. A range of potent small molecule inhibitors of Aurora kinases have been identified and found to have antitumor activity, and some of these agents are undergoing evaluation in clinical trials [10]. However, most synthetic Aurora kinase inhibitors are ATP-competitive, which makes selectivity a potential problem [10]. Despite the high sequence similarity in the ATP-binding pocket, several compounds are nevertheless very specific in their targets. Garuti and colleagues have recently reviewed the main Aurora kinase inhibitors with the focus on their chemical structures, SAR and biological properties [10].

Polo-like kinases (PLKs) are also a group of highly conserved serine/threonine protein kinases that play key roles in processes such as cell division and checkpoint regulation of mitosis [11]. About 80% of human tumors, of various origins, express high levels of PLK transcripts, while PLK mRNA is mostly absent in surrounding healthy tissues, making PLKs an attractive and selective target for cancer drug development [11]. Similar to Aurora kinase inhibitors [10], PLK inhibitors also interfere with different stages of mitosis, such as centrosome maturation, spindle formation, chromosome separation, and cytokinesis [11]. Schöffski recently reviewed PLK inhibitors that entered early clinical development (i.e., BI 2536, BI 6727, GSK461364, ON 019190.Na,

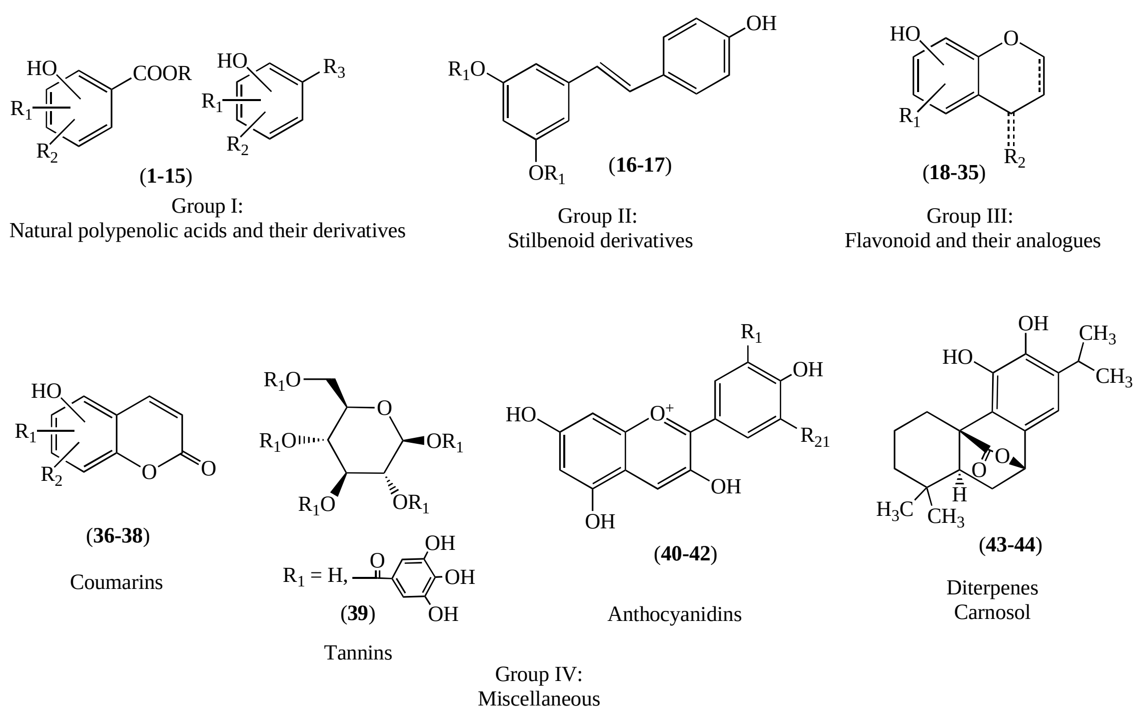


Fig. (1). General chemical structures of the four groups of natural polyphenols.

and HMN-214) as well as those that are still in preclinical evaluation (i.e., ZK-thiazolidinone, NMS-1, CYC-800, DAP-81, and LC-445) [11].

Serine/threonine protein kinase C (PKC) is also involved in malignant transformation, but an anti-PKC approach in cancer therapy has been hampered by the difficulties in developing pharmacological compounds able to selectively inhibit specific PKC isoforms [12]. Gonelli and colleagues [12] reviewed the roles of PKC-epsilon and PKC-delta in promoting and counteracting tumor progression in different types of cancer, along with promising therapeutic perspectives based on small molecule inhibitors of synthetic as well as natural origin.

While several articles have discussed PKCs as potential targets for natural polyphenols [13-15], a search of the PubMed database revealed no reports addressing the potential Aurora and Polo kinase targeting with these natural products. We believe that polyphenols have a significant therapeutic potential for combating various cancers through Aurora and Polo targeting. Furthermore, these natural substances are constituents of numerous diets and they are associated with lower toxicities than synthetic multi-kinase inhibitors (see below). We recently initiated a research program aimed at the discovery of simple polyphenols capable of targeting Aurora kinases [16].

CHEMISTRY OF NATURAL POLYPHENOLS

We have divided anti-kinase polyphenols into four groups: (1) polyphenolic acids and their analogues (Group I), (2) stilbenoid derivatives (Group II), (3) flavonoids and their analogues (Group III), and (4) miscellaneous (Group IV), which includes coumarin, tannin, anthocyanidin and polyphenolic diterpene sub-groups. The structural variations among these groups and subgroups of natural polyphenols are highlighted in Fig. (**1**).

Group I: Polyphenolic Acids and their Analogues

The phenolic acids are usually divided in two main subgroups: benzoic acids (for example gallic (**1**) and procatechuic acids (**3**)),

containing seven carbon atoms (C6-C1) and cinnamic acids (as for example caffeic acid (**5**)), comprising nine carbon atoms (C6-C3, Table **1**). These compounds are found in mono- or polyhydroxylated forms and the presence of more than one phenol function in the molecule characterizes the general name of polyphenol. Hydroxybenzoic and hydroxycinnamic acids are abundant in food and account for about one third of phenolic compounds in human diet. Caffeic acid, for example, is found in many fruits, such as plum, apple, tomato and grapes. The natural polyphenolic derivatives of this group are usually isolated as acids, esters or amides (**2**, **4**, **6** and **7**) [17, 18] either in free or conjugated forms (Table **1**). Due to their structural similarity with these acid derivatives, several others phenolic analogues are reviewed here even if they do not contain acid function (Table **1**). The polyphenols which exert anticancer activity by targeting specific kinases include capsaicinoid derivatives (**8** and **9**, vanilloid derivatives of branched-chain fatty acids), found in some peppers of the *Capsicum* plant family [19, 20], [6]-gingerol (**10**) and [6]-paradol (**11**), two phenols structurally related to the vanilloid moiety with 16 carbon atoms (C6-C10) [21,22], tyrosol derivatives (**12** and **13**, phenylethanol compounds with 8 carbon atoms (C6-C2)), present in a variety of natural sources [23,24], rosmarinic acid (**14**, phenolic derivative of caffeic acid with 18 carbon atoms (C6-C6-C6)), found in many *Lamiaceae* herbs [25], and curcumin (**15**, diferuloyl derivative containing 19 carbon atoms (C6-C7-C6)), isolated from the ginger family (*Zingiberaceae*) [26, 27]. Curcumin has a highly conjugated structure, and it is a major pigment in mustard and turmeric. It is used widely as a food preservative and a yellow coloring agent in foods, drugs and cosmetics. Table **1** also details antiproliferaitive activities of these polyphenolic acids toward various cancer cell lines, specific kinases targeted by these compounds, brief descriptions of *in vivo* studies (if available), plant and/or dietary sources and literature references.

Group II: Stilbenoid Derivatives

Stilbenes are phenolic molecules containing two aromatic rings linked by an ethene bridge (C6-C2-C6, Table **2**). Their distribution in plants is limited and they act as antifungal phytoalexins, secondary metabolites synthesized in response to infection or injury. The most known stilbenoid derivative is *trans*-resveratrol (**16**, 3,5,4'-trihydroxystilbene, Table **2**), isolated from a large variety of plants and found in the diet as for example in red wine, peanuts, mulberries and grapes [40]. Red wine contains 1.5 to 3.0 mg of resveratrol per 1 L. *Trans*-pterostilbene (**17**), another stilbenoid derivative reported to target kinase activity, is shown in Table **2** [41, 42].

Group III: Flavonoids and their Analogues

Flavonoids are characterized by a basic backbone of 15 carbon atoms (C6-C3-C6). The chemical name of the flavone backbone is 2-phenylchromen-4-one or 2-phenyl-1,4-benzopyrone (Table **3**). Flavones believed to exert anticancer properties through the inhibition of kinase activity include for example baicalein (**18**), baicalin (**19**), luteolin (**20**) and apigenin (**21**, Table **3**) [46-48]. Natural flavonoids can be found either in free or conjugated forms (Table **3**). Alcohol or phenol functions can be glycosylated or esterified with gallic acid (Table **3**). Flavonols, a group of flavonoid derivatives containing the 3-hydroxyl group in the pyrone ring, are exemplified by quercetin (**22**), myricetin (**23**) and kaempferol (**24**) [48-50]. Flavanoid derivatives containing the 2-phenyl-3,4-dihydro-2*H*-chromen-3-ol skeleton are more commonly referred to as flavanols (Table **3**). The principal members of this sub-group are catechin, epicatechin (**25**, **26**, **27**, **28** and **29**) and theaflavin derivatives (**30**, **31** and **32**, Table **3**) [51-53]. Additional analogues of the flavone family possessing anti-kinase-mediated anticancer activity are isoflavones, which differ from flavones by the positioning of the aromatic ring in the pyrone moiety (position 3 in isoflavones as opposed to position 2 in flavones, Table **3**). Well-known isoflavones are genistein (**34**) [54] and daidzein (**33**) [55]. Silibinin (**35**) is another example: this flavonoid targets several kinases and is currently in phase II clinical trials in prostate cancer patients [56-58] (Table **3**). In plants, flavanoids occur in nearly all species due to their UV screening properties and their main

Table 1. Natural Polyphenolic Acids and their Analogues

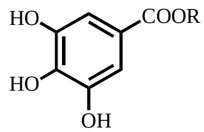
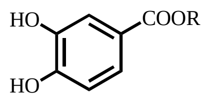
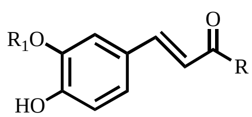
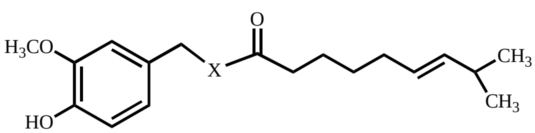
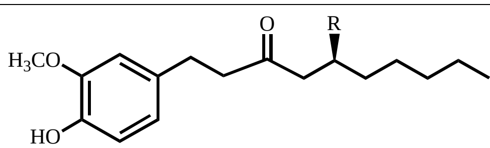
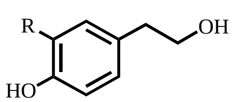
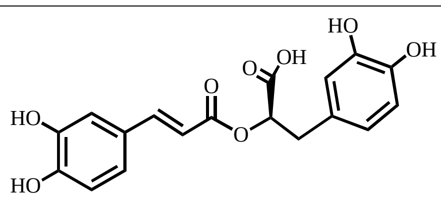
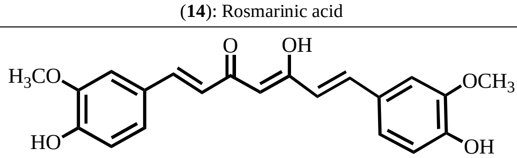
Structure / Name	*In vitro* growth inhibitory IC_{50} (μM) values	Kinases as specific targets (IC_{50} in μM)	Experimental mouse models in which *in vivo* activity has been investigated	Compound source	Ref.
 (**1**): R= H, Gallic acid (**2a**): R= propyl ester (**2b**): R= octyl ester (**2c**): R= lauryl ester	(**2a**) = 8 μM on Hela cervical cancer cells and 10 μM on lung L-132 cancer cells (**2b**) = 45 μM on Hela cervical cancer cells and 20 μM on L-132 lung cancer cells (**2c**) = 1 μM on MDA-MB-231 breast cancer cells	(**2c**) (5 μM) Erk1/2 activation	(**1**): no significant survival increase in P388 syngeneic lymphoma treated with 200 mg/kg (i.p. administration)	Plants Vegetables Beverages additives	[17, 28, 29]
 (**3**): R = H, Protocatechuic acid (**4**): R= alkyl, Esters	(**3**) = 73 μM on AGS gastric carcinoma cells and 40 μM on HepG2 hepatocellular carcinoma cells	(**3**) (30 μM) JNK/p38 activation	(**3**): no significant survival increase in P388 syngeneic lymphoma treated with 400 mg/kg (i.p. administration)	Plants Vegetables Beverages additives	[28, 30, 31]
 (**5**): R = OH, R_1 = H, Caffeic acid (**6**): R = tyramine, R_1 = H, *N*-Caffeoyltyramine (**7**): R = -O(octacosyl), R1 = CH_3, Octacosyl Ferulate	(**5**) = ~ 95 μM in a panel of 60 cancer cell lines (**6**) = ~ 10 μM in HL-60, U937 and Jurkat cancer	(**5**) Fyn kinase inhibition (**6**) (30 μM) protein tyrosine kinase inhibition; (**20** μM) EGFR tyrosine kinase inhibition (**7**) (50 μM) PKC inhibition	(**5**): no significant survival increase in P388 syngeneic lymphoma treated with 600 mg/kg (i.p. administration)	Plants Vegetables Fruits Beverages (Coffee, wine, tea)	[18, 30, 32, 33]
 (**8**): X = O, Capsiate (**9**): X = NH, Capsaicin	(**9**) 100 μM < IC_{50} < 200 μM in HT-29 colon cancer cells	(**8**) (10 μM) Src kinase inhibition (9) (25 to 200 μM) AMPK activation	(**9**): significant decrease of 40% in PC-3 prostate carcinoma xenograft volume with 5 mg/kg (s.c. administration); significant decrease of 42% in AsPC-1 human pancreatic cancer xenograft volume with 2.5 mg/kg (p.o. administration)	Peppers of the *Capsicum* family	[19, 20, 34, 35]
 (**10**): R = OH, [6]-Gingerol (**11**): R = H, [6]-Paradol	(**10**): IC_{50} > 200 μM in HCT-116, SW480, HT-29, LoVo and Caco-2 colon cancer cells	(**10**) (50μM) inhibition of AP-1 DNA binding activity; (150 μM) GSK-3β and PKCε activation	(**10**) 50% of reduction of the metastatic process in B16F10 syngeneic melanoma treated with 3 mg/kg (i.p. administration)	*Zingiberaceae* Ginger roots	[21, 22, 36]
 (**12**): R = H, Tyrosol (**13**): R = OH, Hydroxytyrosol	(**13**) : 50 < IC_{50} < 75 μM in HL-60 leukemic cells	(**12**) PKC inhibition (**13**) (100 μM) inhibition of CDK6 expression; upregulation of CDKi $p21^{WAF1/Cip1}$ and $p27^{Kip1}$		Olive oil Wine	[23, 24]
 (**14**): Rosmarinic acid		(5 μM) inhibition of AP-1 DNA binding activity; (10 μM) inhibition of ERK1/2 activity		Oregano Mint Sweet basil Perilla	[25]
 (**15**): Curcumin	~ 70 μM in a panel of 60 cancer cell lines	(10-20 μM) Inhibition of I-κB, IKK, PhK, mTOR, nPKC, cyclin D1, and cdk-1 expression and/or activity		Turmeric (rhizome of *Curcuma longa*)	[26-28, 37-39]

Table 2. Stilbenoid Derivatives

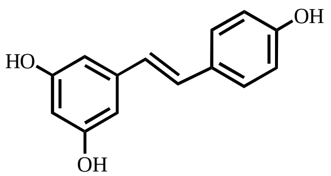
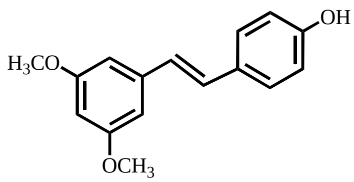
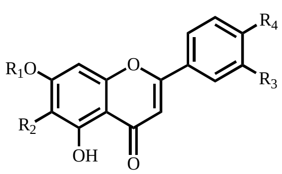
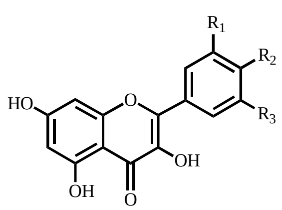
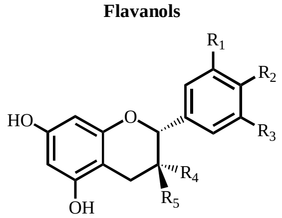
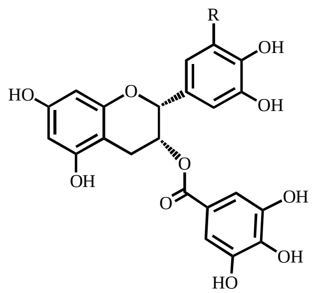
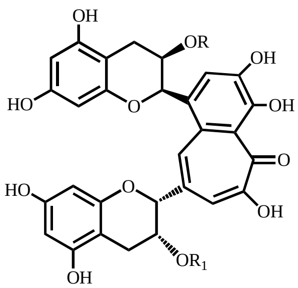
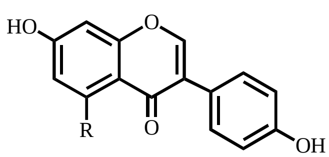
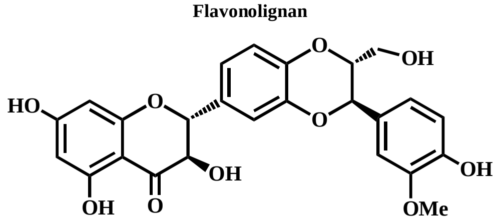
Structure / Name	*In vitro* growth inhibitory IC_{50} (µM) values	Kinases as specific targets (IC_{50} in µM)	Experimental mouse models in which *in vivo* activity has been investigated	Compound source	Ref.
 (**16**): *trans*-Resveratrol	~ 50 µM in a panel of 60 cancer cell lines	(5 µM) Inhibition of creatine, ERK1/2, P38, JNK, and PKC kinase activity, and inhibition of PI3K/Akt phosphorylation	No anti-tumor activity in the P388 syngeneic lymphoma model treated with ~ 20 mg/kg (i.p. administrations)	Grapes Wine	[28, 40, 41, 43]
 (**17**): *trans*-Pterostilbene	40 µM in HT-29 colorectal cancer cells and 35 µM in HL-60 leukemia cells	Down-regulation of Cdk2, Cdk4 and Cdk6 activity		Blueberries	[42, 44, 45]

Table 3. Flavonoids and their Analogues

Structure / Name	*In vitro* growth inhibitory IC_{50} (µM) values	Kinases as specific targets (IC_{50} in µM)	Experimental mouse models in which *in vivo* activity has been investigated	Compound source	Ref.
Flavones  (**18**): $R_1 = R_3 = R_4 = H$, $R_2 = OH$, Baicalein (**19**): R_1 = Glucuronide, $R_2 = OH$, $R_3 = R_4 = H$, Baicalin (**20**): $R_1 = R_2 = H$, $R_3 = R_4 = OH$, Luteolin (**21**): $R_1 = R_2 = R_3 = H$, $R_4 = OH$, Apigenin	(**18**): 50 µM in bladder cancer cells (**21**): ~ 30 µM in a panel of 60 cancer cell lines	(**18**): (60 µM) inhibition of CDC2 kinase (**20**): inhibition of PI3K/Akt and PKC activity (**21**): inhibition of PI3K/Akt, PKC and FAK activity	(**18**) : decrease of 55% in LNCaP prostate cancer xenograft volume with 100 mg/day (i.p. administration)	Herbal medicine Legumes Tea Olives Cherries Broccoli	[46-48, 59]
Flavonols  (**22**): $R_1 = R_2 = OH$, $R_3 = H$, Quercetin (**23**): $R_1 = R_2 = R_3 = OH$, Myricetin (**24**): $R_1 = R_3 = H$, $R_2 = OH$, Kaempferol	(**22**): ~ 60 µM in a panel of 60 cancer cell lines (**23**): ~ 40 µM in a panel of 60 cancer cell lines (**24**): 35 µM in A549 lung cancer cells	(**22**): (5 µM) inhibition of MEK1; (20 µM) inhibition of Raf1 and PKCs (**23**): (5 µM) inhibition of MEK1 and (2.5 µM) MKK4 (**24**): inhibition of PKCs, PI3K, but activation of MAPK	(**22**): significant survival increase of 32% in P388 syngeneic lymphoma treated with 200 mg/kg (i.p. administration) (**23**): significant survival increase of 35% in P388 syngeneic lymphoma treated with 25 mg/kg (i.p. administration)	Red Wine Berries Onions Grapes Tomato Soy	[28, 48-50, 60]
Flavanols  (**25**): $R_1 = R_4 = H$, $R_2 = R_3 = R_5 = OH$, Catechin (**26**): $R_1 = R_5 = H$, $R_2 = R_3 = R_4 = OH$, Epicatechin (EC) (**27**): $R_5 = H$, $R_1 = R_2 = R_3 = R_4 = OH$, Epigallocatechin (EGC)	(**27**): ~ 25 µM in a panel of 60 cancer cell lines	(**25**): (25 µM) down-regulation of FAK		Apple skin Onions Green tea Soybeans Citrus fruits Berries	[28, 51]

(Table 3). Contd…..

Structure / Name	***In vitro*** **growth inhibitory IC_{50} (µM) values**	**Kinases as specific targets (IC_{50} in µM)**	**Experimental mouse models in which *in vivo* activity has been investigated**	**Compound source**	**Ref.**
Flavanols  (**28**): R = H, Epicatechin gallate (ECG) (**29**): R = OH, Epigallocatechin gallate (EGCG)	(**29**): 110 µM in MDA-MB-231 breast cancer cells	(**28**): (250 µM) activation of ERK, p38 (**29**): (250 µM) activation of ERK, JNK and p38; inhibition of MEK1/2, ERK1/2, ELK-1 and cJun phosphorylation; (5 µM) direct inhibition of ERK1/2 and AkT activity, and down-regulation of CDK1 and CDK2 activity; (0.3 µM) Inhibition of Dyrk1A activity	(**29**): decrease of 45% in MDA-MB-231 breast cancer xenograft volume with 3 mg/day (i.p. administration) (**29**): decrease of 20-30% in PC-3 prostate cancer xenograft volume with 1 mg/day (i.p. administration) (**29**): decrease of 40% in MCF-7 breast cancer xenograft volume with 1 mg/day (i.p. administration)	Leaves of *Camellia sinensis* (Green tea)	[52, 61-66]
Flavanols  (**30**): R = H, R_1 = H, Theaflavin (**31**): R = Galloyl, R_1 = H, Theaflavin 3-gallate (**32**): R = Galloyl, R_1 = Galloyl, Theaflavin 3, 3'-digallate	(**30**) and (**31**): ~ 50 µM in NIH3T3 fibroblast and A431 cancer cells (**32**): ~20 µM in NIH3T3 fibroblasts and A431 cancer cells	(**30**), (**31**) and (**32**): HER2/*neu* tyrosine kinase inhibition; down-regulation of PI3K and phosphoAkt; up-regulation of ERK1/2 (**32**): (5 µM) inhibition of EGFR kinase activity; inhibition MEK1/2, ERK1/2, ELK-1 and cJun phosphorylation		Black Tea	[53, 67, 68]
Isoflavones  (**33**): R = H, Daidzein (**34**): R = OH, Genistein	(**34**): ~ 70 µM in a panel of 60 cancer cell lines	(**33**): (100 µM) down-regulation of cyclinD, CDK2 and CDK4 (**34**): inhibition of Cdc2 kinase activity; inhibition of various tyrosine kinase activity		Soybean Citrus fruits Red clover	[28, 54, 55, 69-72]
Flavonolignan  (**35**): Silibinin	30-60 µM in PC-3 prostate cancer cells	Down-regulation of STAT, JNK1/2, p38MAPK, CDKs (2, 4, 6) and cyclins kinase activity (D1 and E)	decrease of 40-55% in PC-3 prostate cancer xenograft volume with 100 mg/day (i.p. administration) decrease of 50% in HT-29 colon cancer xenograft volume with 200 mg/day (p.o. administration)	Fruits *Silybium marianum*	[56-58, 73-75]

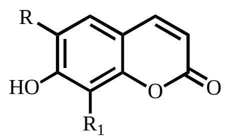
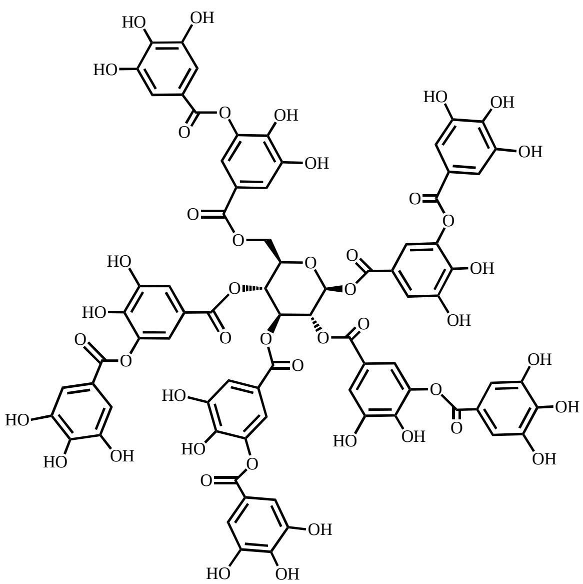
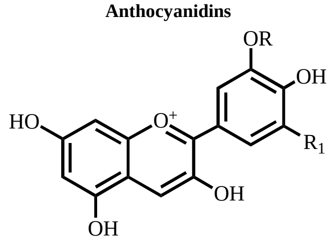
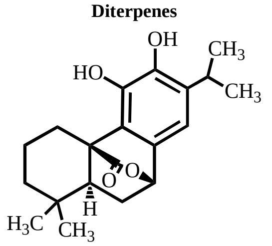
dietary source is tea in many populations. A substantial body of experimental work has established that consumption of green tea is correlated with cancer prevention and there is a considerable interest in biological effects of flavanoids at the cellular level [1]. These compounds interact with cellular signal transduction pathways that regulate cell cycle, differentiation and apoptosis by targeting a number of enzymes, most prominently protein kinases as described in detail below.

Group IV: Miscellaneous

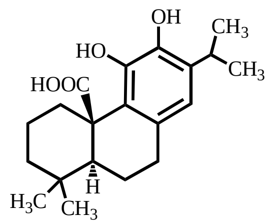
Coumarins

Coumarins are characterized by a benzo-[α]-pyrone skeleton, containing a lactone functionality. The biosynthesis of coumarins in plants transits *via* cyclization of hydroxycinnamic acid [76]. In general, coumarin derivatives manifest great chemical diversity, mainly differing in the oxygenation degree of their benzopyrone moiety. Most of coumarins are

Table 4. Miscellaneous

Structure / Name	*In vitro* growth inhibitory IC$_{50}$ (μM) values	Kinases as specific targets (IC$_{50}$ in μM)	Experimental mouse and rat models in which *in vivo* activity has been investigated	Compound source	Ref.
Coumarins  (**36**): R = OH, R$_1$ = H, Esculetin (**37**): R = OCH$_3$, R$_1$ = H, Scopoletin (**38**): R = H, R$_1$ = OH, Daphnetin	(**36**): 100 μM in various cancer cell lines (**37**): ~ 60 μM in a panel of 60 cancer cell lines	(**36**): (30 μM) activation of JNK, ERK (**37**): (10 μM) activation of PKC (**38**): (~ 10 μM) inhibition of EGFr tyrosine kinase and cAMP dependent protein kinase (PKA); (2 μM) inhibition of PKCs	(**37**): significant survival increase of 30% in P388 mouse syngeneic lymphoma treated with 400 mg/kg (i.p. administration)	Fruits Vegetables Olive oil Plants Beverages (coffee, wine, tea)	[28, 77-80]
Tannins  (**39**): Tannic acid	10 – 50 μM in Mz-ChA-1 malignant cholangiocarcinoma cells	(0.3 μM) Inhibition of PKCs, EGFr tyrosine kinase (5 μM) inhibition of insulin receptor tyrosine kinase (14 μM) inhibition of p60c-src tyrosine kinase		Red Wine Nuts	[81, 82, 88-90]
Anthocyanidins  (**40**): R = H, R$_1$ = H, Cyanidin (**41**): R = OH, R$_1$ = OH, Delphinidin (**42**): R = OCH$_3$, R$_1$ = H, Peonidin	(**40**) and (**41**): in μM range in various human tumor cells	(**40**): inhibition of EGFr tyrosine kinase (**41**): inhibition of EGFr tyrosine kinase and Fyn kinase (**42**): activation of ERK1/2		Fruits Vegetables Blueberries Wine Grape Seeds Red wine	[83-86, 91]
Diterpenes  (**43**): Carnosol	34 μM in PC3 prostate cancer cells	(5 μM) inhibition of Akt, p38, JNK and ERK1/2 phosphorylation (40 μM) activation of AMPK-α, but inhibition of PI3K/Akt pathways	No significant survival increase in P388 mouse syngeneic lymphoma treated with 7 mg/kg (i.p. administration) Significant 40% decrease in DMBA rat syngeneic mammary cancer initiation with 200 mg/kg (i.p. administration)	Rosemary (*Rosmarinus officinalis*)	[28, 87, 92, 93]

(Table 4). Contd…..

Structure / Name	*In vitro* growth inhibitory IC_{50} (µM) values	Kinases as specific targets (IC_{50} in µM)	Experimental mouse and rat models in which *in vivo* activity has been investigated	Compound source	Ref.
Diterpenes  (**44**): Carnosic acid	~ 20 µM in a panel of 60 cancer cell lines	Up-regulation of cyclin-dependent kinase inhibitors p21WAFI and p27Kipl		Rosemary (*Rosmarinus officinalis*)	[28, 94]

found in nature with a 7-hydroxyl function. As a class of natural polyphenols, coumarins have distinguished themselves by providing a wide range of bioactive agents. Early interest in these compounds was due to their anticoagulant properties giving rise to an anticoagulant drug warfarin. Later, many other types of biological activities were discovered ranging from photosensitization to vasodilatation. Coumarin derivatives reported to exert anticancer activity through kinase targeting include esculetin (**36**), scopoletin (**37**) and daphnetin (**38**, Table **4**) [77-80].

Tannins

The designation tannins normally includes compounds of two distinct categories of polyphenolic substances: the hydrolyzable (polymeric derivatives of gallic and/or ellagic acids with glucose) and the non-hydrolyzable or condensed tannins, resulting from the condensation of monomeric flavan-3-ol units. At the centre of the hydrolyzable tannin molecule is a carbohydrate (usually D-Glucose). The hydroxyl groups of the carbohydrate are partially or totally esterified with phenolic groups of gallic and/or ellagic acids. These derivatives are hydrolyzed by weak acids or bases to produce the carbohydrate and phenolic acids. Tannic acid (**39**, Table **4**) is one derivative of this family, which revealed anticancer activity [81, 82].

Anthocyanidins

Anthocyanidins are common plant pigments and are characterized by the carbohydrate-free derivatives of anthocyanins based on the benzopyrylium (2-phenylchromenylium) ion (Table **4**). The benzopyrylium skeleton is derivatized at position 2 with a benzene ring that is generally hydroxylated (Table **4**). The counterion of the chromenylium cation is mostly chloride and this positive charge is a distinguishing feature of cyanidins. Anthocyanidins can be glycosylated leading to anthocyanins and more than 400 anthocyanins have been reported since 2003 [83]. In the present review, we focus on the representative cyanidin (**40**), delphinidin (**41**) and peonidin (**42**) because these compounds revealed anticancer activity through the targeting of specific kinases (Table **4**) [84-86].

Polyphenolic Diterpenes

Diterpenes are formed from 4 isoprene units. Representatives of this class of compounds functionalized with phenolic moieties are commonly referred to polyphenolic diterpenes. Carnosol (**43**) and carnosic acid (**44**) are two polyphenols of this group that are of relevance to kinase targeting and they were isolated from culinary herbs that include rosemary, sage and oregano (Table **4**) [87].

SPECIFIC KINASE TARGETING BY POLYPHENOLS

Group I: Polyphenolic Acids and their Analogues

Lauryl gallate (**2c**) inhibited proliferation and induced apoptosis in MCF-7 and MDA-MB231 human breast cancer cells [29]. The Martin-Perez group demonstrated that this was due in part to activation of mitogen-activated protein kinases (MAPK) by lauryl gallate (**2c**) and, more particularly, the ERK1/2 kinases (Table **1**) [29]. Protocatechuic acid (**3**) was capable of stimulating c-Jun N-terminal kinase (JNK), another p38 MAPK, and as a consequence induced cell death in HepG2 hepatocellular carcinoma and AGS human gastric adenocarcinoma cells (Table **1**) [30,31]. Caffeic and ferulic derivatives (**5**, **6** and **7**) target specifically the PKC protein kinase family and arrest growth of various cancer cells, such as for example U937 human leukemic cells (Table **1**) [18, 32, 33]. Caffeic acid, more specifically, inhibits directly Fyn kinase, one of the members of PKC [33]. Capsiate (**8**) interfered with angiogenesis and vascular permeability in HUVEC endothelial cells by direct inhibition of Src kinase, a tyrosine kinase (Table **1**) [20]. Capsaicin (**9**), an analogue of capsiate (**8**), is known to activate, at a concentration of 25 µM, adenosine monophosphate (AMP)-activated protein kinase (AMPK) and it induces apoptosis of HT-29 colon cancer cells [19]. [6]-Gingerol (**10**) was described as an inducer of apoptosis and cell growth arrest in human colorectal cancer cells (for example HCT-116) [22]. Although multiple mechanisms could explain this anticancer activity, inhibition of protein kinase C (PKCε) and glycogen synthase kinase (GSK-3β) as well as activation of activator protein 1 (AP-1) were all involved in this process (Table **1**) [21,22]. Hydroxytyrosol (**13**) was able to inhibit the progression of cell cycle in HL60 human promyelocytic leukemia cells [24]. This *in vitro* anticancer activity was associated with a reduction in the levels of cyclin-dependent kinase 6 (CDK6) and an increase of CDKi $^{p21WAF1/Cip1}$ and $p27^{Kip1}$ [24]. On the other hand, tyrosol (**12**) was associated with inhibition of protein kinase C (PKC) [23]. Rosmarinic acid (**14**) was shown to antagonize the activation of extracellular signal-regulated protein kinase-1/2 (ERK1/2) in various cancer cells, such as for example colorectal HT-29 or mammary MCF-7 cell lines [25]. This activity is associated with inhibition of AP-1 binding to DNA [25]. Curcumin (**15**) has been widely investigated as a potential therapeutic and cancer preventive agent and it showed useful activities against various types of cancer cells. Multiple mechanisms of action could explain the observed anticancer activities and this subject has already been reviewed [26, 27, 95]. Of relevance to this discussion are the reports describing curcumin's ability to target kinases and, more particularly, inhibit phosphorylase kinase (PhK) [22], IKK [27], I-KB [27], mTOR [38], cdk-25 [39], cyclin D1 [39] and suppress novel protein kinase C (nPKC) [37] (see [95] for additional review).

Group II: Stilbenoid Derivatives

Currently, numerous preclinical findings indicate that resveratrol (**16**) is a promising nature's arsenal for cancer prevention and treatment. Resveratrol targets many components of intracellular pathways including various kinases [40]. This compound is known to target MAP kinases (ERK1/2, p38 MAPK and JNK) by activation or suppression of their intracellular levels and this activity depends on various parameters, such as the specific types of cancer cells and the concentration of the drug (Table **2**) [40]. The inhibition of PI3K/Akt by resveratrol was also observed in multiple cancer cells [40]. Additionally, protein kinase C (PKC) was targeted by this polyphenol as part of the process resulting in the inhibition of oncogene signal transduction [41]. Pterostilbene (**17**), a natural analogue of resveratrol (**16**), was reported to induce apoptosis and cell cycle arrest in human gastric carcinoma cells and this anticancer effect was associated with the down-regulation of cyclin-dependent kinase 2 (Cdk2), Cdk4 and Cdk6 [42]. Wilson *et al*. [96] recently reported toxicity towards *Caenorhabditis elegans* adults for trimethoxylated and dimethoxylated stilbenes, as well as the monomethoxylated stilbene desoxyrhapontigenin. Toxicity was not observed for the monomethoxylated stilbene, pinostilbene, nor for hydroxylated stilbenes [96]. The methoxylated stilbenes that exhibited toxicity also showed stronger inhibitory effects than the hydroxylated stilbenes on germline tumor growth in gld-1(q485) adults [96]. Alltogether, the findings provided by Wilson *et al*. [96] demonstrated that, for the group of stilbenes investigated, methoxylation generally increased bioactivity *in vivo* in a whole organism, with the exception of pinostilbene. Wilson *et al*. [96] state that the potent activities of methoxylated stilbenes provide a basis for further investigations to identify *in vivo* targets for these compounds. The presence of different fnctional groups in the molecules of stilbenoids, i.e. resveratrol and pterostilbene for example, influence their antioxidative effects, and therefore their potential anticancer activity [97]. Resveratrol and pterostilbene could display distinct anticancer activity through the modulation of distinct signaling pathways [16,40-42,98,99].

Group III: Flavonoids and their Analogues

Baicalein (**18**) was able to inhibit proliferation and induce cell death in various human bladder cancer cell lines [46]. This *in vitro* anticancer activity was associated with the inhibition of cyclin-dependent kinase 2 (CDC2) and the opposite effect on p38 MAPK [46]. Luteolin (**20**) and apigenin (**21**) were able to inhibit PKC and PI3K/Akt in various prostate cancer cell lines [47,48]. Quercetin (**22**) was reported to inhibit MEK1, Raf1 and PKC and, thus, inhibit neoplastic cell transformation (Table **3**) [48,60]. Myricetin (**23**) was also capable of inhibiting MEK1 but the inhibition was more potent with the MAP kinase 4 (MKK4) (Table **3**) [49]. Computer modelling suggested that this compound docks onto the ATP-binding site in MKK4 [49]. Kaempferol (**24**) was found to induce growth inhibition and apoptosis in A549 lung cancer cells, which was mediated by activation of MEK-MAPK [50]. Catechin (**25**) inhibited intestinal tumor formation and down-regulated focal adhesion kinase (FAK) in HT-29 and DLD-1 colon cancer cells [51]. Epicatechin (**28**) activated ERK and P38 MAPK in HepG2 human hepatoma cells [61]. Epigallocatechin gallate (EGCG, **29**) was described in many reviews as an inhibitor of carcinogenesis in different animal models [52,62,64]. Its mechanism of action has also been reviewed and the specific inhibition of protein kinases was discussed (Table **3**), including inhibition of MEK1/2, ERK1/2, c-Jun, Akt, Dyrk1A, CDK1 and CDK2 in various types of cancer cells [52,61-64,66]. In addition, activation of ERK and JNK was observed and it was dependent on the concentration of EGCG [61]. Theaflavins **30**, **31** and **32** were described as HER/*neu* tyrosine kinase inhibitors in MCF-7 human breast cancer cells [67]. In DU145 and LNCaP prostate cancer cells, all three of these theaflavins decreased the levels of PI3K and phosphor-Akt and increased Erk1/2 [49]. Theaflavin (**32**) inhibited EGF receptor kinase activity in A431 human epithelial carcinoma cells [68]. Daidzein (**33**) was capable of down-regulating the cyclin D, CDK2 and CDK4 without affecting cyclin E and CDK6 in MCF-7 and MDA-MB-453 human breast cancer cells [69]. Genistein (**34**) was found to inhibit Cdc2 kinase in various hepatoma cell lines [70] and tyrosine kinases in BALB/c murine mammary carcinoma cells [71]. Silibinin (**35**) is currently in phase II clinical trials in prostate cancer patients; however, its anti-tumor effects and mechanisms are not completely understood [58]. This anti-tumor activity against prostate cancer cells was associated with the down-regulation of STAT, JNK1/2, p38 MAPK and Akt signalling and up-regulation of ERK1/2 signalling [56-58].

Group IV: Miscellaneous

Coumarins

Esculetin (**36**) has been shown to induce apoptosis in various human cancer cells [77] and, more particularly, U937 human leukemia cells [78]. This anticancer activity was associated with selective activation of the phosphorylation of extracellular-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) [78]. Scopoletin (**37**) was found to exert a dual action on tumoral lymphocytes exhibiting both a cytostatic and cytotoxic effects [79]. These effects were associated with the induction of apoptosis, which was found to be due to the activation of PKC [79]. On the other hand, daphnetin (**38**) was found to inhibit EGFR and serine/threonine-specific protein kinases, including cAMP-dependent protein kinase (PKA) and protein kinase C (PKC) [80].

Tannins

Tannic acid (**39**) was capable of modulating the subcellular distribution of PKCα, β1, β2 isoforms and the activity of PKCs [88]. This compound was able to inhibit PKC translocation and activity [88]. Tannic acid (**39**) was also described to be a potent *in vitro* inhibitor of EGFR tyrosine kinase [89]. The p60s-src tyrosine kinase and insulin receptor tyrosine kinase were inhibited by tannic acid with weaker efficacy [89] (Table **4**).

Anthocyanidins

Cyanidin (**40**) and delphinidin (**41**) were found to inhibit the growth of various tumor cells *in vitro* in the micromolar range [84]. This anticancer activity was associated with a potent inhibition of EGFR tyrosine kinase [84]. Delphinidin (**41**) was also reported to target the Fyn kinase directly, a member of the non-receptor protein tyrosine kinase family [85]. Phenol **41** was also found to inhibit cell proliferation and cell cycle of BAECs bovin aortic endodelial cells through a transient activation of ERK1/2 [91]. Peonidin (**42**) was found to block phosphorylation of ERK-1 and -2, and thus, inhibited transformation in JB6 P(+) epidermal cells [86].

Polyphenolic Diterpenes

Carnosol (**43**) displayed growth inhibitory effects in human prostate cancer PC3 cells [87]. This anticancer effect was associated with activation of AMPK-α and inhibition of PI3K/Akt pathways [87]. This natural product also inhibited the invasion of B16F10 mouse melanoma cells through down-regulating cJun and inhibition of ERK1/2, Akt, p38, JNK kinases [92]. Carnosic acid (**44**), a natural congener of diterpene **43**, was able to inhibit proliferation of HL-60 and U937 human myeloid leukemia cells [92]. This inhibitory effect was accompanied by an increase in the levels of cyclin-dependent kinase inhibitors p21WAFI and p27Kipl [94].

POLYPHENOL STRUCTURE-ACTIVITY RELATIONSHIPS (SAR) WITH RESPECT TO THEIR ANTICANCER ACTIVITIES AND SPECIFIC KINASE TARGETING

Each natural polyphenol in Tables **1-4** interferes with the activity of one or several protein kinases and, unfortunately, these biological effects cannot be predicted or explained on the basis of the currently available SAR data. Detailed mechanistic understanding of kinase targeting by polyphenols has been attained only in a small number of cases. For example, myricetin (**23**) inhibits MAPK kinase 4 (MKK4) directly by competing with ATP [49]. Computer modelling suggested that myricetin docks onto the ATP-binding site in MKK4 [49]. Myricetin fits snugly onto the ATP-binding site of MKK4, located between the N- and C-lobes of the kinase domain, and can form hydrogen bonds with the backbone of the hinge region in MKK4, as does ATP [49]. This work sets the stage for the development of *de novo* analogues that can be prepared by derivatization of the natural polyphenols or total synthesis in search for stronger ATP-site binders and more potent inhibitors of MKK4. It is also expected that useful SAR will be obtained for this series of polyphenols vis-à-vis the ATP pocket of MKK and, possibly, other kinases due to the highly conserved ATP-site binding requirements among these enzymes. A similar bioinformatics-based approach was also developed for protein kinase C targeting in prostate cancer in order to accelerate the process of identification and discovery of new leads in prostate cancer [48]. Flavonoids (e.g. luteolin (**20**), apigenin (**21**), quercetin (**22**)) and silibinin (**35**) exhibited high affinity for the catalytic domain of protein kinase C (PKC) [48]. All these phenols can serve as excellent starting points for the development of new derivatives by hemisynthesis or total synthesis in order to identify new leads. Tannic acid (**39**) has also been successfully docked into the ATP binding site of EGFR and insulin receptor, which explains the potent inhibition of EGFR and insulin receptor tyrosine kinases by this natural product [89]. Therefore, this investigation also paves the way for the discovery of new inhibitors of EGFR and insulin receptor tyrosine kinases. Capsiate (**8**) is another polyphenol, which was found to inhibit Src kinase activity *via* its preferential binding to the ATP-site of Src kinase [20]. This finding could be useful for blocking the pathologic angiogenesis and vascular permeability induced by VEGF.

Several natural polyphenols have been found to bind to an allosteric site on protein kinases rather than the ATP pocket. Quercetin (**22**) was docked to a separate site, adjacent to the ATP-binding site of mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK1) [60]. This binding event results in stabilization of the inactive conformation of the activation loop of MEK1 [60]. Delphinidin (**41**) inhibited Fyn-kinase by binding to the enzyme in the non-competitive manner with respect to ATP [85]. These examples show that each inhibition or activation event is quite unique and must be studied separately to elucidate the mechanism of action of these compounds. This understanding is useful for the identification of promising new anticancer leads that work through kinase inhibition and several teams have developed new inhibitors of protein kinases [66, 100]. A number of research groups used computer-assisted approaches to design new inhibitors of specific kinases and then prepared these compounds by total syntheses [66, 100]. This led to derivation of useful SAR or QSAR data with respect to specific kinases (e.g. Dyrk1A) [101-103].

ANTI-KINASE DRUGS AND TOXICITY

With variations from drug to drug, tyrosine kinase inhibitors cause skin toxicity, including folliculitis, in more than 50% of patients [9]. Among the tyrosine kinase inhibitors that are already commercially available, the agents that target EGFR, erlotinib and gefitinib, display the broadest spectrum of adverse effects to skin and hair, including folliculitis, paronychia, facial hair growth, facial erythema, and varying forms of frontal alopecia [9]. In contrast, folliculitis is not common during administration of sorafenib and sunitinib, which target VEGFR, PDGFR, FLT3, and others; however, both agents have been associated with subungual splinter hemorrhages [9]. Periorbital edema is a common adverse effect of imatinib [9]. In addition to the hematological side effects of most of TKIs, such as anemia, thrombopenia and neutropenia, the most common extra-hematologic adverse effects are edema, nausea, hypothyroidism, vomiting and diarrhea [9]. Also, a possible long-term adverse effect involving cardiac toxicity with congestive heart failure is under debate in patients receiving imatinib and sunitinib therapy [9].

Crean and colleagues [104] recently reviewed the potential safety profiles of small molecule multi-targeted kinase inhibitors for the treatment of advanced cancer and the results of this systematic review suggest that adverse events (diarrhea, fatigue, nausea, rash, anorexia, vomiting, hand/foot syndrome, and hypertension) are common and varied for patients treated with a multi-kinase inhibitor [104]. However, unlike some systemic cytotoxic therapies, serious and severe adverse events for multi-kinase inhibitors are less frequent [104]. Sub-analyses by a target kinase or kinase family demonstrate that certain groups of multi-kinase inhibitors can be associated with different safety profiles with unique adverse events [104]. It is an attractive possibility that using natural polyphenols as multi-targeted kinase inhibitors will lead to lower toxicities compared with the synthetic compounds.

It should nevertheless be emphasized that the dosing required for *in vitro* IC_{50}s and *in vivo* benefits that we report in Tables **1-4** seem quite high. This feature could relate, at least partly, to the fact that polyphenols i) can display poor hydrosolubility and/or ii) can be rapidly degraded enzymatically, as for example by esterases in some cases. It is thus unlikely that polyphenols can be used directly in clinics. In contrast, controlled release approaches should be beneficial to solve these problems and to translate polyphenols for clinical use and to provide needed doses to human subjects.

CONCLUSION

In recent years, few classes of natural products have received as much attention as polyphenols. More than 8,000 phenolic and polyphenolic compounds have been identified in many different species of plants, and many of them find their way into human diet. Vast epidemiological data suggest that consumption of fruits and vegetables, two important dietary sources of polyphenols, is associated with low risk of cancer and cardiovascular diseases [105]. There is a popular belief that dietary polyphenols are anticarcinogens because of their anti-oxidative properties, however, direct evidence for this proposal is lacking. In contrast, a large body of experimental work indicates that polyphenols interact with key enzymes involved in cellular signal transduction pathways controlling cell cycle, differentiation, apoptosis, angiogenesis and metastasis. Because of their high affinity to proteins, clearly assisted by the capacity to serve as hydrogen bond donors, natural polyphenols and their synthetic derivatives have been widely utilized for the development of bioactive agents that work through protein targeting, and as this review has amply demonstrated, kinase targeting. In addition, the present review has indicated that a single polyphenol is capable of interacting with several protein kinases and this broad reactivity makes these compounds applicable for a number of conditions. For example, gleevec that was originally developed as an inhibitor of BCR-ABL kinase to treat chronic myelogenous leukemia is also used in the treatment of gastrointestinal stromal tumors, and this pharmacological effect results from the inhibition of c-KIT kinase by this drug [106]. Furthermore, multi-kinase inhibition by a single agent may synergistically enhance its effect on cancer cells. For instance, the dual PI3K-mTOR inhibitor PI-103 is more effective than the inhibitors of either kinase alone [107]. Lastly, this multi-kinase-based “polypharmacology” with a natural polyphenol or its synthetic analogue will have distinct advantages over currently used chemotherapy agents, including enhanced efficacy against resistant tumors and significantly reduced adverse effects. It is our hope that the current review provides a useful reference to researchers, who are willing to take this science to the next level of polyphenol-based anticancer drug development, including advancing kinase-targeting polyphenols to clinical trials and obtaining ample SAR data through synthetic chemistry efforts.

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