Recent Advance in the Research of Flavonoids as Anticancer Agents

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Abstract: Flavonoids are ubiquitously in plants which have been shown to possess a variety of biological activities at nontoxic concentrations in organisms. Compelling data indicate that flavonoids have important effects on cancer chemoprevention and chemotherapy, till now, much research has been done about their potential anticancer effect. In this review the discovery and development of flavonoids as potential anticancer agents in recent years have been summarized.

Key Words: Flavonoids, anticancer agents, discovery, development, clinical trial, mechanism, cytotoxicity, SAR.

1. INTRODUCTION

Flavonoids, a class of polyphenolic compounds widely distributed in the plant kingdom, are a group of about 4000 naturally occurring compounds that are ubiquitous in all vascular plants [1]. They are phenyl substituted chromones (benzopyran derivatives) consisting of a 15-carbon basic skeleton (C6-C3-C6), composed of a chroman (C6-C3) nucleus (the benzo ring A and the heterocyclic ring C), with a phenyl (the aromatic ring B) substitution usually at the 2-position. Different substitutions can typically occur in the rings, A and B [2]. They have been shown to possess a variety of biological activities at nontoxic concentrations in organisms [3,4], such as antioxidant, antitumor, anti-inflammatory, antiallergenic and hepatoprotective effect [5]. Owing to the increasing interest in the association between flavonoids and cancer initiation and progression, the study of antitumor action of flavonoids has become an important field. For example, the role of dietary flavonoids in cancer prevention is widely discussed [6], some protective associations have been suggested for flavonoid-rich foods (soy and premenopausal breast cancer; green tea and stomach cancer; onion and lung cancer), as far as genistein (a soy isoflavone) is concerned, there are almost 1,500 publications pertain to its antitumor capabilities [7]. In addition, flavonoids such as the synthetic flavone, flavopiridol; the tea catechin epigallocatechin gallate; or the common dietary flavonol, quercetin, are emerging as prospective anticancer drug candidates and some of them have already entered into clinical trials [8,9]. so, a greater understanding of their anticancer properties might also modify our dietary habits. In other studies, some flavonoids have been investigated as inhibitors of HIV-1 reverse transcriptase, protease, and integrase [10]. Therefore, the isolation and structural modifications of flavonoids will provide us continuing sources of potential anticancer agents, this review article will focus on such work.

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2. NATURAL ANTICANCER FLAVONOIDS

2.1. Flavonoids from the Genus *Artocarpus*

The genus *Artocarpus* (Moraceae) comprises approximately 50 species and is widely distributed in tropical and subtropical regions, including Indonesia. Some members of this genus have been used medicinally to treat various diseases. The molecular diversity and activity of flavonoids from *Artocarpus* have made it a plausible unexplored resource of novel antitumor leads [11], for instance, compound **1** represented the first tetraprenylated dihydrobenzoxanthone-type flavone to be isolated from plants, compound **2** also represented the first natural flavone hydroperoxide structurally analogous to morusin hydroperoxide [12] later, the isolation of **3-5** (containing the unique feature of an isoprenyl side chain at C-3) provided additional examples [13], meanwhile, prenylated flavonoids **6-11**, also showed strong cytotoxicity against P-388 cells (Table **1**) [14-16]. In addition, Artochamin C exhibited significant activity against MCF-7, 1A9, HCT-8, and SK-MEL-2 cell lines with ED_{50} values of 2.0-2.3 μg/mL [17].

Table 1. Cytotoxicity of Flavonoids from the Genus *Artocarpus* Against P-388 Cells

Compound.	No.	IC_{50}(μg/ml)
artoindonesianin A	**1**	21
artoindonesianin B	**2**	3.9
artoindonesianins G	**3**	0.7
artoindonesianins H	**4**	1.8
Artoindonesianinsl	**5**	1.8
artoindonesianin L	**6**	0.6
artelasticin	**7**	3.0
artonins E	**8**	0.06
artonins M	**9**	7.9
artonin O	**10**	0.9
cycloartobiloxanthone	**11**	4.6

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2.2. FLAVONOIDS FROM SOPHORA

The root of *Sophora flavescens* has been reported to possess antitumor activity in Sarcoma 180, lymphoid leukemia 1210 and melanotic melanoma. In 2000, Kang *et al.* isolated four lavandulylated flavanones (compounds **12-15,** see Table **2**) [18]. In addition, De Naeyer *et al.* found that kurarinone (**13**) showed weak estrogenic activity [19]. In the same year, kang TH made further study on above compounds and verified that lavandulyl flavonoids were a new class of *in vitro* apoptogenic agents from Sophora flavescens [20]. In 2002, Tashir *et al.* investigated the effects of 2 flavanones and 8 chemically-defined prenylflavanones from Sophora species on growth and activation of mouse macrophage-like cell line [21]. The results showed 2 flavanones (naringenin and hesperetin) had little or no cytotoxic activity, however, that addition of the isoprenyl group (compounds **17**, **18)** or the lavandulyl and hydroxyl group (compd. **14**) significantly enhanced the cytotoxic activity. The cytotoxic activity of these compounds was significantly influenced by both log P value and ionization potential. Likewise, in 2004, A research group led by Shirataki Y investigated 11 isoflavonoids from Sophora species for their cytotoxic activity against 2 human tumor cell lines (squamous cell carcinoma HSC-2, submandibular gland carcinoma HSG) [22]. The results showed compounds with 2 isoprenyl groups (one in A-ring and the other in B-ring) such as compounds **19**, **20** and those with alpha, alpha-dimethylallyl group at C-5' of B-ring (compounds **21-24**) showed relatively higher cytotoxic activity.

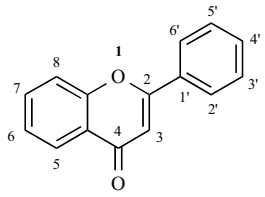
Table 2. Anticancer Flavonoids from Sophora

Compd.	No.
(2*S*)-2'-methoxykurarinone	**12**
(-)-kurarinone	**13**
sophoraflavanone G	**14**
leachianone A	**15**
sophoraflavanone B	**16**
euchrestaflavanone A	**17**
tetrapterol G	**18**
isosophoranone	**19**
secundifloran	**20**
secundiflorol A	**21**
secundiflorol D	**22**
secundiflorol E	**23**
secundiflorol F	**24**

2.3. Anticancer Flavones, Flavonols (Tables 3,4)

2.4. Other Natural Anticancer Flavonoids (Table 5)

Table 3. Natural Anticancer Flavones

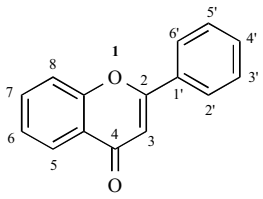


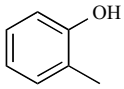
Compd.	No.	5	6	7	8	2'	3'	4'	5'	Ref.
nobiletin	**25**	OMe	OMe	OMe	OMe		OMe	OMe		[23,24]
tangeretin	**26**	OMe	OMe	OMe	OMe			OMe		[25,26]
cirsimaritin	**27**	OMe	OMe					OH		[27]
chrysoeriol	**28**	OH		OH			OMe	OH		[27]
5,6-Dihydroxy-7,3',4'-trimethoxyflavone	**29**	OH	OH	OMe			OMe	OMe		[28]
5,6,4'-Trihydroxy-7,3'-dimethoxyflavone	**30**	OH	OH	OMe			OMe	OH		[28]
baicalein	**31**	OH	OH	OH						[29, 30]
wogonin	**32**	OH		OH	OMe					[31, 32]
apigenin	**33**	OH		OH				OH		[32, 33]
5,7,2'-Trihydroxyflavone	**34**	OH		OH		OH				[34]
5,7,2',3'-Tetrahydroxyflavone	**35**	OH		OH		OH	OH			[32, 34]

(Table 3. Contd….)

Compd.	No.	5	6	7	8	2'	3'	4'	5'	Ref.
velutin	**36**			OMe			OMe	OH		[35]
7,3',5'-Tri-O-methyltricetin	**37**			OMe			OMe	OH	OMe	[35]
genkwanin	**38**			OMe				OH		[35]
lethedocin	**39**			OMe			OMe	OMe	OH	[35]

Table 4. Natural Anticancer Flavonols



Compd.	No.	3	5	6	7	8	2'	3'	4'	5'	Ref.
HPT	**40**	OMe	OMe	OMe	OMe	OMe		OMe	OMe		[36,37]
	41	OMe	OH	OMe	OMe	OMe		OH	OMe		[38]
morin	**42**	OH	OH		OH		OH		OH		[39]
casticin	**43**		OH	OMe	OMe			OH	OMe		[40]
myricetin	**44**	OH	OH		OH			OH	OH	OH	[41,88]
quercetin	**45**	OH	OH		OH			OH	OH		[42-45]
8-C-(o)-hydroxy benzylpachypodo	**46**	OMe	OH		OMe			OMe	OH		[46]

HPT: 3,5,6,7,8,3',4'-heptamethoxyflavone

2.5. Anthocyanidins, Homoisoflavanone and Flavonolignan (Table 6)

3. SYNTHETIC ANTICANCER FLAVONOIDS

Like natural anticancer flavonoids, many synthetic flavonoids also exhibited significant anticancer activities. Now, we focus on the structural modifications of flavones and chalcones, along with the design of target compounds and the exploration of SAR.

3.1. Thioflavones

The isosteric replacement of an oxygen atom by a sulfur atom is useful for the design and synthesis of analogues, which are expected to display modified chemical and biological behavior.

3.1.1. 5,6,7,8-substituted-2-phenylthiochromen-4-ones

The similar skeletons between the bioactive 2-phenyl-4-quinolones and some flavones suggested that similar activities might be anticipated following the substitution of the heteroatom by a bioisostere such as sulfur. Consequently, a series of 5,6,7,8-substituted-2-phenylthiochromen-4-ones were synthesized and evaluated for activities [97]. As shown in Table **7**, compounds **115-118** displayed significant cytotoxic activity (ED_{50} < 4.0 μg/mL), Compounds **116**, **117** and **120** displayed topoisomerase I inhibitory activities, and compound **119** inhibited topoisomerase II activity. The topoisomerase inhibitory effects observed *in vitro* were unexpected. Despite the limitation of study, it was clear that heteroatom replacement by sulfur was tolerable because antitumor activities were retained.

3.1.2. 2'-aminothioflavones

PD98059 (**121**) is a unique inhibitor of MEK1/2, which acts alike as an allosteric inhibitor, to seek for specific inhibitors of the ERK-MAP kinase signaling pathway, a series of thioflavones related to **121** were synthesized, SAR indicated that the amino group at the 2'-position was essential and the methoxy group of the 2-phenyl group should be situated at the *ortho* position of the amino group. In a cell-based

Table 5. Other Natural Anticancer Flavonoids

Flavonoids	Compd.	No.	Source	Ref.
flavanones	naringenin	**47**	Citrus	[47]
	propolin A	**48**	*Taiwanese propolis*	[48]
	propolin B	**49**	*Taiwanese propolis*	[48]
	propolin C	**50**	*Taiwanese propolis*	[49]
	cathayanon A	**51**	*Morus cathayana*	[50]
	cathayanon B	**52**	*Morus cathayana*	[50]
	(-)-isoglabrachromene	**53**	*Lonchocarpus aff. Fluvialis*	[51]
isoflavonoids	wighteone	**54**	*Erythrina indica*	[52]
	8-Hydroxygenistein	**55**	*Soybean miso*	[53]
	tectorigenin	**56**	*Pueraria thunbergiana*	[54]
	auriculasin	**57**	*Millettia taiwaniana*	[55]
	pervilleanone	**58**	*M. pervilleana*	[56]
	3'-O-demethylpervilleanone	**59**	*M. pervilleana*	[56]
	pendulone	**60**	*Wistaria brachybotrys*	[57]
	(3S)-7-hydroxy-2',3',4',5',8-pentamethoxyisoflavan	**61**	*Eysenhardti polystachya*	[58]
	(3S)-3',7-dihydroxy-2',4',5',8-tetramethoxyisoflavan	**62**	*Eysenhardti polystachya*	[58]
	isoduartin	**63**	*Eysenhardti polystachya*	[58]
	2,3,9-trimethoxypterocarpan	**64**	*Platymiscium floribundum*	[59]
biflavonoids	isocryptomerin	**65**	*Selaginella illdenowii*	[60]
	4',7"-di-O-methylamentoflavone	**66**	*Selaginella illdenowii*	[60]
	7"-O-methylrobustaflavon	**67**	*Selaginella illdenowii*	[60]
	ginkgetin	**68**	*Selaginella illdenowii*	[61]
	neocalycopterone	**69**	*Calycopteris floribunda*	[62]
	neocalycopterone-4-methyl ether	**70**	*Calycopteris floribunda*	[62]
	taiwanhomoflavone-A	**71**	*Cephalotaxus wilsoniana*	[63]
	taiwanhomoflavone-B	**72**	*Cephalotaxus wilsoniana*	[64]
	robustaflavone-4'-methyl ether	**73**	Selaginella delicatula	[65]
	2",3"–dihydrorobustaflavone-7,4',-dimethyl ether	**74**	Selaginella delicatula	[65]
	7"-O-Methyl-agathisflavone	**75**	*Ouratea hexasperma*	[66]
	amentoflavone	**76**	*O. semiserrata*	[66]
	calodenin B	**77**	*Ochna macrocalyx*	[67]
	dihydrocalodenin B	**78**	*Ochna macrocalyx*	[67]
	7,7"di-*O*-methyl-2,3,2",3"-tetrahydroochnaflavone	**79**	*Quintinia acutifolia*	[68]
	2,3,2",3"-tetrahydroochnaflavon	**80**	*Quintinia acutifolia*	[68]
	2",3"-dihydroochnaflavone	**81**	*Quintinia acutifolia*	[68]

(Table 5. Contd….)

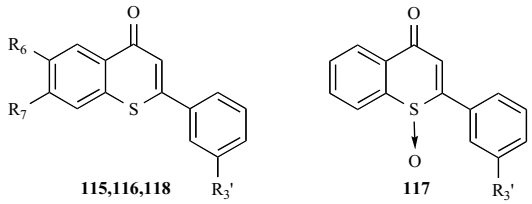
Flavonoids	Compd.	No.	Source	Ref.
chalcones	DMC	**82**	*Cleistocalyx operculatus*	[69-72]
	isoliquiritigenin	**83**	*licorice,shallot,beansprouts*	[73-75]
	xanthoangelol	**84**	*Angelica keiskei*	[76,77]
	xanthoangelol I	**85**	*Angelica keiskei*	[78]
	xanthoangelol J	**86**	*Angelica keiskei*	[78]
	xanthoangelol F	**87**	*Angelica keiskei*	[79]
	xanthoangelol H	**88**	*Angelica keiskei*	[79]
	isobavacholone	**89**	*Angelica keiskei*	[79]
	4-hydroxyderricin	**90**	*Angelica keiskei*	[79,80]
	licochalcone-A	**91**	*Glycyrrhiza glabra*	[81]
	obochalcolactone	**92**	*Cryptocarya obovata*	[82]
	flavokawain A	**93**	*kava*	[83]
	rhuschalconeIV	**94**	*Rhus pyroides*	[84]
glycosides	rutin	**95**	*Scphora japonica L.*	[85]
	myricetin 3-O-beta-D-sorboside	**96**	*L. axillare*	[86]
	myricetin 3-O-neohesperidoside	**97**	*Physalis angulata*	[87]
	myricetin-3-galactoside	**98**	*Warburgia andensis*	[88]
	gossypin	**99**	*cotton*	[89]
	5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-3-yl-5-O-alpha-L-(3,4,5-trihydroxybenzoyl)arabinofuranoside	**100**	*Triplaris cumingiana*	[90]
	pectolinarin	**101**	*L. reflexa*	[91]
	linariin	**102**	*L. reflexa*	[91]
	isolinariin A	**103**	*L. reflexa*	[91]
	isolinariin B	**104**	*L. reflexa*	[91]
	pectolinarigenin-7-O-β-glc	**105**	*L. reflexa*	[91]

DMC: 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone

Table 6. Anticancer Anthocyanidins, Homoisoflavanone and Flavonolignan

Flavonoids	Compd.	No.	Ref.
anthocyanidins	purple corn color (PCC)	**106**	[92]
	cacao liquor proanthocyanidins (CLPr)	**107**	[93]
	delphinidin	**108**	[94]
	pelargonidin	**109**	[94]
	cyaniding	**110**	[94]
	petunidin	**111**	[94]
	malvidin	**112**	[94]
homoisoflavanone	5,7-dihydroxy-3-(3-hydroxy-4-methoxybenzyl) -6-methoxychroman-4-one	**113**	[95]
flavonolignan	palstatin	**114**	[96]

Table 7. ***In Vitro*** **Cytotoxic Activities of Some Substituted 2-Phenylthiochromen-4-ones in Various Tumor Cell (EC_{50} (μg /mL)**

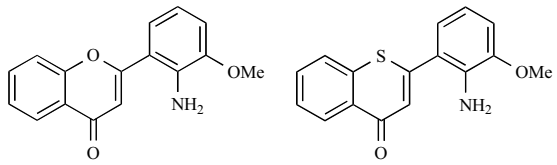


115,116,118 **117**

Compd.	R_6	R_7	$R_{3'}$	KB	HCT-8	P-388	RPMI	TE671
115	OH			–	–	–	0.55	2.87
116	OH	OH		5.5	1.45	4.51	3.92	5.50
117				5.5	5.79	1.18	5.5	3.66
118	OCH_3	OCH_3	OCH_3	5.5	6.35	0.61	5.5	–

Cancer cell lines: Human epidermoid carcinoma of the nasopharynx (KB), human lung carcinoma (A-549), human ileocecal carcinoma (HCT-8), murine leukimia (P-388), human melanoma (RPMI), and human CNS tumor (TE671). "–" means inactive.

assay, compound **122** (Fig. **1**) showed a more potent inhibitory effect than **121** on the Raf-induced activation of the ERK-MAP kinase pathway as well as cell proliferation [98].

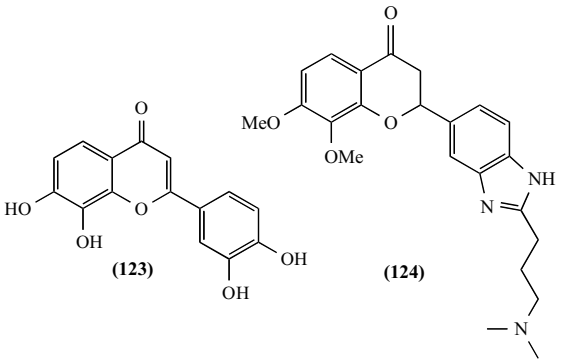


(121) **(122)**

Fig. (1). The structure of PD98059 and compd. **122**.

3.2. Catecholic Flavonoids as Telomerase Inhibitors

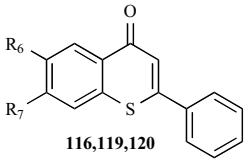
A group led by Menichincheri M identified 7,8,3',4'-tetrahydroxyflavone (**123**) as a new telomerase inhibitor with an *in vitro* activity in a Flash-Plate assay (IC50, 0.2 mM) [99]. accordingly, they made medicinal chemistry studies on this lead compound and achieved new catecholic derivatives (Table **9**) still endowed with submicromolar potencies, among them, compound **124** which characterized by im proved chemical profile represented a new lead structure to be considered for further investigation.



(123) **(124)**

Fig. (2). The structure of compd. **124**.

Table 8. Human DNA Topoisomerase I and II Inhibitory Activities of Substituted 2-Phenylthiochromen-4-ones (% inhibition (100 μM))



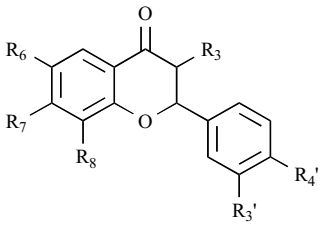
116,119,120

Compd.	R_6	R_7	topoisomerase I [a]	topoisomerase II[b]
116	OH	OH	100	0
119	OAc	OAc	0	100
117			100	0
120	NH_2		100	0

[a]Measured as ATP-independent relaxation of supercoiled plasmid DNA compared to enzyme and DNA control reactions. Camptothecin at 100 μm served as the positive inhibitor control.

[b]Measured as ATP-dependent unknotting of P4 DNA compared to enzyme and DNA control reactions.

Table 9. Flavone Substituents and Telomerase Inhibition Data (FP Assay)



Compd.	R_7	R_8	R_3'	R_4'	R_3	R_6	IC_{50}(μM)
125	OH	OH	OH	OH	H	Cl	0.82
126	OH	OH	OH	OH	F	H	0.6
127	OH	OH	OH	OH	Cl	H	0.8
128	OH	OH	OH	OH	CN	H	0.13

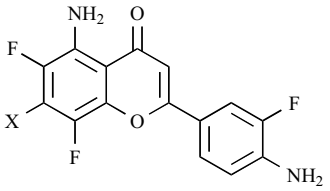
3.3. 5,4'-diaminoflavone Derivatives

Akama T designed and prepared a series of amino-substituted flavone derivatives, among them, 5,4'-diaminoflavone (**129**) exhibited a remarkable antiproliferative effect against MCF-7 irrespective of the presence or absence of estrogen [100]. Later, they synthesized a series of 5,4'-diaminoflavone derivatives aiming at the metabolically stable derivatives [101]. The results showed that 5,4'-diamino-6,8,3'-trifluoroflavone (**130**) exhibited strong avtivity, furthermore, noticing the fact that the antiproliferative activity of 129, was modulated by the addition of apigenin, they hypothesized that the 7-position was important and explored the SAR of the substituents at the 7-position of 130, As a result, 7-methyl (**131**), 7-hydroxymethyl (**132**), 7-(acyloxy)methyl (**133**-**137**), and 7-aminomethyl (**138**) derivatives were found to exhibit comparable or superior antitumor activity to compound 126 against MCF-7 cells both *in vitro* and *in vivo* (Table **10**) [102].

3.4. Synthetic Flavonoids as Aromatase Inhibitors

Besides antiestrogens and progestins, aromatase inhibitors are used today for the treatment of advanced breast cancer of postmenopausal women. In 1990, 7-Hydroxyflavone was found to be an effective competitive aromatase inhibitor with an apparent Ki value of 0.25 mM [103]. Based on this compound, from 2002 to 2004, Pouget *et al.* synthesized a series of flavonoids and investigated for their inhibitory effect against aromatase. In 2002, B ring substituted flavanones with a 7-methoxy group on A ring were synthesized [104], among them, 3',4'-dihydroxy-7-methoxyflavanone (**139**) was found to be twice more potent than aminoglutethimide, the first aromatase inhibitor clinically used. A month later, they again prepared pyridinyl-substituted flavanone derivatives, it was observed that the introduction of a pyridinylmethylene group at carbon 3 on flavanone nucleus led to a significant increase of aromatase inhibitory effect. Moreover, configuration had a substantial influence on the aromatase inhibitory activity since (E)-isomers were found to be more active than (Z)-isomers [105]. Based on above work, they continued to synthesize 4-imidazolylflavans, among them, compounds 2,4-*trans*-4-Imidazolyl-7-methoxyflavan (**140**) and 2,4-*trans*-7-Hydroxy-4-imidazolylflavan (**141**) demonstrated high potential against aromatase [106]. In 2004, as a continution of their work, four 4-triazolylflavans were synthesized and were found to exhibit moderate to high inhibitory activity against aromatase [107]. In the same year, they continued their synthetic work and summarized SAR as follow: first, these compounds bond to the active site of aromatase in an orientation in which A and C rings mimicked rings D and C of the androgen substrate, respectively; It also appeared that the C-4 keto group of flavonoids was essential for aromatase inhibition because it interacts with the heme of the enzyme; With respect to substitutions in the A ring, a 7-hydroxyl group was essential for enhanced aromatase inhibitory activity while a 7-methoxy group was also responsible for an anti-aromatase effect. Finally, it demonstrated that additional hydroxyl groups at position 3′ and/or 4′ on the 7-methoxyflavanone

Table 10. *In Vitro* Cytotoxicity of 7-Substituted-5,4'-diamino-6,8,3'-trifluoroflavone Derivatives against HeLa S_3 and MCF-7 Cell Lines (IC_{50} (μM))



Compd.	X	HeLa S_3	MCF-7
133	CH_2OCOMe	4.9	0.026
134	$CH_2OCO(CH_2)_4CH_3$	34	0.16
135	$CH_2OCOCH_2NMe_2$	9.2	0.026
136	$CH_2OCO(CH_2)_2NMe_2$	11	0.019
137	$CH_2OCO(CH_2)_3NMe_2$	4.5	0.029
138	CH_2NH_2	8.8	0.026

skeleton led to an increase in aromatase inhibition. In addition, as Table **11** showed, compound **145** was only 2.2-fold less active than the letrozole which was used as the first-line therapy for metastatic breast cancer [108].

3.5. Synthetic Chalcones

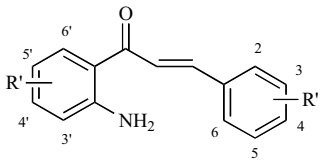
The ease of preparation and the biological activity of chalcones clearly showed that as a class of anticancer agent, they deserved greater attention.

3.5.1. Mannich Bases of Chalcones

A group led by Dimmock JR prepared 44 Mannich bases of chalcones and evaluated their cytotoxic activity [109]. The results revealed that Mannich bases of chalcones were novel cytotoxic agents whose activity was influenced by a number of physicochemical parameters including the π, σ, and MR constants of the aryl rings and redox potentials along with other structural features revealed by X-ray crystallography and molecular modeling.

3.5.2. 2'-amino Chalcones

As the fragmented analogues of 2-phenyl-4-quinolones, new 4',5',2,3,4-substituted 2′-amino chalcones (Fig. **3**) were synthesized and evaluated for the cytotoxicity against a panel of human tumor cell lines [110]. SAR study showed that 2'-Amino chalcones demonstrated significantly increased antitumor activity compared with the corresponding chalcones and better tumor selectivity than the corresponding 2-phenyl-4-quinolones, while, the epoxide derivatives generally showed greatly reduced activity. The most promising lead molecule **150** also had high activity toward multi-drug resistant KB-VIN, and ovarian 1A9 cell lines.



147 R_2= CH_3, R_3= OCH_3
148 R_2= F, R_4=R_5'=OCH_2O
149 R_3= OCH_3, R_4'=R_5'=OCH_2O
150 R_4= F, R_4'=R_5'=OCH_2O

Fig. (3). The structure of compounds **147-150**.

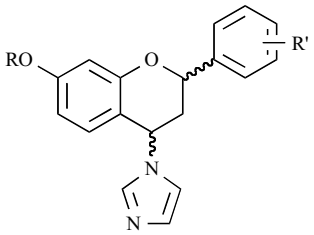
3.5.3. Chalcones Prepared by Parallel Synthesis

Lawrence *et al.* prepared a series of chalcones (Table **12**). The cytotoxicity of these chalcones was conveniently determined upon the crude products directly in 96-well microtiter test plates by the conventional MTT assay [111]. This method revealed seven chalcones showed significant activity, among them, compound **151** was impressively cytotoxic (IC_{50} 30 nM), it caused cell cycle arrest at the G (2) /M point and bond to tubulin at the colchicine binding site.

3.5.4. Fluorinated Chalcone Derivatives

Nakamura *et al.* synthesized fluorinated 3,4-dihydroxychalcones and evaluated their biological activities [112]. Among them, compound **158** (2',4'-Dimethoxy-6-fluoro-3,4-dihydroxy chalcone) was most anticarcinogenic and killed the cells of MCF-7 and SF-268 almost completely. It might act on cancer cells in a way quite different from that of the conventional anticancer agents and thus might be an extremely useful anticancer agent.

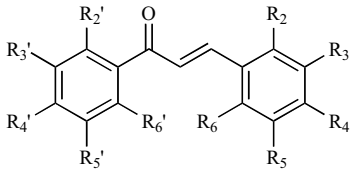
Table 11. Aromatase Inhibitory Activity of Compounds



Compd.	R	R′	IC_{50}(μM)	RP[a]
140	CH_3		0.091	57
141	H		0.041	126.8
142	CH_3	3′-OH	0.130	40
143	CH_3	4′-CI	0.200	26
144	CH_3	4′-CN	0.133	39
145	CH_3	4′-OH	0.040	130
146	H	4′-OH	0.077	68
Letrozole			0.018	289

[a]The relative potency (RP) was calculated from the ratio of IC_{50} values to that measured for aminoglutethimide

Table 12. Cell Growth Inhibitory Properties of Chalcones Prepared by Conventional Methods Originating from the Parallel Synthesis Study Tested against the K562 Cell Line



Compd.	$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{5'}$	$R^{6'}$	R^2	R^3	R^4	R^5	R^6	IC_{50} (μM)
151	H	OMe	OH	H	H	OMe	H	OMe	H	OMe	0.03
152	OMe	H	H	OMe	H	OMe	H	OMe	H	OMe	0.04
153	H	OMe	OMe	OMe	H	H	H	OMe	H	H	0.1
154	F	H	OMe	H	H	F	H	H	Br	H	0.1
155	H	OMe	OMe	OMe	H	H	H	NMe_2	H	H	0.2
156	H	OMe	OMe	OMe	H	OMe	H	OMe	H	OMe	0.2
157	H	H	Me	H	H	H	H	Cl	H	H	0.6

3.5.5. Boronic Chalcone Derivatives

Based on the envision that the boronic acid analogue might form a stronger salt bridge with K51 of MDM2 than the corresponding carboxylic acid analogues. Kumar *et al.* synthesized a set of boronic acid-chalcone derivatives and tested their activity [113]. The results showed compounds **159-165** (Fig. **4**) were 5-10-folds more toxic to human breast cancer cell lines compared to normal breast epithelial cell lines. The selective cytotoxicity was more significant than other known chalcones.

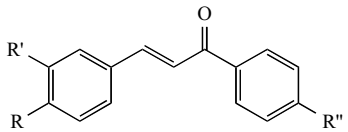
3.5.6. Chalcones and their Derived Pyrazoles

Bhat *et al.* synthesized a series of substituted chalcones and their corresponding pyrazoles, it was concluded that pyrazoles were more active than hydroxy pyrazoles, which in turn, were generally more active than their corresponding chalcones [114]. SAR revealed that the introduction of pyrazole nucleus between two aryl rings of chalcones played an integral role for the increase in cytotoxic potential.

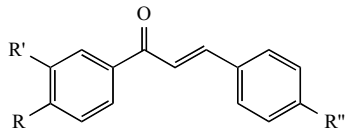
3.6. Derivatives of Chrysin, Baicalein, Quercetin

C or O-substituted hydrophobic derivatives of chrysin were synthesized to investigated structural requirements of the A ring toward Pgp modulation [115], it was reported that only isoprenylated derivatives were able to inhibit Pgp-mediated daunomycin efflux from leukemic K562/R7 cells and enhanced intracellular accumulation of the drug, a much higher effect was observed with dimethylallyl substitution at position 6 or even higher at position 8, the effect of 8-dimethylallylchrysin (**166**) was stronger than that of cyclosporin A. later, a series of chrysin derivatives were prepared, the preliminary biological activities screening tests indicated that 8-bromo-5-hydroxy-7-methoxychrysin (**167**) was identified as the most potent anti-HT-29(human colon carcinoma cell line) and 5,7-dimethoxy-8-iodochrysin (**168**) showed the most significant activity against SGC-7901(gastric cancer cell line) [116].

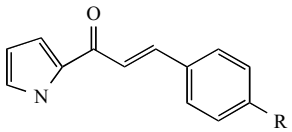
In 2004, 5,6,7-trimethylbaicalein derivatives were prepared and determined for their cell viability, the results indicated that most of the derivatives showed improved inhibition of proliferation of Hep G2 cells. 4'-Amino-5,6,7-trimethylbaicalein (**169**) was the most potent, in which the cell viability was reduced to <2% at the 25 microM level [117]. In the same time, alkylated baicalein of A ring were synthesized and assessed for their activity against P-gp 170, the results indicated that alkylation of R6 or R7 alone or both, could enhance the interaction of baicalein with P-gp 170 as well as the amount of intracellular accumulation of vinblastine, among the compounds, the most potent molecule



159 R=I, R'=H, R"=$B(OH)_2$
160 R=F, R'=F, R"=$B(OH)_2$
161 R=F, R'=Br, R"=$B(OH)_2$
162 R=I, R'=H, R"=$OCH_2B(OH)_2$



163 R, R'=CI, R"=$B(OH)_2$



164 R=H
165 R= $B(OH)_2$

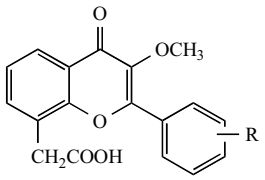
Fig. (4). The structure or Compd. **159-165**.

was 5-methoxy-6,7-dipropyloxyflavone (**170**). Its inhibitory activity was higher than vinblastine and baicalein, with more selectivity than baicalein [118].

In 2002, Krol *et al.* synthesized derivatives of quercetin and tested their antitumor activity *in vitro* on L1210 (murine lymphocytic leukaemia) and P-815 (murine mastocytoma), the experiments showed that sulfonic derivatives of these two flavonoids were less potent than the original agents in their cytostatic and cytotoxic activities [119]. However, their solubility in water was greater than that of the original agents and higher culture medium concentration of these derivatives was obtained. The results indicated that the ability of flavonoids to act tumoricidally was reciprocally correlated with their lipophilicity.

3.7. Derivatives of FAA (flavone-8-acetic Acid, 171) and Flavopiridol (172)

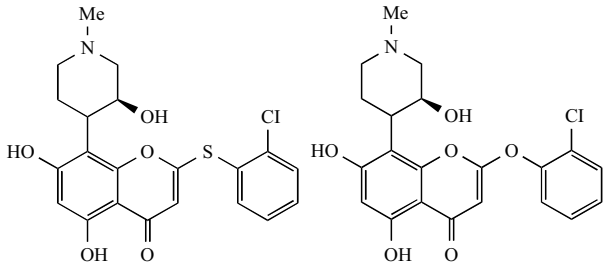
In 1996, Valenti *et al.* synthesized some coumarin-, flavonol- and flavanon-acetic acids and evaluatied their cytotoxicity on a human colon carcinoma cell line (LoVo), some compounds were more active than FAA [120]. From 1996 to 2000, Aitken *et al.* prepared 60 derivatives of FAA with different substituent groups and gave some trials of structure variation [121-124]. In 2003, a series of novel FAA derivatives were evaluated for their biological activity as reversible inhibitors of aminopeptidase N/CD13 [125]. Among them, 2',3-dinitroflavone-8-acetic acid (**173**) proved to be the most efficient and exhibited an IC(50) of 25 microM which was 2.5 times higher than that of bestatin, in contrast to bestatin, compound **173** did not induce any cytotoxicity to cultured human model cells. At the same time, Gobbi *et al.* synthesized new analogues of FAA with an alkoxy group in position 3 and different substituents on the benzene ring in position 2 of the flavone nucleus [126]. The results showed these compounds were able to induce significant indirect toxicity, particularly compounds **174** and **175** (Fig. **5**), bearing electron-withdrawing substituents in the 3'position, which proved to be 7.3- and 3.7-fold more active than DMXAA (5,6-dimethylxanthenone-4-acetic acid) on human monocytes and were selected for further evaluation.



174 R=3'-CF_3
175 R=3'-CI

Fig. (5). FAA derivatives.

In 2000, Murthi *et al.* studied the SAR of flavopiridol analogues [127], the results showed that both the presence and the position of the nitrogen moiety on the D ring were critical requirements for CDK inhibitory activity. In the same year, Kim *et al.* prepared thio- and oxoflavopiridols [128], representative compounds **176** and **177** (Fig. **6**) displayed CDK1 selective inhibitory activity.



(176) **(177)**

Fig. (6). Flavopiridol analogs.

3.8. Complexes of Flavonoids

Zhou *et al.* prepared eight new rare earth metal(III) quercetin complexes **178**-**185** (Fig. **7**), the results showed that the suppression ratio of the complexes against the tested tumour cells were superior to quercetin [129].

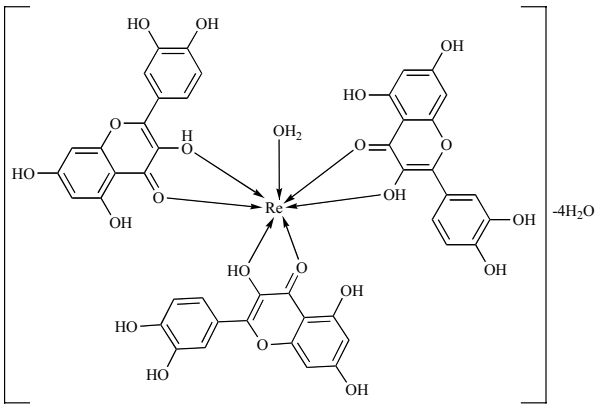


Fig. (7). The structure of complexes tentatively proposed. Re=La(III), Nd(III), Eu(III), Gd(III), Tb(III), Dy(III), Tm(III) and Y(III).

In 2003, Zeng and colleagues synthesized a novel La (III) complex of chrysin (**186**, Fig. **8**), the results indicated that La (III) complex and chrysin bond to DNA both by intercalation modes, but the affinity to DNA of chrysin was lower than that of La (III) complex. The inhibiting effects of La (III) complex and chrysin against two kinds of tumor cells (A-549 and P388) were studied, the results showed that when the concentrations of the two compounds were 10 μM, the La (III) complex had a much higher inhibitory effect than chrysin did [130].

4. ANTICANCER MECHANISMS OF FLAVONOIDS

4.1. Flavonoids as Cancer-Chemopreventive Agents

In 1992, Liu *et al.* found cirsimaritin and chrysoeriol exhibited high inhibition of benzo[a]pyrene metabolism and the activation of benzo[a]pyrene to ultimate carcinogenic DNA-binding metabolites at a concentration of only 10 mg/ml. [27]. In 1996, Calomme M and co-workers investigated the inhibition of bacterial mutagenesis by citrus flavonoids [26]. The experiments showed tangeretin was antimutagenic against all indirectly-acting mutagens tested, nobiletin acted as an antimutagen against benzo[a]pyrene

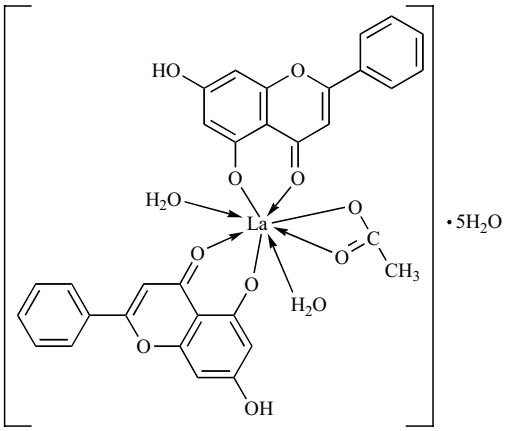


Fig. (8). The structure of $LaL_2 \cdot OAc \cdot 7H_2O$ complex.

and 2-aminofluorene. Because of the antimutagenic properties, the citrus flavonoids tested, especially tangeretin and nobiletin, might play a role in the chemoprevention of cancer. In 1999, Song *et al.* conducted a full-term cancer chemoprevention study with DMBA-treated female Sprague Dawley rats [131]. They found that 4'-bromoflavone(4'BF (**187**), a potent inducer of phase II detoxification enzymes, could be viewed as a highly effective cancer chemopreventive agent. In 2000, Chang *et al.* isolated three novel flavonoids, (+)-tephrorins A (**188**) and B (**189**) and (+)-tephro-sone (**190**) from *Tephrosia purpurea* [132]. Compounds were evaluated for their potential cancer chemopreventive properties using a cell-based quinone reductase induction assay. The results showed these compounds significantly induced QR activity, with the observed CD（concentration to double enzyme induction）values being 4.0, 5.9, and 3.1 μM, respectively. In 2001, Kawabata *et al.* showed that morin exhibited chemopreventive effect on chemically induced rat tongue carcinogenesis through modification of detoxifying enzyme activities and/or cell proliferation activities [39]. In the same year, Miyashita *et al.* investigated the potential of purple corn color (PCC), a natural anthocyanin, to modify colorectal carcinogenesis in male F344/ DuCrj rats [92], in the study, PCC exerted protection against PhIP promotion of colon tumor development, without any evidence of adverse effects at 5.0% in the diet. In 2003, Yamagishi *et al.* investigated the effects of cacao liquor proanthocyanidins (CLPr) on tumorigenesis in a male rat multi-organ carcinogenesis model [93]. The results showed feeding male rats a diet containing CLPr was associated with a significant inhibition of lung carcinogenesis and a tendency toward inhibition in thyroid carcinogenesis, it suggested that CLPr had potential as a chemopreventive agent.

In addition, compounds **34**, **35**, **40**, **57**,**60**, **85-89** exhibited inhibitory effects on the EBV-EA activation induced by TPA and had antitumor-promoting activity in mouse skin carcinogenesis [34, 36, 37, 55, 57, 78, 79].

4.2. Flavonoids Inhibiting Tumor Cells Growth or Proliferation

Lee *et al.* examined cytotoxic effects of six isoflavonoids. Among them, tectorigenin and genistein exhibited cytotoxicity against various human cancer cells and caused apoptotic changes of DNA in the cells, as did genistein [54]. It also inhibited autophosphorylation of epidermal growth factor (EGF) receptor by EGF and decreased the expression of Bcl-2 protein, with less activity than genistein.The results suggested tectorigenin might be a possible therapeutic agent for leukemia. In 1991, Kandaswami *et al.* examined the effects of four plant flavonoids on the *in vitro* growth of a human squamous cell carcinoma cell line (HTB43). The results showed polymethoxylated flavonoids, nobiletin and tangeretin markedly inhibited cell growth at all concentrations tested on days 5 and 7. While quercetin and taxifolin exhibited no significant inhibition at any of the concentrations tested. This difference in activity may be due to the relatively greater membrane uptake of the polymethoxylated flavonoids since methoxylation of the phenolic groups decreases hydrophilicity of the flavonoid [23]. In 1992, Kandaswami again investigated the above flavonoids against three cell lines in tissue culture：tangeretin and nobiletin markedly inhibited the proliferation of a squamous cell carcinoma (HTB 43) and a gliosarcoma (9L) cell line at 2-8 mg/ml concentrations [24]. In 1995, Hirano *et al.* showed that tangeretin inhibited growth of HL-60 cells *in vitro*, partially through induction of apoptosis, without causing serious side-effects on immune cells [25]. In 1998, Guthrie N and Carroll KK investigated the inhibition of mammary cancer by citrus flavonoids [133]. The results demonstrated that citrus flavonoids were effective inhibitors of both estrogen receptor-negative MDA-MB-435 and estrogen receptor-positive MCF-7 human breast cancer cell *in vitro*. Furthermore, 1:1 combinations of flavonoids with tocotrienols and/or tamoxifen inhibited proliferation of the cells more effectively than the individual compounds. In 2002, Manthey and Guthyie, again studied activities of citrus flavonoids against six human cancer cell lines [134]. They found the synthetic compounds exhibited strong antiproliferative acti-vities, similar to the naturally occurring compounds, In many cases the IC50 values occurred below 10 microm. Other hydroxylated flavone and flavanone aglycons also exhibited antiproliferative activities against the cancer cell lines, with the flavones showing greater activities than the flavanones. Glycosylation of these compounds removed their activity. In 2005, Kanno *et al.* investigated the effects of naringenin on tumor growth in various human cancer cell lines and sarcoma S-180-implanted mice. The results show naringenin induced cytotoxicity was low in Caco-2 and high in leukemia cells compared to other cell lines, it inhibited tumor growth in sarcoma S-180-implanted mice and also inhibited tumor growth by peroral injection [47] In 2000, Dimas *et al.* got two myricetin derivatives (3,7,4',5'-tetramethyl ether of myricetin and 3',5-diacetyl of myricetin [135]. compound **90** exhibited higher cytostatic and cytotoxic effects than myricetin, the resuits verified their conclusion that acetylation improves the activity of the flavonoids of the kaempferol series. In 2003, Pettit *et al.* isolated one flavonolignan (palstatin), which proved to be a new cancer cell growth inhibitor [96]. In the same year, Seo *et al.* isolated compounds 5,6-dihydroxy-7,3',4'-trimethoxyflavone (**29**) and 5, 6,4'-trihydroxy-7,3'-dimethoxyflavone (**30**), compound **29** and **30** inhibited growth of a colon tumor (SW620) by 44.6 % and 14.6 %, respectively [28]. At the same time, Lawrence NJ

and co-workers isolated the naturally occurring aurone **191** (Fig. **9**) from Uvaria hamiltonii [136]. The resemblance of aurone **192** to the tumour vascular targeting agent combretastatin A-4 made it an appealing target for total synthesis, accordingly, they developed an efficient synthesis of the natural aurone from the key benzofuranone and prepared a series of aurones analogs. Among these compounds, aurone **192** was the most active (IC(50) K562 50 nM) and caused significant G2/M cell-cycle arrest.

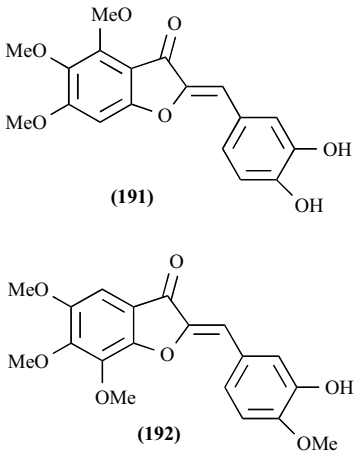


Fig. (9). The struture of compds. **191, 192**.

In the same year, Kozikowski *et al.* developed an improved synthesis of trimeric, tetrameric, pentameric, and higher oligomeric epicatechin-derived procyanidins having ll-4beta,8-interflavan connectivity. They also investigated anticancer activity of procyanidins. The results confirmed both the synthetic and natural pentamer (**193**) inhibited the growth of several breast cancer cell lines. Using the MDA MB 231 line, it was established that this outcome was based on the induction of cell cycle arrest in the G0/G1 phase [137]. In 2004, Fu *et al.* showed licochalcone-A (LA), a novel flavonoid isolated from licorice root (Glycyrrhiza glabra), causes G2 and late-G1 arrests in androgen-indepen dent PC-3 prostate cancer cells [81]. Kobayawa *et al.* found casticin (**43**) inhibited the growth of KB cells markedly (IC50, 0.23 mM), their study suggested that G2-M arrest by casticin might be relevant to its antimitotic activity [40]. later, Chen YC and co-workers verified that flavone induced apoptosis in colorectal carcinoma cells *in vitro* and *in vivo* with activation of caspase 3, ROS production and increasing p21 protein [138]. In the same year, Tokalov *et al.* prepared the estrogenic flavanone rac-8-prenylnaringenin (8-PN, **194**) and 3 derivatives: rac-7-(O-prenyl)naringenin-4'-acetate (7-O-PN, **195**), rac-5-(O-prenyl)naringenin-4',7-diace-tate (5-O-, **196**), and rac-6-(1,1-dimethylallyl) naringenin (6-DMAN, **197**), they foud that all flavonoids affected cell proliferation [139]. In 2005, Davis-Searles PR and coworkers isolated seven distinct flavonolignan compounds from commercial silymarin extracts [140]. Among these compounds, two pairs of diastereomers, silybin A (**198**) and silybin B (**199**) and isosilybin A (**200**) and isosilybin B (**201**) were notable. In contrast, silibinin was composed only of a 1:1 mixture of silybin A and silybin B. Each pure compound was assessed for antiproliferative activities against LNCaP, DU145, and PC3 human prostate carcinoma cell lines. Isosilybin B was the most consistently potent suppressor of cell growth. Isosilybin A and isosilybin B were also the most effective suppressors of prostate-specific antigen secretion by androgen-dependent LNCaP cells. In the same year, noticing the fact that consumption of the traditional kava preparation correlated with low and uncustomary gender ratios (more cancer in women than men) of cancer incidences in three kava-drinking countries, Zi X and Simoneau AR showed that flavokawain A (**92**, a novel chalcone from kava extract) induced apoptosis in bladder cancer cells by involvement of Bax protein-dependent and mitochondria-dependent apoptotic pathway and suppressed tumor growth in mice (57% of inhibition) [83]. At the same time, Zheng and colleagues reported for the first time that apigenin induced apoptosis through p53-dependent pathway in human cervical carcinoma cells [33]. At the same time, Zhang *et al.* made the first report of tumor cell proliferation inhibitory activity by anthocyanidins [94]. In their study, Five anthocyanidins (componds **108-112**) and four anthocyanins were tested for cell proliferation inhibitory activity against human cancer cell lines, the anthocyanins assayed did not inhibit cell proliferation of cell lines tested at 200 mg/mL. However, anthocyanidins showed cell proliferation inhibitory and suppressed the growth of breast cancer cells.

4.3. Flavonoids as Tubulin Polymerization Inhibitors

In 1995, Shi Q found that 5,3'-dihydroxy-3,6,7,8,4'-pentamethoxyflavone (**41**) appeared to be the first example of a flavonol to exhibit potent inhibition of tubulin polymerization [38]. In 2002, Gupta K and Panda D found that quercetin inhibited polymerization of microtubules and depolymerized microtubules made from purified tubulin *in vitro* [43].

4.4. Enzyme-Targetting Anticancer Flavonoids (Table 13)

Table 13. Enzyme-Targetting Anticancer Flavonoids

Enzyme	Compd.	Ref.
topoisomerase	**8, 44, 75, 76, 98, 115-120**	[88, 66,97]
telomerase	**123-128**	[99]
aromatase	**140-146**	[103]
aminopeptidase	**173**	[125]
CDK	**172, 176, 177**	[128]

4.5. Flavonids as Anti-Invasive, Anti-Adhesion or Antiangiogenesis Agents

In 2001, Shen RC and Lin M fund two natural Diels-Alder type adducts, cathayanon A (**51**) and cathayanon B (**52**) inhibited the adhesion of HL-60 to BAEC (Bovine Arterial Endothalium cells) with inhibitory rate of 44.72 and 39.02% respectively [50]. In the same year, Rooprai *et al.* investigated the effects of four anti-invasive agents including tangeretin and nobiletin on various parameters of brain tumour invasion, nobiletin was most efficient at inhibiting invasion, migration and adhesion in four representative cell lines (an ependymoma, a grade II oligoastrocytoma, an anaplastic astrocytoma and a glioblastoma multiforme) [141].

In 2002, Iwasaki *et al.* found that Ipriflavone (7-isopro-poxy-isoflavone, **202**) not only directly inhibited the growth of cancer cells but also reduced osteoclasts to prevent the soft tissue tumor burden and osteolytic bone metastases. [142]. In 2003, Tan WF showed that quercetin had antiangiogenic potential and this effect might be related to an influence on the expression and activity of matrix metalloproteinase-2 [44], later, Ma found that tamoxifen inhibited CWR22 prostate tumor by modulating the angiogenesis and its antineoplastic effects could be potentiated by combined use with quercetin [45]. In the same year, Babu BH and colleagues showed that gossypin (3,5,8,3',4'-pentahydroxy-7-O glucosyl flavone) reduced the tumor burden in solid tumor harboring animals ($p < 0.001$) and effectively inhibited the formation of new blood vessels on tumor mass. [89]. In 2004, Shim *et al.* found homoisoflavanone (compd. **113**) was a potent inhibitor of angiogenesis [95]. It inhibited basic fibroblast growth factor (bFGF)-induced *in vitro* angiogenesis and *in vivo* angiogenesis of the chorioallantoic membrane (CAM) of chick embryo without showing any toxicity.

4.6. Flavonoid Derivatives for Reversing Doxorubicin-Resistant

In 2000, van Acker *et al.* investigated a dosing sche-dule of one administration of monoHER (**203**) (7-Mono-hydroxyethylrutoside) just before doxorubicin [143]. The results showed that 500 mg/kg monoHER administered only 1 h before doxorubicin provided complete protection against the cardiotoxicity. In 2001, they succeeded in designing a better cardioprotector than monoHER: frederine (**204**), which merited further investigation as a possible protector against doxorubicin-induced cardiotoxicity in cancer patients [144]. In the same year, van Acker *et al.* again studied a series of 3,7-disubstituted-2(3',4'-dihydroxyphenyl) flavones as potential cardioprotective agents in doxorubicin antitumor therapy [145]. They selected compounds 3',4'-dihydroxy-3-glucosylflavone (**205**) and N-(3-(7,3',4'-trihydroxyflavon-3-yl)oxypropyl)-N,N,N-trimethylammonium chloride (**206**) as most promising for further investigation. In 2002, Ikegawa *et al.* investigated the inhibition of P-glycoprotein by flavonoid derivatives in doxorubicin-resistant human myelogenous leukemia (K562/ADM) cells, they found that pentamethylquercetin (**207**), pentaallylquercetin (**208**) and pentaethylmorin (**209**) remarkably increased the uptake of [3H]vincristine by K562/ADM cells by 10.6, 10.8 and 14.4-fold, respectively [146]. These inhibitory potencies for P-gp were more potent than typical P-gp inhibitors, cyclosporine A and verapamil. In 2005, Zhang XY and co-workers observed that proanthocyanidin from grape seeds enhanced doxorubicin-induced antitumor effect and reversed drug resistance in doxorubicin-resistant K562/DOX cells [147].

5. SAR OF FLAVONOIDS AS ANTICANCER AGENTS

Although a lot of studies have been done to explore SAR, there is little understanding about it due to scattered information, López-Lázaro compiled and revised the literature studying SAR to show structural requirements involved in the anticancer activity of flavonoids, obtaining some conclusions with rational explanation of the multiple controversial results [148]. In this review, we also verified concering conclusions with some supplements: first, some less common substitutions such as prenyl, isoprenyl and lavanduly could increase activity significantly; second, some amino-substi-tuted flavonoids exhibited superior activity and amino was necessary in some cases; third, some complexes of flavonoids showed higher activity than their ligands-flavonoids.

6. SOME FLAVONOIDS IN CLINICAL TRIAL

6.1. Flavopiridol

Flavopiridol is a novel semisynthetic flavone analogue of rohitukine, a leading anticancer compound from an Indian tree. Flavopiridol inhibits most cyclin-dependent kinases and displays unique anticancer properties. It is the first cyclin-dependent kinase inhibitor to be tested in Phase II clinical trials [149]. In 2004, Sato *et al.* found that administration of a low dose of flavopiridol could be a potent new therapeutic approach for improving the efficacy of radiotherapy against esophageal cancer [150]. Kim JC and co-workers showed that radiation effects could be enhanced by combined docetaxel and flavopiridol treatment in lung cancer cells [151]. At the same time, Mason *et al.* found that favopi-ridol increased therapeutic ratio of radiotherapy by preferentially enhancing tumor radioresponse [152]. In 2005, Zhang *et al.* demonstrated that the therapeutic efficacy by combining flavopiridol with HAT (anti-Tac antibody) could be significantly improved, thus, it provided support for a clinical trial in the treatment of ATL (Adult T-cell leukemia) [153].

6.2. DMXAA (210)

The novel vascular targeting agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA) has completed phase 1 clinical trial and has shown tumor antivascular activity in both mice and humans. In 2005, Zhao studied mechanisms of tumor vascular shutdown induced by it, the results supported the hypothesis that DMXAA increased tumor vascular permeability both directly and through the induction of other vasoactive mediators, thus, it might be useful clinically to potentiate the vascular permeability of other anticancer modalities such as cytotoxic drugs, antibodies, drug conjugates and gene therapy [154].

6.3. Aminoflavone (211)

Aminoflavone (5-amino-2-(4-amino-3-fluorophenyl)-6,8-difluoro-7-methyl-4H-1-benzopyran-4-one AF; NSC 686288) is a candidate for possible advancement to phase I clinical trial. In 2002, Kuffel *et al.* observed that AF was uniquely able to induce its own metabolic activation *via* CYP1A1/1A2 in duction to cytotoxic DNA-damaging species directly in tumor cells [155]. In 2005, Meng *et al.* found that aminoflavone produced replication-dependent DNA lesions and S-phase checkpoint activation following DPC(DNA-protein cross-links) formation [156].

6.4. Phenoxodiol (212)

Phenoxodiol (2H-1-benzopyran-7-O1,3-(4-hydroxyphenyl)) is a synthetic derivative of the plant isoflavone daidzein and is currently undergoing clinical testing as a cancer therapeutic drug. In 2002, Constantinou AI and Husband A evaluated it as a potential inhibitor of topoisomerases, the results showed phenoxodiol inhibited the catalytic activity of topo II in a dose-dependent manner and it stabilized the topo II-mediated cleavable complex, demonstrating that phenoxo-

diol was a topo II-specific poison [157]. In 2003, Constantinou AI and co-wrkers evaluated the potential cancer chemopreventive effects of phenoxodiol in female Sprague-Dawley rats [158]. The data suggested that phenoxodiol was an effective chemopreventive agent against DMBA (dimethylbenz[a]anthracene) -induced mammary carcinogenesis.

6.5. Silybin (213)

In 1996, Scambia *et al.* tested the antiproliferative effect of silybin on gynaecological malignancies, they found that silybin exerted synergism with cisplatin and doxorubicin [159]. In 2005, a group led by Gallo D assessd the antitumor activity of the silybin-phosphatidylcholine complex (IdB 1016, **214)** against human ovarian cancer. the findings suggested IdB 1016 was a good candidate, with a relevant clinical potential, for use in the management of recurrent ovarian cancer, a phase II, non-randomised clinical study was ongoing in their institute aimed at evaluating the efficacy of daily administrations of IdB 1016 in the serological recurrence of ovarian cancer [160].

DISCUSSION

In conclusion, since the important role of dietary flavonoids in cancer prevention was realized, much research has been conducted and great developments have been achieved in recent years: first, isolation of natural antitumor flavonoids has provided us with such feasibilities as follow: (a) some lead compounds will derive from natural antitumor flavonoids for their structure diversity and significant activities; (b) herbs containing antitumor flavonoids will also be used to fight with tumor. (c) consumption of dietary antitumor flavonoids (take citrus flavonoids including nobiletin and tangeretin as an example) will contribute to the prevention of tumor. Next, synthesis of potent antitumor flavonoids will pave the way for later work (QSAR, activity screen, exploration of mechanisms and so on); in addition, some compounds (DMXAA, flavopiridol and so on) have entered into clinical trial; Finally, identificatin of antitumor mechanisms of flavonoids will serve for drug design and antitumor targets discoveries.

Taken together, with a greater understanding of their anticancer properties and further studies of SAR, flavonoids will be exploited well as promising anticancer agents.

ABBREVIATIONS

TPA = 12-*O*-tetradecanoylphorbol-13-acetate

DMBA = Dimethylbenz[a]anthracene

EBV-EA = Epstein-Barr virus early antigen

PhIP = 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine

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