文章编号:1001-6880(2016)10-1676-10

胡椒属植物抗血小板和抗血栓活性研究进展

夏梦媛[1,2],王　俐[1*],王跃虎[2*]

[1]云南农业大学;[2]中国科学院昆明植物研究所,昆明 650201

摘　要:在我国,药用的胡椒属植物中,约1/3具有活血功能。研究发现,二十种胡椒属植物的提取物显示出抗血小板聚集活性。目前,从11种胡椒属植物中发现了抗血小板活性化合物51个,主要包括生物碱(占47%)、木脂素(占24%)、苯丙素(占22%)等。其中,海风藤酮、丁香酚、羟基胡椒酚乙酸酯等的抗血小板活性较为显著,pellitorine、荜茇酰胺、荜茇宁和丁香酚等表现出了体内抗凝及抗血栓活性。有必要在胡椒属化学成分抗血栓作用机制及抗血栓新靶点的活性筛选上,进行更深入的研究。

关键词:胡椒属;抗血栓;抗血小板;抗凝血

中图分类号:R284.2;Q946.91　　**文献标识码**:A　　DOI:10.16333/j.1001-6880.2016.10.032

Antiplatelet and Antithrombotic Activities of *Piper* Plants

XIA Meng-yuan[1,2],WANG Li[1*],WANG Yue-hu[2*]

[1]*Yunnan Agricultural University*;[2]*Kunming Institute of Botany*,*Chinese Academy of Sciences*,*Kunming 650201*,*China*

Abstract:Among medicinal *Piper* plants used as traditional Chinese medicines,there are about 1/3 species with the function of promoting blood circulation (Huoxue in Chinese). Crude extracts from 20 *Piper* plants are active against platelet aggregation. Fifty-one antiplatelet compounds,including alkaloids (47%),lignans (24%),phenylpropanoids (22%),*etc*,have been isolated from the genus. Kadsurenone,eugenol and hydroxychavicol acetate showed significantly antiplatelet activity *in vitro*. Moreover,pellitorine,piperlongumine,piperlonguminine and eugenol possessed anticoagulant and antithrombotic effects *in vivo*. Further study on antithrombotic mechanisms and activity screening in new antithrombotic targets of *Piper* constituents is warranted.

Key words:*Piper*;antithrombotic;antiplatelet;anticoagulation

血栓性疾病,包括脑卒中、心肌梗死、动脉粥样硬化、外周血管疾病或血管堵塞基础上发生的心肌缺血、心绞痛等,严重地危害着人类的健康。在我国,仅脑卒中患者就多达600~700万,每年新增病例约200万,每年死于脑卒中的病人达150万[1]。抗血栓药物主要分为抗凝血药物(anticoagulants)、抗血小板聚集类药物(antiplatelet drugs)和溶血栓药(thrombolytics)三大类[2]。中药在血栓性疾病的治疗中有独到之处,特别是具有活血、化瘀功能的中药,如丹参 *Salvia miltiorrhiza* Bunge[3,4]、三七 *Panax pseudoginseng* Wall. var. *notoginseng* (Burkill) Hoo et Tseng[5-8]、剑叶龙血树 *Dracaena cochinchinensis* (Lour.) S. C. Chen 等[9,10]。

胡椒属(*Piper*)是胡椒科(Piperaceae)最大的一个属,大约将近2000个种,主要分布在热带地区,在中国境内大概有60个种[11],其中约30个种药用[12],具有活血功能就11个,约占药用的1/3,包括蒌叶 *P. betle* L.,苎叶蒟 *P. boehmeriifolium* (Miq.) Wall. ex C. DC.,毛蒟 *P. hongkongense* C. DC.,风藤(海风藤,小叶爬岩香)*P. kadsura* (Choisy) Ohwi (*P. arboricola* C. DC.),大叶蒟 *P. laetispicum* C. DC.,粗梗胡椒(思茅胡椒)*P. macropodum* C. DC. (*P. szemaoense* C. DC.),变叶胡椒 *P. mutabile* C. DC.,毛叶胡椒 *P. puberulilimbum* C. DC,假蒟 *P. sarmentosum* Roxb.,石南藤 *P. wallichii* (Miq.) Hand.-Mazz. 以及蒟子 *P. yunnanense* Tseng[13,14]。

本文就胡椒属植物及其化学成分的抗血小板、抗凝血及抗血栓活性进行综述,检索的数据库包括Web of Science、Google Scholar、SciFinder 以及中国知网(CNKI),时间从1980年至2016年,检索关键词包括胡椒属(*Piper*)、抗血栓(antithrombotic)和抗血小板(antiplatelet)和抗凝血(anticoagulation)等。

收稿日期:2016-04-13　　接受日期:2016-05-31

基金项目:科技部国家科技基础性工作专项(2012FY110300)

*通讯作者　Tel:86-871-65223318;E-mail:2758502919@qq.com;wangyuehu@mail.kib.ac.cn

1 胡椒属植物粗提物抗血小板聚集活性

早在二十世纪八十年代,李长龄、韩桂秋等开展了百余种中草药的抗血小板活化因子(platelet-activating factor,PAF)诱导的血小板聚集活性筛选,发现胡椒属药用植物活性最强[15-17]。根据文献统计,有 20 种胡椒属植物对血小板活化因子、花生四烯酸(arachidonic acid, AA)、二磷酸腺苷(adenosine diphosphate,ADP)、胶原(collagen)或 U46619(一种血栓素 A_2 受体激动剂)诱导的血小板聚集有抑制活性(表 1)。活性最强的是假蒟、山蒟、石南藤和风藤,其二氯甲烷提取物在 10 μg/mL 浓度时,对 PAF 诱导的兔血小板聚集抑制率超过 70%,优于醇提取物[15-17];台湾荖藤 *P. taiwanense* Lin & Lu 甲醇提取物对胶原诱导的人血小板聚集也有显著的抑制活性,半数抑制浓度(IC_{50})值达到 3.6 μg/mL[18]。胡椒属植物精油也有抗血小板聚集活性,但活性较弱[19]。

2 胡椒属中具有抗血小板聚集活性的化合物

胡椒属植物主要含有生物碱、苯丙素、木脂素(包括新木脂素)、萜类、甾体、卡瓦吡喃酮(kawapyrones)、胡椒内酯(piperolides)、黄酮、链烯基苯酚(alkenylphenols)等[12]。目前从胡椒属植物中发现抗血小板聚集活性的成分主要有生物碱(**1**~**24**,表 2,图 1)、木脂素(**25**~**36**,表 3,图 2)、苯丙素(**37**~**47**,表 4,图 3)、黄酮(**48** 和 **49**,表 4,图 3)、三萜(**50**,表 4,图 3)和卡瓦吡喃酮(**51**,表 4,图 3)等 51 个化合物。生物碱占的比例最高(47%),其次是木脂素(24%)和苯丙素(22%)。

表 1 胡椒属植物粗提物的抗血小板活性

Table 1 Antiplatelet activity of crude extracts from *Piper* plants

中文名 Chinese name	拉丁名 Latin name	部位 Part	溶剂(提取物) Solvent (extracts)	血小板 Platelet	诱导剂(浓度) Inducer (concentration)	IC_{50}或抑制率(样品浓度) IC_{50} or Inhibition rate (sample concentration)	文献 Ref.
树胡椒	*P. aduncum* L.	地上部分	水(精油)	豚鼠	AA (50 μM)	149 μg/mL	[19]
		地上部分	水(精油)	豚鼠	ADP (3 μM)	196 μg/mL	[19]
		地上部分	水(精油)	豚鼠	U46619 (1 μM)	168 μg/mL	[19]
苎叶蒟	*P. boehmeriifolium* (Miq.) Wall. ex C. DC.	未知	乙醇	兔	PAF (7.2 nM)	35.21 μg/mL	[20]
	未知	乙醇	兔	AA (350 μM)	98.4 μg/mL	[21]	
	未知	乙醇	兔	ADP (3 μM)	85.7 μg/mL	[21]	
蒌叶	*P. betle* L.	花序	甲醇	兔	AA (100 μM)	207 μg/mL	[22]
		花序	甲醇	兔	胶原 (10 μg/mL)	335 μg/mL	[22]
黄花胡椒	*P. flaviflorum* C. DC.	未知	乙醇	兔	PAF (7.2 nM)	40.74 μg/mL	[20]
	未知	乙醇	兔	ADP (3 μM)	201.7 μg/mL	[21]	
山蒟	*P. hancei* Maxim.	未知	CH_2Cl_2	兔	PAF [a]	>70% (10 μg/mL)	[16]
		未知	醇	兔	PAF [a]	81% (10 μg/mL)	[17]
		未知	醇	兔	PAF (0.13-1.3 μM)	40.34 μg/mL	[23]
		未知	醇	兔	AA (66.7-93.3 μg/mL)	345.46 μg/mL	[23]
风藤	*P. kadsura* (Choisy) Ohwi	未知	CH_2Cl_2	兔	PAF [a]	>70% (10 μg/mL)	[16]
	未知	乙醇	兔	PAF (7.2 nM)	31.6 μg/mL	[21]	
荜拔(荜茇)	*P. longum* L.	未知	乙醇	兔	PAF (7.2 nM)	60.26 μg/mL	[20]
	未知	乙醇	兔	ADP (3 μM)	194.5 μg/mL	[21]	
短蒟	*P. mullesua* Buch.-Ham. ex D. Don	未知	乙醇	兔	PAF (7.2 nM)	64.43 μg/mL	[20]
	未知	乙醇	兔	AA (350 μM)	28.7 μg/mL	[21]	
	未知	乙醇	兔	ADP (3 μM)	114.5 μg/mL	[21]	

中文名 Chinese name	拉丁名 Latin name	部位 Part	溶剂(提取物) Solvent (extracts)	血小板 Platelet	诱导剂(浓度) Inducer (concentration)	IC_{50}或抑制率(样品浓度) IC_{50} or Inhibition rate (sample concentration)	文献 Ref.
无中文名	*P. obliquum* Ruiz & Pav.	地上部分	水(精油)	豚鼠	AA (50 μM)	164 μg/mL	[19]
	地上部分	水(精油)	豚鼠	ADP (3 μM)	106 μg/mL	[19]	
	地上部分	水(精油)	豚鼠	U46619 (1 μM)	188 μg/mL	[19]	
角果胡椒	*P. pedicellatum* C. DC.	未知	乙醇	兔	PAF (7.2 nM)	153.35 μg/mL	[20]
樟叶胡椒	*P. polysyphonum* C. DC.	未知	乙醇	兔	PAF (7.2 nM)	30.45 μg/mL	[20]
假蒟	*P. sarmentosum* Roxb.	未知	CH_2Cl_2	兔	PAF [a]	>70% (10 μg/mL)	[16]
缘毛胡椒	*P. semiimmersum* C. DC.	未知	乙醇	兔	PAF (7.2 nM)	60.57 μg/mL	[20]
野芦子藤	*Piper* sp.	未知	乙醇	兔	PAF (7.2 nM)	32.59 μg/mL	[20]
		未知	乙醇	兔	AA (350 μM)	70.1 μg/mL	[21]
芦子藤	*Piper* sp.	未知	乙醇	兔	PAF (7.2 nM)	42.74 μg/mL	[20]
细芦子藤	*Piper* sp.	未知	乙醇	兔	PAF (7.2 nM)	43.05 μg/mL	[20]
		未知	乙醇	兔	ADP (3 μM)	87.4 μg/mL	[21]
大钻骨风	*Piper* sp.	未知	乙醇	兔	PAF (7.2 nM)	103.68 μg/mL	[20]
台湾荖藤	*P. taiwanense* Lin & Lu	根	甲醇	人	胶原 (10 μg/mL)	3.6 μg/mL	[18]
球穗胡椒(腺脉蒟)	*P. thomsonii* (C. DC.) Hook. f.	未知	乙醇	兔	PAF (7.2 nM)	108.69 μg/mL	[20]
		未知	乙醇	兔	ADP (3 μM)	91.3 μg/mL	[21]
石南藤	*P. wallichii* (Miq.) Hand. -Mazz.	未知	CH_2Cl_2	兔	PAF[a]	70% (10 μg/m)	[16]
阿司匹林 [b]				人	胶原(10μg/mL)	88.8 μM	[18]

注:[a]文献[16,17]中没有给出诱导剂浓度;[b]阳性对照。
Note: [a]The concentration of the inducer was not presented in the references[16,17]; [b]positive control.

尽管生物碱占活性化合物的比例最大,但活性强度低于木脂素和苯丙素,活性最好的是 taiwannamide C(3),其抑制胶原诱导兔血小板聚集的 IC_{50} 值为 8.9 μM[24]。木脂素中活性最好的是来自风藤中的海风藤酮(kadsurenone,**25**),其抑制 PAF 诱导兔血小板聚集的 IC_{50} 值达 2.6 μM[25]。苯丙素类化合物抗血小板聚集的活性最为突出,如丁香酚(eugenol,**39**)对 AA 诱导的人血小板聚集有显著抑制作用,IC_{50} 值达到 0.5 μM[26];羟基胡椒酚(hydroxychavicol,4-allylcatechol,**37**)和羟基胡椒酚乙酸酯(hydroxychavicol acetate,**38**)对胶原诱导的人血小板聚集有较强抑制作用,IC_{50} 值分别为 5.3 μM 和 2.1 μM[18]。Tognolini 等研究表明,植物精油中苯丙素的含量跟精油抗血小板聚集活性成正相关,从而认为,在抗血小板活性筛选中,苯丙素类化合物是非常值得关注的一类天然产物[27]。

在胡椒属化学成分抗凝血酶诱导的血小板聚集方面,报道较少。研究显示,荜茇宁(piperlonguminine,**17**)对凝血酶诱导的小鼠血小板聚集和胡椒内酰胺 B(piperolactam B,**21**)对凝血酶诱导的兔血小板聚集有一定的抑制活性[28,29]。

表 2 胡椒属植物中具有抗血小板活性的生物碱(1~24)

Table 2 Antiplatelet alkaloids (**1-24**) from *Piper* plants

化合物名称 Compound name	来源 Source	血小板 Platelet	诱导剂(浓度) Inducer (concentration)	IC_{50}或抑制率(样品浓度) IC_{50} or Inhibition rate (sample concentration)	文献 Ref.
taiwannamide A (1)	*P. taiwanense* Lin & Lu	兔	胶原 (10 μg/mL)	33.6 μM	[24]
taiwannamide B (2)	*P. taiwanense* Lin & Lu	兔	胶原 (10 μg/mL)	17.3 μM	[24]
		兔	AA (50 μM)	30.9 μM	[24]

化合物名称 Compound name	来源 Source	血小板 Platelet	诱导剂(浓度) Inducer (concentration)	IC_{50}或抑制率(样品浓度) IC_{50} or Inhibition rate (sample concentration)	文献 Ref.
		兔	PAF (2 ng/mL)	64.5 μM	[24]
taiwannamide C (3)	*P. taiwanense* Lin & Lu	兔	胶原 (10 μg/mL)	8.9 μM	[24]
		兔	PAF (2 ng/mL)	53.5 μM	[24]
1-cinnamoylpyrrolidine (4)	*P. taiwanense* Lin & Lu	兔	AA (50 μM)	30.5 μM	[24]
1-(*m*-methoxycinnamoyl) pyrrolidine (5)	*P. sarmentosum* Roxb. (*Piper lolot* C. DC.)	兔	AA (100 μM)	7.3 μg/mL	[30]
	P. taiwanense Lin & Lu	兔	胶原 (10 μg/mL)	17.4 μM	[24]
		人	胶原 (10 μg/mL)	17.4 μM	[18]
piperlotine A (6)	*P. sarmentosum* Roxb. (*Piper lolot* C. DC.)	兔	AA (100 μM)	15.2 μg/mL	[30]
piperlotine C (7)	*P. sarmentosum* Roxb. (*Piper lolot* C. DC.)	兔	AA (100 μM)	26.6 μg/mL	[30]
piperlotine D (8)	*P. sarmentosum* Roxb. (*P. lolot* C. DC.)	兔	AA (100 μM)	43.4 μg/mL	[30]
piperlotine E (9)	*P. sarmentosum* Roxb. (*Piper lolot* C. DC.)	兔	AA (100 μM)	11.5 μg/mL	[30]
		兔	PAF (5 nM)	58.6 μg/mL	[30]
假蒟亭碱 (sarmentine,10)	*P. sarmentosum* Roxb. (*P. lolot* C. DC.)	兔	AA (100 μM)	49.4 μg/mL	[30]
	P. sarmentosum Roxb. (*P. lolot* C. DC.)	兔	PAF (5 nM)	52.6 μg/mL	[30]
pellitorine (11)	*P. sarmentosum* Roxb. (*P. lolot* C. DC.)	兔	AA (100 μM)	53.0 μg/mL	[30]
futoamide (12)	*P. taiwanense* Lin & Lu	人	胶原 (10 μg/mL)	48.3 μM	[18]
philippinamide (13)	*P. philippinum* Miq.	兔	胶原 (10 μg/mL)	60% (100 μM)	[31]
N-trans-feruloy-3-*O*-methyldopamine (14)	*P. philippinum* Miq.	兔	胶原 (10 μg/mL)	84% (100 μM)	[31]
荜茇酰胺 (piperlongumine, 15)	*P. longum* L.	兔	AA (100 μM)	76% (150 μM)	[32]
		兔	胶原 (2 μg/mL)	50% (30 μM)	[32]
		兔	PAF (10 nM)	100% (150 μM)	[32]
	P. tuberculatum Jacq.	人	AA (20 μM)	100% (200 μM)	[33]
		人	ADP (4 μM)	52% (200 μM)	[33]
		人	胶原 (2 μg/mL)	59% (200 μM)	[33]
	P. arborescens Roxb.	兔	AA (100 μM)	53.7 μM	[29]
		兔	胶原 (10 μg/mL)	21.5 μM	[29]
胡椒碱 (piperine,16)	*P. longum* L.	兔	AA (100 μM)	54% (150 μM)	[32]
		兔	AA (100 μM)	134.2 μM	[34]
		兔	PAF (10 nM)	76% (150 μM)	[32]
		兔	胶原 (1 μg/mL)	158.0 μM	[34]
荜茇宁(piperlonguminine,17)	*P. longum* L.	小鼠	凝血酶 (3 U/mL)	>50% (30 μM)	[28]
pipernonaline (18)	*P. longum* L.	兔	胶原 (2 μg/mL)	82% (150 μM)	[32]
		兔	PAF (10 nM)	56% (150 μM)	[32]
1, 2, 3-trimethoxy-4, 5-dioxo-6a,7-dehydroaporphine (19)	*P. arborescens* Roxb.	兔	胶原 (10 μg/mL)	61.0 μM	[29]
2-hydroxy-1-methoxy-4*H*-dibenzo[*de*, *g*] quinoline-4, 5-(6*H*)-dione (20)	*P. taiwanense* Lin & Lu	兔	AA (100 μM)	100% (20 μg/mL)	[35]
		兔	胶原 (10 μg/mL)	66% (20 μg/mL)	[35]
胡椒内酰胺 B (piperolactam B,21)	*P. taiwanense* Lin & Lu	人	胶原 (10 μg/mL)	90.8 μM	[18]

化合物名称 Compound name	来源 Source	血小板 Platelet	诱导剂(浓度) Inducer (concentration)	IC_{50}或抑制率(样品浓度) IC_{50} or Inhibition rate (sample concentration)	文献 Ref.
	P. arborescens Roxb.	兔	AA (100 μM)	31.7 μM	[29]
		兔	胶原 (10 μg/mL)	29.3 μM	[29]
		兔	凝血酶(0.1 U/mL)	83.7 μM	[29]
胡椒内酰胺 E (piperolactam E,22)	*P. taiwanense* Lin & Lu	兔	胶原 (10 μg/mL)	98% (50 μg/mL)	[35]
piperarborenine C (23)	*P. arborescens* Roxb.	兔	AA (100 μM)	88.5 μM	[29]
		兔	胶原 (10 μg/mL)	60.3 μM	[29]
piperarborenine D (24)	*P. arborescens* Roxb.	兔	胶原 (10 μg/mL)	82.8 μM	[29]

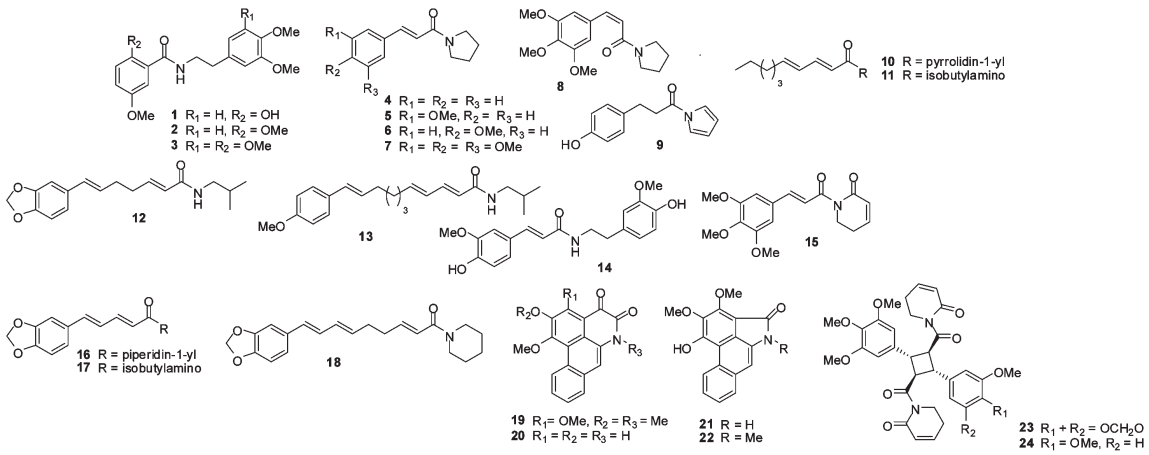

图 1 胡椒属植物中抗血小板活性生物碱(1~24)的结构式

Fig. **1** Chemical structures of antiplatelet alkaloids (**1-24**) from *Piper* plants

表 3 胡椒属植物中具有抗血小板活性的木脂素(25~36)

Table **3** Antiplatelet lignans (**25-36**) from *Piper* plants

化合物名称 Compound name	来源 Source	血小板 Platelet	诱导剂(浓度) Inducer (concentration)	IC_{50}或抑制率(样品浓度) IC_{50} or Inhibition rate (sample concentration)	文献 Ref.
海风藤酮(kadsurenone,25)	*P. kadsura* (Choisy) Ohwi	兔	PAF [a]	2.6 μM	[25]
		兔	PAF (2 ng/mL)	8 μg/mL	[36]
		兔	AA (55 μM)	28.3 μM	[37]
denudatin B (26)	*P. wallichii* (Miq.) Hand.-Mazz.	兔	PAF (2 ng/mL)	10 μg/mL	[36,38]
neotaiwanensol A (27)	*P. taiwanense* Lin & Lu	人	胶原 (10 μg/mL)	63.9 μM	[18]
taiwandimerol A (28)	*P. taiwanense* Lin & Lu	人	胶原 (10 μg/mL)	55.8 μM	[18]
taiwandimerol B (29)	*P. taiwanense* Lin & Lu	人	胶原 (10 μg/mL)	72.5 μM	[18]
(-)-丁香树脂醇[(-)-syringaresinol,30]	*P. wallichii* (Miq.) Hand.-Mazz.	兔	PAF (40 ng/mL)	520 μM	[39]
(+)-diayangambin (31)	*P. arborescens* Roxb.	兔	PAF (2 ng/mL)	65.4 μM	[29]
piperphilippinin I (32)	*P. philippinum* Miq.	兔	AA (100 μM)	56% (100 μM)	[31]
piperphilippinin II (33)	*P. philippinum* Miq.	兔	胶原 (10 μg/mL)	57% (100 μM)	[31]

化合物名称 Compound name	来源 Source	血小板 Platelet	诱导剂(浓度) Inducer (concentration)	IC_{50}或抑制率(样品浓度) IC_{50} or Inhibition rate (sample concentration)	文献 Ref.
piperphilippinin IV (34)	*P. philippinum* Miq.	兔	AA (100 μM)	81% (100 μM)	[31]
		兔	胶原 (10 μg/mL)	58% (100 μM)	[31]
piperphilippinin V (35)	*P. philippinum* Miq.	兔	AA (100 μM)	69% (100 μM)	[31]
(-)-3′,4′-*O*,*O*-demethylenehinokinin (36)	*P. philippinum* Miq.	兔	AA (100 μM)	100% (100 μM)	[31]
		兔	胶原 (10 μg/mL)	58% (100 μM)	[31]

注:[a] 文献[25]中没有诱导剂 PAF 的浓度。
Note: [a]The concentration of the inducer PAF was not presented in the reference [25].

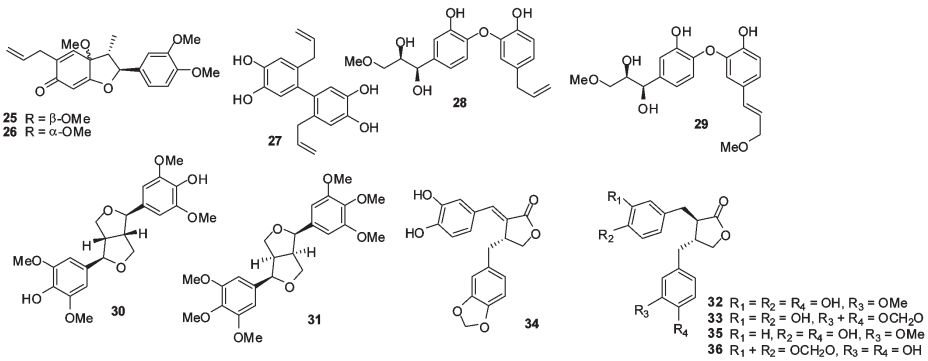

图 2 胡椒属植物中抗血小板活性木脂素(25~36)的结构式

Fig. **2** Chemical structures of antiplatelet lignans (**25-36**) from *Piper* plants

表 4 胡椒属植物中具有抗血小板活性的苯丙素(37~47)及其它成分(48~51)

Table **4** Phenylpropanoids (**37-47**) and other constituents (**48-51**) with antiplatelet activity from *Piper* plants

化合物名称 Compound name	来源 Source	血小板 Platelet	诱导剂(浓度) Inducer (concentration)	IC_{50}或抑制率(样品浓度) IC_{50} or Inhibition rate (sample concentration)	文献 Ref.
羟基胡椒酚 (hydroxychavicol, 37)	*P. taiwanense* Lin & Lu	人	胶原(10 μg/mL)	5.3 μM	[18]
		兔	AA (100 μM)	9.9 μM	[35]
羟基胡椒酚乙酸酯 (hydroxychavicol acetate, 38)	*P. taiwanense* Lin & Lu	人	胶原(10 μg/mL)	2.1 μM	[18]
	合成	兔	AA (100 μM)	3.5 μM	[35]
丁香酚 (eugenol, 39)	*P. taiwanense* Lin & Lu	兔	AA (100 μM)	20.2 μM	[35]
	商业公司	人	AA (1.0 mM)	0.5 μM	[26]
混合物 (2-hydroxy-5-(prop-2-enyl) phenyl acetate 和 taiwanensol C, 40 和 41)	*P. taiwanense* Lin & Lu	人	胶原(10 mg/mL) [a]	8.8 μM	[40]
混合物 (taiwanensols A 和 B, 42 和 43)	*P. taiwanense* Lin & Lu	人	胶原(10 mg/mL) [a]	35.2 μM	[40]
苯丙酸甲酯 (44)	*P. sarmentosum* Roxb. (*P. lolot* C. DC.)	兔	AA (100 μM)	53.4 μg/mL	[30]
		兔	PAF (5 nM)	83.2 μg/mL	[30]

化合物名称 Compound name	来源 Source	血小板 Platelet	诱导剂（浓度） Inducer (concentration)	IC_{50}或抑制率(样品浓度) IC_{50} or Inhibition rate (sample concentration)	文献 Ref.
3,4-亚甲二氧基桂皮醛（45）	*P. philippinum* Miq.	兔	AA（100 μM）	86%（100 μM）	[31]
反-3,4,5-三甲氧基桂皮酸甲酯（46）	*P. arborescens* Roxb.	兔	胶原(10 μg/mL)	58.6 μM	[29]
		兔	PAF（2 ng/mL）	77.7 μM	[29]
(+)-bornyl caffeate（47）	*P. philippinum* Miq.	兔	AA（100 μM）	75%（100 μM）	[31]
		兔	胶原(10 μg/mL)	58%（100 μM）	[31]
3-phenyl-1-(2,4,6-trihydroxyphenyl)propan-1-one（48）	*P. sarmentosum* Roxb.（*P. lolot* C. DC.）	兔	AA（100 μM）	19.0 μg/mL	[30]
		兔	PAF（5 nM）	61.0 μg/mL	[30]
3-(4-methoxyphenyl)-1-(2,4,6-trihydroxyphenyl) propan-1-one（49）	*P. sarmentosum* Roxb.（*P. lolot* C. DC.）	兔	AA（100 μM）	31.2 μg/mL	[30]
		兔	PAF（5 nM）	71.4 μg/mL	[30]
(+)-醉椒素[(+)-kavain, 50]	*P. methysticum* G. Forst.	人	AA（100 μM）	78 μM	[41]
乌苏酮酸（ursonic acid,51）	*P. betle* L.	人	AA（1.7 mM）	260 μM	[42]
		人	PAF（0.8 μM）	190 μM	[42]
阿司匹林[b]		人	AA（1.0 mM）	14.5 μM	[26]

注：[a] 文献[40]中诱导剂胶原的浓度可能有误；[b] 阳性对照。
Note: [a]The concentration of the inducer collagen may not be correct in the reference[40]; [b]positive control.

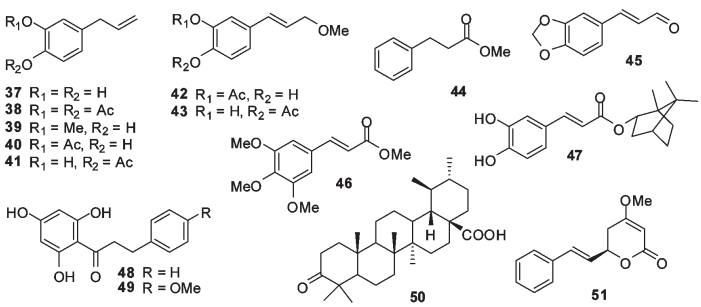

图 3 胡椒属植物中抗血小板活性苯丙素(37～47)及其它成分(48～51)的结构式

Fig. 3 Chemical structures of phenylpropanoids (**37-47**) and other constituents (**48-51**) with antiplatelet activity from *Piper* plants

3 胡椒属植物及其化学成分的抗凝血及抗血栓作用

四藤汤(海风藤、红藤、鸡血藤、络石藤)水煮液浓缩物显著延长人血浆复钙时间(recalcification time,RT)、凝血酶原时间(prothrombin time,PT)和凝血酶时间(thrombin time,TT),显示出体外抗凝血作用[43]。

生物碱 pellitorine(**11**)或荜茇宁(**17**)在体外能延长人血浆的活化部分凝血活酶时间(activated partial thromboplastin time, aPTT)和凝血酶原时间(PT);在体内,荜茇宁(8.25 μg/mouse = 0.413 mg/kg,口服)或 pellitorine(36.5 μg/mouse,静脉注射)能延长小鼠断尾出血时间[28,44]。

在胶原(114 μg/mouse)加肾上腺素(13.2 μg/mouse)诱导的小鼠肺血栓模型中,口服 50 mg/kg 剂量的荜茇酰胺(piperlongumine,piplartine,**15**)保护率为 48%,优于口服 50 mg/kg 阿司匹林,后者保护率为 39%[45]。在异丙肾上腺素(isoproterenol)诱导的 Wistar 大鼠心肌梗死模型中,丁香酚(**39**)(50 mg/kg,口服)显示出了抗炎和抗血栓效果[46]。

4 胡椒属植物化学成分抗血小板和抗血栓的作用机制

前人对胡椒属植物中部分活性化合物的作用机制开展过研究。早些时候的研究认为,荜茇酰胺(**15**)是血栓素 A_2(thromboxane A_2,TXA_2)受体拮抗剂[47]。后来还发现,荜茇酰胺抗血小板聚集是通过

抑制环氧合酶(cyclooxgenase,COX)活性和降低 TXA_2 的形成来实现的[33]。

荜茇宁(**17**)和 pellitorine(**11**)既能抑制凝血酶和活化凝血因子 X(FXa)活性,同时也能抑制凝血酶和 FXa 在人脐静脉内皮细胞(human umbilical vein endothelial cells,HUVECs)中的生成[28,44]。

胡椒碱(**16**)抗血小板聚集作用是因为这个化合物能抑制胞浆型磷脂酶 A_2(cytosolic phospholipase A_2,$cPLA_2$)和 TXA_2 合成酶活性,而对环氧合酶 1(COX-1)的活性没有影响[34]。

海风藤酮(**25**)对 COX-1 有比较好的抑制作用(IC_{50} = 25.6 μM),其活性明显优于差向异构体 denudatin B (**26**)[48]。

羟基胡椒酚 (**37**)能抑制 AA 或胶原诱导的血小板 TXB_2 形成,IC_{50} 分别为 0.91 ± 0.32 μM 和 1.2 ± 0.4 μM。羟基胡椒酚对 COX-1 和 COX-2 均有一定抑制作用,IC_{50} 分别为 79.8 ± 2.8 μM 和 64.8 ± 10.5 μM。这个化合物还能抑制 AA(IC_{50} = 3.9 ± 0.8 μM)或胶原诱导的血小板 Ca^{2+} 动员(mobilization),对凝血酶诱导的 Ca^{2+} 动员影响较小[49]。

丁香酚 (**39**)对 TXA_2 的形成有抑制作用[26],它也可选择性抑制 COX-1(IC_{50} = 59.3 ± 10.6 μM),对 COX-2 抑制作用很弱,浓度 500 μM 时,抑制率仅 19%[49]。

5 胡椒属植物抗血栓的临床应用

较早的临床试验表明,石南藤(文献中给出的拉丁名是 *Piper wallichii*,但给出的中文名是海风藤,本文以拉丁名为准)总黄酮经静脉注射,对冠心病心绞痛病人显效率为 73.2% (41/56),改善率 23.2% (13/56),总有效率 96.4% (54/56)[50];其总黄酮对脑血栓治疗显效率 69.8% (44/63),改善率 17.4% (11/63),总有效率 87.3% (55/63)[51]。含有海风藤的四藤汤(红藤、海风藤、络石藤、鸡血藤)对脑血栓病人也有治疗作用[52]。

6 结论与展望

在我国,具有活血功能的胡椒属植物 11 种,约占药用总数的 1/3 左右。研究发现,二十种胡椒属植物的提取物显示出抗血小板聚集活性,尤其是假蒟、山蒟、石南藤和风藤的二氯甲烷提取物,以及台湾荖藤的甲醇提取物,活性极强。风藤和石南藤的抗血栓效果在临床上也得到确认。目前,从胡椒属植物中已经鉴定出了抗血小板聚集的活性成分 51 个,包括生物碱(占 47%)、木脂素(占 24%)、苯丙素(占 22%)等。其中,海风藤酮(**25**)、丁香酚(**39**)、羟基胡椒酚乙酸酯(**38**)等的抗血小板活性较为显著,pellitorine(**11**)、荜茇酰胺(**15**)、荜茇宁(**17**)和丁香酚(**39**)等表现出了体内抗凝及抗血栓活性。

在未来的研究中,选取出血风险较小的抗血栓新靶点,如磷脂酰肌醇 3-激酶(phosphatidylinositol 3-kinase,PI3K)和凝血因子 XI(FXI)[53,54],对胡椒属植物化学成分进行抑制活性筛选,有利于发现有开发潜力的先导化合物。在体内活性及作用机制方面也值得深入研究。

参考文献

1 Wang HR, *et al*. Comparison of therapeutic effect of recombinant tissue plasminogen activator by treatment time after onset of acute ischemic stroke. *Sci Rep*, 2015, 5: 11743.

2 Xing JH (邢峻豪), *et al*. Advances in antithrombotic drugs. *Prog Pharm Sci* (药学进展), 2014, 38: 174-184.

3 Huang ZS, *et al*. Salvianolic acid A inhibits platelet activation and arterial thrombosis via inhibition of phosphoinositide 3-kinase. *J Thromb Haemost*, 2010, 8: 1383-1393.

4 Liu L, *et al*. Salvianolic acid B inhibits platelets as a P2Y (12) antagonist and PDE inhibitor: Evidence from clinic to laboratory. *Thromb Res*, 2014, 134: 866-876.

5 Sun FZ (孙凤志), *et al*. Advances in Huoxue and Zhixue effects of *Panax notoginseng*, a traditional Chinese medicine. *J Med Res* (医学研究杂志), 2013, 42: 24-26.

6 Xiang QL (向秋玲), *et al*. Protective effect of panaxatriol saponins on cerebral ischemia. *J Sun Yat Sen Univ* (*Med Sci*) (中山大学学报:医学科学版), 2008, 29: 705-709.

7 Chen JW (陈健文), *et al*. Promoting blood circulation by removing blood stasis of panaxatriol saponins. *Trad Chin Med Pharmacol Clin* (中药药理与临床), 2008, 24: 38-41.

8 Lau AJ, *et al*. Antiplatelet and anticoagulant effects of *Panax notoginseng*: comparison of raw and steamed *Panax notoginseng* with *Panax ginseng* and *Panax quinquefolium*. *J Ethnopharmacol*, 2009, 125: 380-386.

9 Hao HZ, *et al*. Antiplatelet activity of loureirin A by attenuating Akt phosphorylation: *in vitro* studies. *Eur J Pharmacol*, 2015, 746: 63-69.

10 Xin N, *et al*. Dragon's Blood extract has antithrombotic properties, affecting platelet aggregation functions and anticoagulation activities. *J Ethnopharmacol*, 2011, 135: 510-514.

11 Tseng YC, *et al*. Piperaceae. In: Wu, ZY, Raven PH, Hong, D. Y. editors. Flora of China. Beijing/St. Louis: Science Press/Missouri Botanical Garden Press, 1999. Vol 4, 110-

129.

12 Wang YH, *et al*. Anticancer principles from medicinal *Piper* plants. *J Tradit Complement Med*, 2014, 4: 8-16.

13 Editorial Board of Zhonghua Bencao´, State Administration of Traditional Chinese Medicine of the People's Republic of China (国家中医药管理局《中华本草》编委会). Zhonghua Bencao (中华本草). Shanghai: Shanghai Scientific and Technological Press, 1999. Vol 3, 424-449.

14 Wu ZY (吴征镒), *et al*. Xinhua Bencao Gangyao (新华本草纲要). Shanghai: Shanghai Scientific and Technological Press, 1988. Vol 1, 190-196.

15 Li CL (李长龄), *et al*. Anti-PAF effects of about 100 traditional Chinese medicines. *Physiol Sci* (生理科学), 1987, 7: 316-316.

16 Li CL (李长龄), *et al*. Anti-PAF effects of more than 100 traditional Chinese medicines. *Chin Pharmacol Bull* (中国药理学通报), 1987, 3: 298-298.

17 Li CL (李长龄), *et al*. Anti-PAF effects of alcohol extracts from *Piper hancei*. *Physiol Sci* (生理科学), 1987, 7: 316-317.

18 Chen S, *et al*. Neolignans and phenylpropanoids from the roots of *Piper taiwanense* and their antiplatelet and antitubercular activities. *Phytochemistry*, 2013, 93: 203-209.

19 Guerrini A, *et al*. Bioactivities of *Piper aduncum* L. and *Piper obliquum* Ruiz & Pavon (Piperaceae) essential oils from eastern Ecuador. Environ. *Toxicol Pharmacol*, 2009, 27: 39-48.

20 Shen ZQ (沈志强), *et al*. PAF-antagonist screening from 12 alcohol extracts of *Piper* species native to Yunnan. *Acad J Kunming Med Coll* (昆明医学院学报), 1997, 18: 23-25.

21 Shen ZQ (沈志强), *et al*. Study on antiplatelet activity of alcohol extracts from *Piper* species native to Yunnan. *Nat Prod Res Dev* (天然产物研究与开发), 1999, 11: 27-31.

22 Lei D, *et al*. Antioxidative and antiplatelet effects of aqueous inflorescence *Piper betle* extract. *J Agric Food Chem*, 2003, 51: 2083-2088.

23 Zhao SF (赵淑芬), *et al*. The inhibitory effect of alcoholic extracts of *Piper hancei* on platelet aggregation. *J Cap Univ Med Sci* (首都医学院学报), 1996, 17: 28-31.

24 Chen IS, *et al*. Amides with anti-platelet aggregation activity from *Piper taiwanense*. *Fitoterapia*, 2007, 78: 414-419.

25 Shen YZ, *et al*. Characterization of a platelet-activating factor receptor antagonist, kadsurenone: specific inhibition of platelet-activating factor *in vitro* and *in vivo*. *J Chin Pharm Sci*, 1994, 3: 59-64.

26 Raghavendra R, *et al*. Spice active principles as the inhibitors of human platelet aggregation and thromboxane biosynthesis. *Prostag Leukot Essent Fatty Acids*, 2009, 81: 73-78.

27 Tognolini M, *et al*. Comparative screening of plant essential oils: phenylpropanoid moiety as basic core for antiplatelet activity. *Life Sci*, 2006, 78: 1419-1432.

28 Lee W, *et al*. Anticoagulant activities of piperlonguminine *in vitro* and *in vivo*. *BMP Rep*, 2013, 46: 484-489.

29 Tsai IL, *et al*. New cytotoxic cyclobutanoid amides, a new furanoid lignan and anti-platelet aggregation constituents from *Piper arborescens*. *Planta Med*, 2005, 71: 535-542.

30 Li CY, *et al*. Isolation and identification of antiplatelet aggregatory principles from the leaves of *Piper lolot*. *J Agric Food Chem*, 2007, 55: 9436-9442.

31 Chen YC, *et al*. Lignans, an amide and anti-platelet activities from *Piper philippinum*. *Phytochemistry*, 2007, 68: 2101-2111.

32 Park BS, *et al*. Antiplatelet effects of acidamides isolated from the fruits of *Piper longum* L. *Phytomedicine*, 2007, 14: 853-855.

33 Fontenele JB, *et al*. Antiplatelet effects of piplartine, an alkamide isolated from *Piper tuberculatum*: possible involvement of cyclooxygenase blockade and antioxidant activity. *J Pharm Pharmacol*, 2009, 61: 511-515.

34 Son DJ, *et al*. Piperine inhibits the activities of platelet cytosolic phospholipase A2 and thromboxane A2 synthase without affecting cyclooxygenase-1 activity: different mechanisms of action are involved in the inhibition of platelet aggregation and macrophage inflammatory response. *Nutrients*, 2014, 6: 3336-3352.

35 Chen YC, *et al*. A new aristolactam alkaloid and anti-platelet aggregation constituents from *Piper taiwanense*. *Planta Med*, 2004, 70: 174-177.

36 Teng CM, *et al*. Comparison of the actions of some platelet-activating factor antagonists on platelets and aortic smooth muscles. *Eur J Pharmacol*, 1991, 205: 151-156.

37 Ammit AJ, *et al*. Platelet-activating factor (PAF) receptor antagonists inhibit arachidonic acid induced platelet aggregation in rabbit whole blood. *Lipids*, 1991, 26: 1189-1192.

38 Han GQ (韩桂秋), *et al*. The isolation and identification of PAF receptor antagonist from *Piper wallichii* (Miq) Hand-Mazz. *J Beijing Med Univ* (北京医科大学学报), 1987, 19: 243-245.

39 Shi YN, *et al*. Lignans and aromatic glycosides from *Piper wallichii* and their antithrombotic activities. *J Ethnopharmacol*, 2015, 162: 87-96.

40 Chen S, *et al*. Three new phenylpropanoids from the roots of *Piper taiwanense* and their inhibitory activities on platelet aggregation and *Mycobacterium tuberculosis*. *Chem Biodivers*, 2014, 11: 792-799.

41 Gleitz J, *et al*. Antithrombotic action of the kava pyrone (+)-kavain prepared from *Piper methysticum* on human platelets. *Planta Med*, 1997, 63: 27-30.

42 Saeed SA, *et al*. Triterpenes and β-sitosterol from *Piper betle*: isolation, antiplatelet and anti-inflammatory effects. *Biochem Soc Trans*, 1993, 21: 462S-462S.

43 Yang J (杨嘉), *et al*. Chinese herbal medicine research of antithrombotic effect. *Nat Prod Res Dev* (天然产物研究与开发), 1997, 9: 17-20.

44 Ku SK, *et al*. Antithrombotic activities of pellitorine *in vitro* and *in vivo*. *Fitoterapia*, 2013, 91: 1-8.

45 Lee SE, *et al*. Proteomic evaluation on antiplatelet activity of piperlongumine derived from *Piper longum*. *Mol Cell Toxicol*, 2010, 6: 295-303.

46 Mnafgui K, *et al*. Anti-inflammatory, antithrombotic and cardiac remodeling preventive effects of eugenol in isoproterenol-induced myocardial infarction in Wistar rat. *Cardiovasc Toxicol*, 2015, Accepted.

47 Iwashita M, *et al*. Piperlongumine, a constituent of *Piper longum* L., inhibits rabbit platelet aggregation as a thromboxane A 2 receptor antagonist. *Eur J Pharmacol*, 2007, 570: 38-42.

48 Coy ED, *et al*. COX, LOX and platelet aggregation inhibitory properties of Lauraceae neolignans. *Bioorg Med Chem Lett*, 2009, 19: 6922-6925.

49 Chang M, *et al*. Hydroxychavicol, a novel betel leaf component, inhibits platelet aggregation by suppression of cyclooxygenase, thromboxane production and calcium mobilization. *Br J Pharmacol*, 2007, 152: 73-82.

50 He ZY (何作云), *et al*. A preliminary study on the treatment of coronary heart disease with total flavone of *Caulis Piperis Futokadsurae*. *Chin J Integr Tradit West Med* (中西医结合杂志), 1983, 3: 271-271.

51 Zhang JM (张基谟), *et al*. The treatment of 87 cases with cerebral infarction using total flavone of *Caulis Piperis Futokadsurae* and animal experiments. *J Apoplexy Nerv Dis* (中风与神经疾病杂志), 1987, 4: 180-182.

52 Jiang M (姜明). The clinical application of 38 cases with cerebral thrombosis using self-made modified Siteng decoction. *Mod Med Health* (现代医药卫生), 2010, 26: 1708-1709.

53 Yu HW (禹华玮), *et al*. Coagulation factor Ⅺ, a new target for antithrombotic therapy. *Prac J Med Pharm* (实用医药杂志), 2014, 31: 170-172.

54 He ZL (何志龙), *et al*. Research advances in antithrombotic new target of PI3K. *Pharm Biotechnol* (药物生物技术), 2014, 21: 373-376.

(上接第 1675 页)

61 de Bono JS, *et al*. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant pros-tate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*, 2010, 376: 1147-1154.

62 Paller CJ, *et al*. Cabazitaxel: a novel second-line treatment for metastatic castration-resistant prostate cancer. *Drug Des Devel Ther*, 2011, 5: 117-124.

63 Diéras V, *et al*. Cabazitaxel in patients with advanced solid tumors: results of a phase I and pharmacokinetic study. *Eur J Cancer*, 2013, 49(1): 25-34.

64 Shionoya M, *et al*. DJ-927, a novel oral taxane, overcomes P-glycoprotein-mediated multidrug resistance *in vitro* and *in vivo*. *Cancer Sci*, 2003, 94: 459-466.

65 Saif MW, *et al*. Tesetaxel, a new oral taxane, in combination with capecitabine: a phase Ⅰ, dose-escalation study in patients with advanced solid tumors. *Cancer Chemother Pharmcol*, 2011, 68: 1565-1573.

66 Bouvier E, *et al*. First enzymatically activated taxotere prodrugs designed for ADEPT and PMT. *Bioorg Med Chem*, 2004, 12: 969-977.

67 Plazuk D, *et al*. Synthesis and biological activities of ferrocenyl derivatives of paclitaxel. *Med Chem Commun*, 2012, 3: 498-501.

68 Chen M(陈明). Design, synthesis and antitumor research of novel taxane derivatives. Xi′an: The Fourth Military Medical University(第四军医大学), PhD. 2014.

69 Mei M(梅梅), *et al*. Resistance reversal effect of a novel taxane compound NPB304 and its collaboration with verapamil. *Acta Pharm Sin*(药学学报), 2014, 49: 1279-1288.

70 Sparreboom A, *et al*. Pharmacogenomics of ABC transporters and its role in cancer chemotherapy. *Drug Resist Updat*, 2003, 6: 71-84.

71 Lu HF, *et al*. Synthesis, cytotoxicity, metabolic stability and pharmacokinetic evaluation of fluorinated docetaxel analogs. *Eur J Med Chem*, 2011, 46: 1743-1748.

72 Chang J, *et al*. Design, synthesis and cytotoxicity of novel 3′-N-alkoxycarbonyl docetaxel analogs. *Bioorg Med Chem Lett*, 2013, 23: 6834-6837.

73 Zhou Q, *et al*. Lx2-32c, a novel taxane derivative, exerts anti-resistance activity by initiating intrinsic apoptosis pathway *in vitro* and inhibits the growth of resistant tumor *in vivo*. *Biol PharmBull*, 2012, 35: 2170-2179.

74 Zhao Y, *et al*. Synthesis, cytotoxic activity, and SAR analysis of the derivatives of taxchinin A and brevifoliol. *Bioorgan Med Chem*, 2008, 16: 4860-4871.