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Anti-Breast Cancer Agents from Chinese Herbal Medicines

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Abstract: Chinese Herbal Medicines (CHM) have been used in disease prevention and treatment for centuries in China. A number of anti-breast cancer agents isolated from CHM recently, showed very interesting structures, although some of the mechanism of action is not quite clear. These unique chemical structures could be an important information resource for new anti-breast cancer drugs' design and discovery. This review summarizes these findings on anti-breast cancer agents from CHM.

Keywords: Breast cancer, Chinese herbal medicine(CHM), herb, natural product.

1. INTRODUCTION

Breast cancer is the most common cancer among women, which carries a lifetime risk of ~10% in western populations [1-3]. In China, breast cancer has become one of the fastest growing cancers in the past 30 years, rising rate is about 96% high, only slightly lower than lung cancer [4].

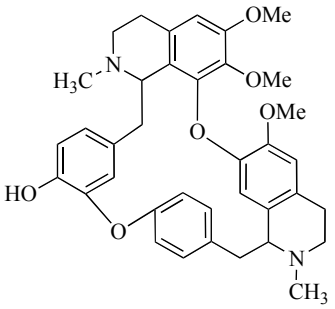
Breast cancers can be divided into several classes on the basis of the receptor status of the breast cancer cells. Human estrogen-receptor (HER) positive tumors include luminal types a and b, whereas ER negative tumors include subtypes in which HER2 is over expressed and a basal-like subtype that is triple negative for ER, the progesterone receptor (PR) and HER2. Most breast cancers are estrogen-dependent, approximately 60% in premenopausal women and 75% in postmenopausal women [5]. Improvements in adjuvant therapy and screening have led to a reduction in breast cancer mortality in the past few decades.

Traditional Chinese herbal medicines (CHM) which have been used in disease prevention and treatment for centuries could be alternative strategy to western cancer therapies. A number of anti-breast cancer agents have been discovered from CHM, although some of the mechanisms of action have not been elucidated yet. The special chemical structure information has been rarely exposed to western journal before, which could be an important resource for new anti-breast cancer drugs' design and discovery. These findings are summarized as several categories below according to its structure features.

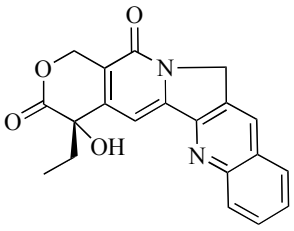
2. ALKALOIDS

Alkaloids exist widely in CHM and natural products. It has been used for many diseases treatment with long history. The anti-breast cancer activity of more than 20 alkaloids isolated from CHM has been investigated *in vitro* by determining the inhibitory activity against growth of human mammary cancer cell line BCAP [6].

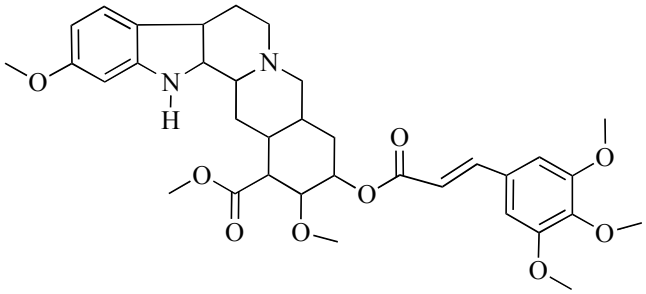
The results showed that berbamine (**1**) and camptothecin (**2**) demonstrated significant inhibition for the growth of human mammary cancer cell line BCAP cell with EC_{50} values of 1.6, and 1.8 μM, respectively. Rescinnamine (**3**) and tomatidine (**4**) were found to have weak inhibition with IC_{50} values of 32.9 and 32.3 μM respectively. These ingredients have the potential to be developed as candidate or leading compounds for anti-tumor drugs in the future.



Berbamin (**1**)



Camptothecin (**2**)



Rescinnamin (**3**)

*Address correspondence to this author at the School of Traditional Chinese Pharmacy, Shanghai University of Traditional Chinese Medicine, 1200 Cai Lun Road, Zhangjiang Hi-Tech Park, Shanghai 201203, PR China;
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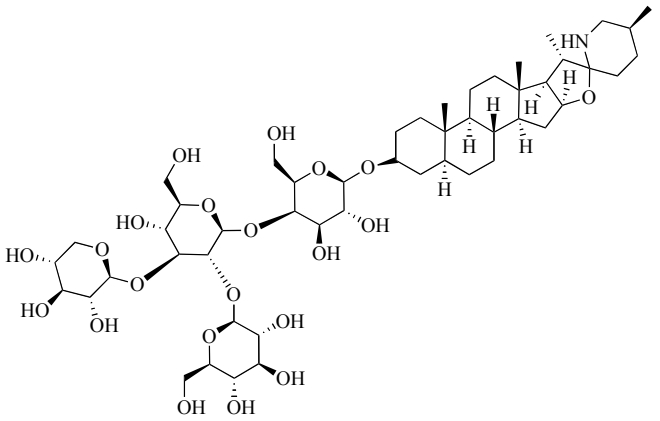
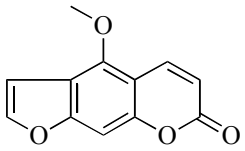


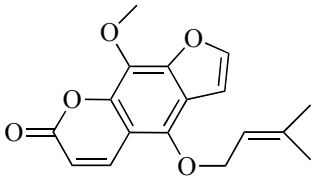
Tomatidin (**4**)

3. COUMARINS

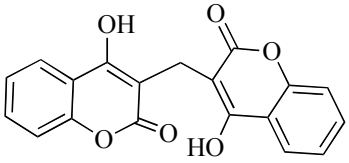
About forty coumarins compounds isolated from the traditional chinese medicine have been screened for their antitumor activity [7], It was found that bergapten (**5**), cnidilin (**6**), dicoumarol (**7**), and notoptol (**8**) exhibited weak inhibition for the growth of BCAP cell line, with IC_{50} values of 41.6, 27.7, 66.2, and 66.7 μM respectively, these activities also exhibited dose-dependent response.



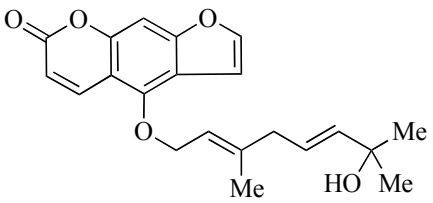
Bergapten (**5**)



Cnidilin (**6**)

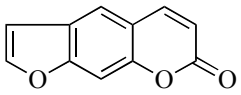


Dicoumarol (**7**)

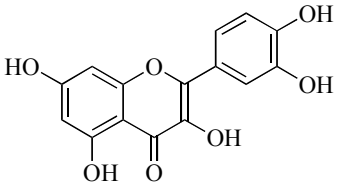


Notoptol (**8**)

The inhibitory effects of psoralen (**9**) and quercetin (**10**) on the proliferation of human breast cancer cell lines MCF-7 have been examined [8, 9]. The estrogen-like effect of psoralen and its interaction with ER wes evaluated with ER antagonist ICI182,780. Psoralen (10 μM) and quercetin (10 μM) were found to be able to inhibit proliferation of MCF-7 cells compared with vehicle control, the cell cycle was impulsed from G1 to S, cell apoptosis was obviously increased at early stage. The above function on boosting MCF-7 cell apoptosis could be inhibited by adding ER antagonist ICI182,780. Psoralen (10 μM) and quercetin (10 μM) could up-regulate ER protein level without altering level of ER. The results showed Psoralen and quercetin had the estrogen-like activities through the estrogen response pathway, and the estrogenic activity was exerted through its interaction with ER expression.



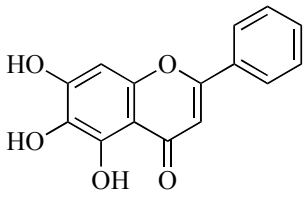
Psoralen (**9**)



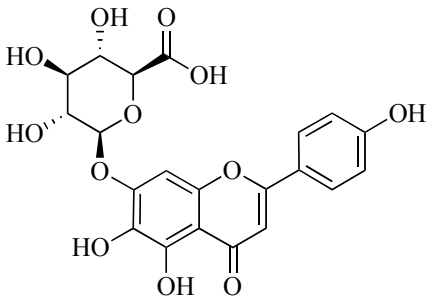
Quercetin (**10**)

4. FLAVONOIDS, AND POLYPHENOLS

Franek and Zhou etal. reported baicalin (antipyretic, **11**), Flavins scutellarin (a circulatory stimulant, **12**) and two extracts from salvia miltiorrhiza (SM-470, circulatory stimulant) and camellia sinensis (Cam-300, antipyretic), inhibited the proliferation of the human breast cancer cell lines MCF-7 and T-47D, and baicalin is the most potent inhibitor [10]. Moreover, the combination of these compounds from different botanical classes offers enhanced therapeutic benefits; the combination of SM-470 with scutellarin, cam-300 or baicalin, augmented the inhibition of cell proliferation. A synergistic inhibitory effect on MCF-7 cell proliferation was also observed when SM-470 and baicalin were applied together. In contrast, inhibition of T-47D cell proliferation using the same combination was dependent on baicalin only. Baicalin and SM-470 in combination produced additive effects, suggesting these compounds may act by different mechanisms.

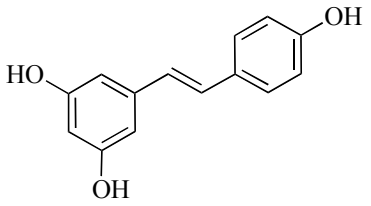


Baicalin (**11**)

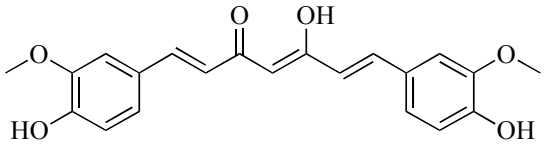


Scutellarin (**12**)

Resveratrol (RES, **13**), a chemopreventive molecule, has been found to be able to inhibit the proliferation of tumor cells of different etiologies [11]. The studies showed that RES altered the cell cycle and induced apoptosis in MCF-7 breast tumor cells by interfering with the estrogen receptor (ER)-dependent phosphoinositide 3-kinase (PI3K) pathway. Apoptotic death by RES in MCF-7 was also mediated by Bcl-2 down-regulation since overexpression of this protein abolished apoptosis. RES-induced apoptosis in MCF-7 might involve in an oxidative, caspase-independent mechanism, whereby inhibition of PI3K signaling could converge to Bcl-2 through NF-κB and calpain protease activity.



Resveratrol (**13**)



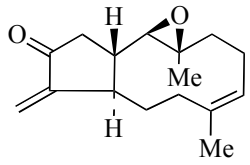
Curcumin (**14**)

Curcumin (**14**) has been reported to be able to inhibit the proliferation both in estrogen receptor (ER) positive MCF-7 cells and ER negative MDA-MB-231cells [12]. Curcumin's antiproliferative effects are estrogen- dependent in ER positive MCF-7 cells. Curcumin inhibited the expression of ER downstream genes including pS2 and TGF-α (transforming growth factor-α) in ER-positive MCF-7 cells, and this inhibition was also dependent on the presence of estrogen. In addition, curcumin exerted strong anti-invasive effects *in vitro* which was not estrogen- dependent in the ER2 negative MDA-MB-231 breast cancer cells. These anti-invasive effects appeared to be mediated through the down-regulation of MMP-2 (matrix metalloproteinase) and the up-regulation of TIMP-1 (tissue inhibitor of metalloproteinase). Curcumin inhibited the transcript levels of two major angiogenesis factors VEGF (vascular endothelial growth factor) and b-FGF (basic fibroblast growth factor) in ER-negative MDA-MB-231 cells.

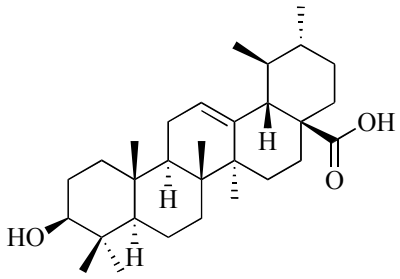
Curcumin was also found to inhibit the proliferation of MCF-7 cells in G1/S phase [13]. Fluorescent staining can detect the apoptotic cells. The expression of BAX mRNA was increased and the BCL-2 was decreased. The studies showed curcumin not only inhibited proliferation but also induced apoptosis of MCF-7 cells. The possible mechanism is relevant with the function of curcumin: down-regulating BCL-2 but up-regulating BAX.

5. TERPENOIDS

The medicinal herb feverfew [Tanacetum parthenium (*L.*) Schultz-Bip.], has been used as a folk remedy for the treatment of migraine and arthritis for long time. Parthenolide (**15**), a sesquiterpene lactone, is considered as the primary bioactive compound in feverfew having anti-migraine, anti-tumor, and anti-inflammatory properties. Wu etc. have measured the inhibitory activity of parthenolide and golden feverfew extractions against two human breast cancer cell lines (Hs605T and MCF-7) and one human cervical cancer cell line (SiHa) [14]. Feverfew ethanolic extraction inhibited the growth of all three types of cancer cells with an EC_{50} value of 1.5mg/mL against Hs605T, 2.1mg/mL against MCF-7, and 0.6 mg/mL against SiHa. Among the tested constituents of feverfew, parthenolide demonstrated the highest inhibitory effect with EC_{50} values against Hs605T, MCF-7, and SiHa of 2.6, 2.8, and 2.7μg/mL, respectively. The combination of parthenolide and flavonoids (apigenin and luteolin) in feverfew extracts also were investigated. The results revealed that apigenin and luteolin might have moderate to weak synergistic effects with the presence of parthenolide on the inhibition of cancer cell growth of Hs605T, MCF-7, and SiHa



Parthenolide (**15**)



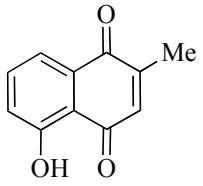
Ursolic acid (UA, **16**)

Ursolic acid (UA, **16**), apentacyclic triterpene acid, has been studied for the inhibitory effects of on MCF-7 cell apoptosis [15,16]. The results showed that twenty-four hours after UA treatment, apoptotic cells increased dose-dependently and the morphology changes of MCF-7 cells displayed many hallmark features of apoptosis, including chromatin aggregation and fragmented nuclei. Cytochrome C induced by 50 μmol/L of UA released into cytoplasm. It was concluded that apoptosis induced by UA in MCF-7 cells is related to the ratio increasing of Bax/bcl-2 and the releasing of cytochrome C. Cell cycle analysis by FCM showed that 50 μmol/L of the drug arrested MCF-7 cell cycle at G0-G1 phase. The results suggested that UA evoking MCF-7 cell apoptosis was correlated with the up-regulation of p53.

6. QUINONE AND OTHER CHEMICAL CLASSES

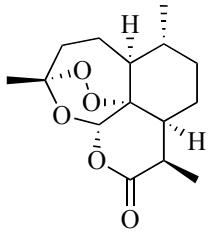
Plumbago zeylanica Linn. (*Plumbaginaceae*) has been used for treatment of some tumor diseases in Chinese herbal

medicines with long history, of which plumbagin (**17**) is one of very important bioactive components. Liu etal also observed the anti-tumor activity of plumbagin *in vitro*[17]. In their studies, cancer cell lines MDA-MB-231 were cultured *in vitro*, MTT method and colony-forming method were used to detect the inhibitory effects, and human embryonic lung fibroblast MRC-05 was adopted as control to measure the cytotoxic effect of plumbagin on normal cell. The results showed that plumbagin had significant activity on MDA-MB-231, Its IC_{50} value was 0.263 g/L and CC_{50} value was 5.13 g/L. The selective cytotoxic effect of the plumbagin is promising for further exploration.

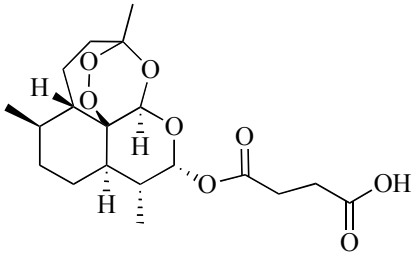


Plumbagin (**17**)

The effects of Artemisinin (**18**) and its analog artemisunate (**19**) on the proliferation of human breast cancer MCF-7 cell line and their mechanism were studied [18]. The inhibition of cell proliferation was determined by SRB method, cell cycle was determined by flow cytometry (FCM) analysis, and apoptosis was confirmed by sub-G1 cells content and DAPI method. The cell cycle of MCF-7 was changed dramatically when treated 24h with either 10 μM artemisinin or artemisunate, the distribution of MCF-7 cells among S phase was reduced significantly, while increased during G0+G1. However, artemisinin had weaker effect on the proliferation of MCF-7 cell, while artemisunate effectively inhibited the proliferation of MCF-7 with the IC_{50} of 0.31μM. Apoptosis induced by 1μM artemisunate was higher than by 10μM artemisinin, too. The inhibitory effect of artemisunate on the proliferation of tumor cell was stronger than that of Artemisinin *in vitro*.



Artemisinin (**18**)



Artemisunate (**19**)

7. CONCLUSIONS

A central tenet of modern medicine is that a drug should be a pure compound that selectively interacts with one target in order to cure one disease; an ideal modern drug should work for all patients. In contrast, CHM drugs are mixtures of raw herbs, which comprise multiple compounds regulating multiple targets for a class of medical indications. Although modern medicine and CHM may seem very different, they should have a common foundation, as herbs of a given CHM class have a common structural scaffold, which may account for their potency for some targets. These structures and activity information could inspire medicinal chemists to seek new ways of optimizing drug leads.

Table 1. The Anti-Breast Agents and Its Effects

Categories	Active Agents	Effects
Alkaloids	Berbamine (1)	Anti-mammary cancer
	Camptothecin (2)	Anti-mammary cancer
	Rescinnamine (3)	Anti-mammary cancer
	Tomatidine (4)	Anti-mammary cancer
Coumarins	Bergapten (5)	Anti-breast cancer
	Cnidilin (6)	Anti-breast cancer
	Dicoumarol (7)	Anti-breast cancer
	Notoptol (8)	Anti-breast cancer
	Psoralen (9)	Estrogen-like activity
	Quercetin (10)	Estrogen-like activity
Flavonoids and polyphenols	Baicalin (11)	Anti-breast cancer
	Scutellarin (12)	Anti-breast cancer
	Resveratrol (13)	Interfering PI3K pathway
	Curcumin (14)	Inhibit transcript of VEGFR and b-FGF
Terpenoids	Parthenolide (15)	Anti-breast, anti-cervical cancer
	Ursolic cid (UA,16)	Anti-breast cancer
Quinone and other chemical classes	Plumbagin (17)	Anti-breast cancer
	Artemisinin (18)	Anti-breast cancer
	Artemisunate (19)	Anti-breast cancer

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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Declared none.

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