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Comparison of cytotoxic activity of herbal extracts on the most commonly used breast cancer cell lines (MCF7 and SKBR3): A systematic review

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ABSTRACT: Herbal drug development is considered as an imperative part of complementary and alternative medicine. Bioactive compounds of botanical sources represent potential anti-cancer agents for modern therapeutics. Primary *in vitro* data of herb extracts' effects against cancer cell lines could be considered as indicators of potential toxicity to reduce the number of *in vivo* experiments. This study aims to review the findings of published articles concerning the *in vitro* efficacy of herbal extracts against breast cancer cell lines (MCF7 and SKBR3). *In vitro* studies of herbal extracts published until July 2018 were included in this review. Totally, nine extracts with IC_{50}<4 exhibited the most inhibitory effect on breast cancer cell lines. This investigation has highlighted the fact that plant extracts have the potential to act as promising anticancer agents, making them appropriate components to be applied for chemoprevention or cancer treatment in case the researchers would find the right plant, the right solvent and the right fraction for the right disease.

KEYWORDS: Plant extraction; breast cancer; cytotoxicity; MCF7; SKBR3.

1. INTRODUCTION

Breast cancer death rates are growing around the world due to the chemoresistance and chemo-related side effects. Heterogeneity in breast cancer arises from various cellular and molecular biology of this cancer, as more than 50 different breast cancer cell types are currently developed [1].

As the result of early studies having been conducted on cell lines of breast cancer, the understanding upon the molecular mechanisms involved in this cancer has been considerably developed [2].

A source of homogeneous cells with similar molecular characteristics is a valuable tool to evaluate various molecular mechanisms once affected by an external agent [2]. Cell lines could be used as a primary model for predicting the effects of a drug or a plant extract on a particular type of cancer [3]. This cell line-based approach has been widely used in large and small laboratories for the initial and inexpensive evaluation of plant extracts, particularly herbal medicines on various cancerous cells.

Herbal medicine as an imperative branch of complementary and alternative medicine has increasingly grown in the last decade for cancer-related goals [2], making them a reliable means to increase efficacy and reduce toxicity associated with chemotherapy in different malignancies [1, 4]. Many experiments have demonstrated that natural products can effectively regulate proliferation, differentiation and expression of breast cancer cells *in vitro* and *in vivo* [5].

The present review article is an effort to indicate cytotoxic activity of herbal extracts on the commonly used breast cancer cell lines, MCF7 and SKBR3, introducing the most effective plant extracts for further herb-related researches and also *in vivo* experiments. This study has summarized the amount of cytotoxicity, family, used parts and growth region of studied plants.

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2. RESULTS

2.1. Literature search

Initial database searches provided 341 eligible articles within the literature for inclusion. Then, we removed 19 duplicate ones and 41 other abstracts, mostly due to a lack of inclusion criteria, and finally the full texts of 281 articles were evaluated, among them 46 articles were excluded after reviewing the full texts, mainly because of IC_{50} unavailability. Overall, 235 articles in which 192 of them included MCF7 cell line and 43 of them involved SKBR3 cell line data provided the suitability criteria to be reported in this study. Finally, 295 plant extracts have been screened in this review.

2.2. Most commonly used breast cancer cell lines in *in vitro* studies

Initially, our goal was to investigate the effect of plant extracts on all breast cell lines. Therefore, we gathered the list of breast cancer cell lines from ATCC website. Then, we started exploring experiments on these cell lines with the aim of investigating the effect of plant extracts against them. Our findings showed that more than 60% of herb-effected studies have conducted on MCF7 and SKBR3 cell lines (Figure 1). MCF7, as the most commonly used breast cancer cell line, have provided an efficacious *in vitro* model to study the effectiveness of plant extracts. Therefore, we focused on these two cell lines (MCF7 and SKBR3) to continue our study.

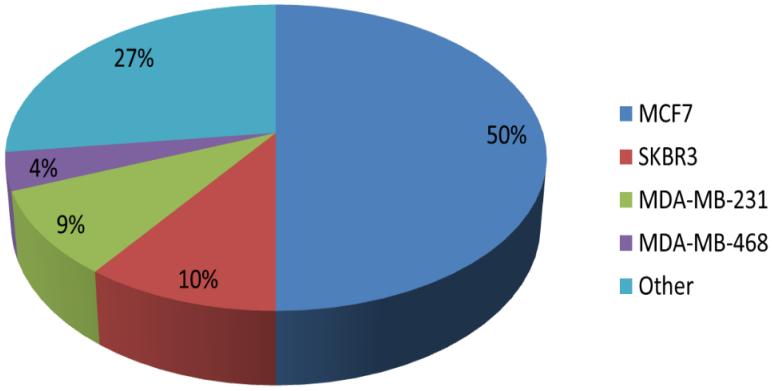

Figure 1. Most commonly used breast cancer cell lines in *in vitro* studies.

2.3. Cytotoxicity Evaluation

In this study, we evaluated the *in vitro* cytotoxic activity of 235 medicinal plants against MCF7 and SKBR3 cells. Cytotoxicity was evaluated by the IC_{50} value. The American National Cancer Institute assigns a limit (IC_{50} value 20 and 4 µg/ml for 48-72 h incubation, respectively) for the significant cytotoxic effect of a promising anticancer product [6]. Therefore, we investigated plant extracts with $IC_{50} \leq 4$ µg/ml as the most effective compounds. Accordingly, *Cassia garrettiana* (IC_{50}: 0.02 µg/ml) presented the highest cytotoxic effect on MCF7 cells, followed by *Allium sativum* (IC_{50}: 0.12 µg/ml) and *Centratherum anthelminticum* (L.) Kuntze (IC_{50}: 0.39 µg/ml) and the least cytotoxicity was noticed in *Muscari comosum* (IC_{50}: 9.13 mg/ml). On the other hand, *Garcinia morella* Desr (IC_{50}: 2.18 µg/ml) displayed the highest cytotoxic effect on SKBR3 cells which is followed by *Phellodendron amurense* tree (IC_{50}: 2.5 µg/ml) and *Ziziphus jujube* (IC_{50}: 3.7 µg/ml) and the least cytotoxicity was observed in *Cichorium intybus* (IC_{50}: 300 µg/ml).

2.4. India has the most researches for the herbal treatment on MCF7 and SKBR3

India has published the highest number of articles (75 articles) in the field of herbal treatment on breast cancer cell lines. Iran (30 articles) and China (17 articles) stand in the second and the third place, respectively.

3. DISCUSSION

According to plant screening program (US NCI), crude extracts and pure compounds can be considered as cytotoxic agents against cancerous cells if they exhibit IC_{50} value less than 20 and 4 µg/ml after 48-72 h incubation, respectively [7]. Accordingly, we decided to highlight species with the most cytotoxic effect. Therefore, we investigated plant species with an IC_{50} value less than 4 µg/ml.

3.1. Promising anticancer plant extracts against MCF7

3.1.1. Cassia garrettiana (Cassigarol E) (IC_{50}: 0.02 µg/ml)

Cassia garrettiana has been reported to show anti-fungal, anti-tumor and anti-metastatic activities. Ethanol extract of *C. garrettiana* heartwood has displayed marked anti-cancer effect at the concentration of 25 µg/mL against MCF7 cells and Cassigarol E isolated from *C. garrettiana* induced remarkable cytotoxicity against MCF7 whereas other herbs with more phenolic and flavonoids components did not exhibit such anticancer effects [8].

3.1.2. Allium sativum (IC_{50}: 0.12 µg/ml)

Garlic, also known as *Allium sativum*, is a rich source of organosulfur compounds. It has previously been demonstrated to be active as an anti-thrombotic, hypolipidemic, anti-microbial, hypoglycemic, anti-arthritic, and anti-oncogenic. It has been reported that a small dose (0.25 µg/ml) of crude garlic extract can inhibit the proliferation of breast cancer cells by 80–90%. Previous studies demonstrated that garlic has the potential to exert cytotoxic effects against multiple cancerous cells not just specific malignancies [9].

3.1.3. Centratherum anthelminticum (IC_{50}:0.39 µg/ml)

Centratherum anthelminticum (L.) Kuntze seeds (known as black cumin) exhibited pharmacological properties such as anti-inflammatory, anti-viral, anti-fungal, anti-microbial and anti-diabetic effects. It has recently been reported that vernodalin, the predominant compound of the chloroform fraction of *C. anthelminticum*, possessed significant cytotoxic activity against the breast cancer (MCF7), nasopharynx (KB), ovarian cancer (CAOV-3) and melanoma (Sk-mel 28) cell lines. Therefore, vernodalin can be considered as the responsible agent in the cell growth inhibition in cancer, although further researches are needed to verify vernodalin as a potential cytotoxic compound [10].

3.1.4. Magydaris tomentosa (IC_{50}: 0.94 µg/ml)

Magydaris tomentosa has been reported to display anti-bacterial, anti-coagulant, anti-proliferative and also cytotoxic activities. Petroleum ether extract of *M. tomentosa* flowers has been shown to result in noticeable anti-cancer activity at concentration of 0.94 µg/mL against MCF7 cells. Xanthotoxin, xanthotoxol, isopimpinellin, and bergaptene isolated from the *M. tomentosa* have been found to be cytotoxic on MCF7 cells [11].

3.1.5. Ferula gummosa (IC_{50}: 1 µg/ml)

Ferula gummosa is used for stomach pain, epilepsy and also as a wound-healing remedy. Ethanolic extract of *F. gummosa* gum has been shown to induce significant anti-cancer activity at concentration of 1 µg/ml against MCF7 cells. Isolated compounds from the *F. gummosa* including coumarins, terpenoids and alkaloids induce high cytotoxicity against MCF7 cells [12].

3.1.6. Piper cubeba (IC_{50}: 2.72 µg/ml)

Piper cubeba, known as tailed pepper, has demonstrated anti-inflammatory, anti-proliferative, anti-type IV allergic, anti-leishmanial and anti-hepatitis C virus. A concentration of 2.72 µg/ml from *piper cubeba* methanol extract fraction has been shown to possess significant anticancer effect against MCF-7 cell line. Cubebin, as the main cytotoxic content of the extract has been displayed to trigger anti-proliferation activity against cancerous cells [13].

3.2. Promising anticancer plant extracts against SKBR3

3.2.1. Garcinia morella Desr (IC_{50}:2.18 µg/ml)

Garcinia morella Desr has been reported to show various activities such as anti-bacterial, anti-fungal, anti-inflammatory, anti-oxidative and anti-cancer effects. Methanol extraction of *Garcinia Morella* fruit has been demonstrated to induce anti-proliferative activity against SKBR3 cells with IC_{50} of 4.56 in the first 24h which was reduced to 2.49 and 2.18 in 48h and 72h, respectively [14].

3.2.2. Phellodendron amurense tree (IC_{50}: 2.5 µg/ml)

Nexrutine a fractioned extract from the *P. amurense* tree has exhibited anti-inflammatory and anti-proliferative activities. Nexrutine has been found to exhibit anti-cancer activity at concentration of 2.5 µg/ml

in SKBR3 cell line. The effect of nexrutine is related to G1 cell cycle arrest and induction of apoptosis. Other studies have also revealed that nexrutine treatment plays an important role in the inhibition of cell proliferation in various cancers [15].

3.2.3. Ziziphus jujube (IC_{50}: 3.7 µg/ml)

Ziziphus jujube has been used for curing various diseases such as digestive disorders, weakness, liver complaints, obesity, urinary troubles, diabetes, skin infections, fever, pharyngitis, bronchitis, anemia, diarrhea, insomnia and cancer. The n-hexane (ZE1), chloroform and methanol extracts of *Ziziphus jujube* fruit have inhibited cell viability by 50% at the concentration of 3.7 µg/ml in SKBR3 cells. The anti-cancer activity of *Ziziphus jujube* is due to triterpenic acids in the extract. It has also induced apoptosis in SKBR3 breast cancer cells [16].

Nowadays drug resistance is increasing in cancer cells, making the treatment approaches more complicated. Medicinal herbs with their anti-cancer property could be applied as a complementary drug in treatment of malignancies [17]. Studying the plant extracts helps us recognize their effective compounds. Investigation through molecular mechanism of herbs could lead to identification of intracellular function and also recognition of new targets for cancer treatment [18, 19].

One of the mechanisms involved in cancerous cells, is the overexpression of HER2 and ER which are highly expressed in SKBR3 and MCF7 [20, 21]. *Cassia garrettiana* and *Phellodendron amurense* insert their cytotoxic effect with the least IC_{50} (2.5 µg/ml and 0.02 µg/ml) on MCF-7 and SKBR3, respectively. The difference between IC_{50} in MCF-7 and SKBR3 could be related to the difference in expression of HER2 and ER in these cell lines. However, further study is needed for investigation through expression of HER2 and ER. Moreover, a comparison upon the effect of these extracts could demonstrate whether they are effective on HER2 or ER. The assessment of synergistic and antagonistic effect of different plant extracts or their effective compounds could result in discovering new potential anti-cancer combinations [22].

4. CONCLUSION

Comparing the impacts of 295 plant extracts having been screened in this review revealed efficacy of 9 plant extracts with IC_{50} value less than 4 µg/ml for the most cytotoxicity against breast cancer cells, so these extracts can be used for the isolation of their pure components with anti-tumor potential for chemoprevention or cancer treatment. We suggest studying these cytotoxic extracts against other breast cancer cell lines to provide additional data regarding their anti-cancer properties. However, analyzing the effect of these natural products on normal cells is still required to elaborate the effective dose with the least toxic effect. Future studies could focus on the use of different solvents for extraction of the phytochemicals in distinct parts of the plants and finding out new compounds through combining various fractions of these 9 plant extracts to discover more cytotoxic agents with the least adverse effects.

5. MATERIALS AND METHODS

5.1. Studies eligible for review

PubMed and Google Scholar databases were searched using the terms 'plant extract', 'breast cancer', 'breast cancer cell line', 'MCF7 or MCf-7', 'SKBR3 or SKBR-3', 'IC_{50}', 'cytotoxicity' with English language restriction. In animal studies, those which had no effect or did not present their results with IC_{50} value were excluded. Studies were considered eligible if a) studied cell line was breast cancer (MCF7 and SKBR3); b) treatment substance was one of the plant extract or its derivatives; c) cytotoxicity result was reported in the form of IC_{50}; d) cytotoxicity result was reported in the µg/ml; e) the cytotoxic effect of the extract was investigated using MTT assay, Trypan Blue exclusion assay and Sulforhodamine B (SRB) assay.

5.2. Data abstraction

Titles and abstracts of collected articles were screened and the full text of selected literatures were evaluated. The search ended in July 2018. The findings were independently assessed by two of the authors (ND and MD).

5.3. The main characteristics of the articles

The selected articles were screened and specific characteristics of the studies were recorded. These characteristics include: plant species and family, type of breast cancer cell line (*e.g.* MCF7 or SKBR3), used

plant part in the study (*e.g.* root, leaf…), growth region of plant, the kind of effect and IC_{50} value. This process has been summarized in Table 1 and 2. To minimize selection bias, screening of the studies was independently performed by two of the authors (PM and OY).

Table 1. List of plants screened for cytotoxicity in mcf7 cell line.

Plant family	Plant species	Local name	Plant part	Extract	IC_{50} (µg/ml)	Region	Ref
Acanthaceae	*Strobilanthes crispus*	Pecahbeling	L	ND	8.5*	Malaysia	[23]
	Phlogacanthus thyrsiformis	Chuwa	L	ND	49	India	[24]
	Phlogacanthus thyrsiformis	Chuwa	L, I	ND	52.34	India	[24]
	Thunbergia laurifolia		A	ND	843*	Thailand	[25]
	Andrographis paniculata	Rang Chuet	L	M	57.33	India	[26]
	Eremomastax speciosa		L	M	44	Cameroon	[27]
Amaranthaceae	*Beta vulgaris*	Beet	R	ND	70**	ND	[28]
	Beta vulgaris	Beet	R	ND	300***	Japan	[29]
	Beta vulgaris	Beet	R	E	25µM	France	[30]
	Beta vulgaris	Beet	R	M	272.9µM	India	[31]
	Achyranthes aspera	Puthkanda	R	E	>500	India	[32]
Amaryllidaceae	*Allium sativum*	Garlic	ND	ND	0.125	USA	[9]
	Allium atroviolaceum		Bu	ND	75.7***	Iran	[33]
	Allium hirtifolium	Iranian Shallot	ND	Ch	24***	Iran	[34]
	Allium autumnale		Bu, St	ND	5000**	Cyprus	[35]
Anacardiaceae	*Sclerocarya birrea*	Maroela	S	Ac	87.6*	Africa	[36]
	Mangifera indica	Mango	P	ND	ND	Egypt	[37]
	Mangifera indica	Mango	ND	ND	15	Malaysia	[38]
	Mangifera zeylanica	Etamba	B	H	87.64	Sri Lanka	[39]
	Rhus verniciflua		B	E	ND	East Asia	[40]
	Buchanania lanzan	charoli	B	ND	100	India	[41]
Annonaceae	*Annona muricata*	Soursop	L	E	14.67	Indonesia	[42]
Apiaceae	*Daucus carota*		ND	ND	30**	Lebanon	[43]
	Magydaris tomentosa		I	PE	0.94***	Italy	[11]
	Ferula gummosa		S,G	E	1***	Iran	[12]
	Anethum graveolens L.		A	Ess. oil	67	Tajikistan	[44]
	Foeniculum vulgare		L,S	ND	>100	South Africa	[45]
	Petroselinum sativum		S	ND	100*	KSA	[46]
	Ferula szowitsiana DC		W	M	>300	Iran	[47]
	Ferula hirtella Boiss		A	M	186	Iran	[47]
	Ferula oopoda Boiss		W	M	260	Iran	[47]
	Ferula gummosa		ND	E	1765	Iran	[48]
	Glehnia littoralis		R	ND	ND	Pacific countries	[49]
	Laserpitium latifolium L.		R, rh	Ch	>184	Serbia	[50]
	Centella asiatica		W	M	47	Cameroon	[27]
Apocynaceae	*Holarrhena floribunda*		L	M	250**	Nigeria	[51]
	Cistus monspeliensis		L	H	ND	Tunisia	[52]
	Cistus villosus		L	H	ND	Tunisia	[52]
	Rauwolfia serpentina	Sarpagandha	R	E	>500	India	[32]
	Picralima nitida		R	ND	22.76	Nigeria	[53]
	Wrightia tinctoria	Dudhi	B	ND	10	India	[41]
	alistonia scholaris		L	Al	18.5	India	[54]
Aquifoliaceae	*Ilex paraguariensis*		L,St	M	ND	Brazil	[55]
Arecaceae	*Phoenix dactylifera*	Date	Po	M	15.1**	Egypt	[56]
	Euterpe oleracea	Açaí	S	ND	40***	Brazil	[57]
	Phoenix dactylifera	Date palm	S	ND	>80	India	[58]
	Areca catechu		L	M	1461pg/ml	India	[59]
Aristolochiaceae	*Aristolochia indica*	Isharmul	R	E	>500	India	[32]
Asparagaceae	*Agave americana*		F	A	775.1 pg/ml	India	[59]
Asteraceae	*Sonchus oleraceus*		L	ND	ND	Egypt	[37]
	Artemisia princeps		L	A, Sm	ND	South Korea	[60]
	Centratherum	Kalajiri	S	C	0.39	India	[10]
	anthelminticum		R	ND	5***	Iran	[61]
	Arctium lappa	Elephant's	L	E	15***	Malaysia	[62]
	Elephantopus scaber	foot	A	ND	10***	Iran	[63]

Plant family	Plant species	Local name	Plant part	Extract	IC_{50} (µg/ml)	Region	Ref
	Chamaemelum nobile		L, I	M	17.11	Portugal	[64]
	Achillea millefolium L.	Yarrow	L	ND	23.77	Andes	[65]
	Smallanthus sonchifolius	Yacon	A	ND	23.82	Andes	[24]
	Eupatorium odoratum L.	Kalijhar	L	ND	58.869	India	[24]
	Artemisia indica	Titeypati	L	M	2.62µM	Bangladesh	[66]
	Blumea lacera	Kukursunga	L	PE	80 µM	India	[67]
	Elephantopus scaber		W	E	>500	India	[32]
	Cichorium intybus	Kasni	L	ND	ND	Italy	[68]
	Cynara cardunculus		L	ND	ND	Italy	[68]
	Picris hieracioides		L	ND	ND	Italy	[68]
	Sonchus oleraceus	Rush crimps	I	M	15.78	Jordan	[69]
	Inula viscosa		ND	ND	200*	Korea	[70]
	Ixeris dentatatum		A	M	ND	Iran	[71]
	Achillea vermicularis						
Berberidaceae	*Berberis aristata*		St	M	220	India	[72]
Boraginaceae	*Borago officinalis*	Borage	L	ND	ND	Italy	[68]
	Echium vulgare		L, I	ND	ND	Italy	[68]
Brassicaceae	*Lepidium sativum*	Cress	L	ND	ND	Italy	[68]
	Lepidium sativum	Cress	S	A	ND	KSA	[73]
	Brassica oleracea	Broccoli	S	ND	96.7	Brazil	[74]
Burseraceae	*Commiphora guidottii*	Opoponax	ND	ND	66.91	UK	[75]
Caesalpiniaceae	*Cassia garrettiana*	Samae-sarn	Wo	E	0.021	Thailand	[8]
Capparaceae	*Capparis sicula*	Caper	L, F	ND	ND	Italy	[68]
Caprifoliaceae	*Nardostachys jatamansi*		R	ND	60	India	[76]
Caricaceae	*Carica papaya*	Papaya	S, L, F	ND	>200	Malaysia	[77]
Cistaceae	*Tuberaria lignose*	Sweet	ND	A	135.1	Portugal	[78]
	Cistus salviifolius		L, I	M	5.11	Tunisia	[79]
Clusiaceae	*Garcinia mangostana*	Mangosteen	ND	ND	45*	Indonesia	[80]
	Garcinia mangostana	Mangosteen	ND	ND	2.5**	India	[81]
	Garcinia celebica		L	H	60*	Indonesia	[82]
Combretaceae	*Terminalia bellerica*		St	E	9	India	[83]
	Terminalia macroptera		R	M	34	Cameroon	[27]
	Anogeissus latifolia		St, L	E	20.1	India	[83]
Cornaceae	*Cornus mas* L.		F	HA	37**	Iran	[84]
	Alangium salvifolium	Ankol	B	ND	97	India	[41]
Costaceae	*Cortus speciosus*	Betlaure	L	ND	1.32	India	[24]
Crassulaceae	*Rhodiola algida*		rh	A	>450***	China	[85]
Cruciferae	*Farsetia aegyptia*		L	E	17.9	Egypt	[86]
Cucurbitaceae	*Bryonia laciniosa*		L	M,A,Ch	>18	India	[87]
	Momordica cochinchinensis		A	ND	117	Thailand	[88]
	Cucurbita pepo	Pumpkin	S	ND	100**	Austria	[89]
	Citrullus colocynthis	Bitter Apple	F	Alk	17.2	India	[90]
	foetidissima	Utuvishe	St, L	M	>100	South Africa	[90]
Cupressaceae	*Juniperus excelsa*	Ors	F	ND	ND	Iran	[91]
Dilleniaceae	*Dillenia suffruticosa*	Simpoh air	R	ND	17.8**	Malaysia	[92]
	Dillenia suffruticosa	Simpoh air	R	E	36***	Malaysia	[93]
	Dillenia suffruticosa	Simpoh air	w	ND	9.5	Malaysia	[94]
Ebenaceae	*Diospyros lycioides*	Bluebush	L	Ac	63*	South Africa	[95]
Erythroxylaceae	*Erythroxylum cuneatum*		L	ND	31.63	Malaysia	[96]
Euphorbiaceae	*Euphorbia mauritanica*	Gifmelkbos	St, L	ND	100	South Africa	[96]
	Euphorbia hirta		W	ND	ND	Malaysia	[97]
	Jatropha gossypifolia		R	ND	25.55	Nigeria	[53]
	Jatropha curcas		R	ND	36.55	Nigeria	[53]
	Phyllanthus niruri		L	M	84.88	India	[98]
	Manihot utillissima		ND	E	52.49	Malaysia	[41]
Fabaceae	*Dalbergia latifolia* Roxb.	Black	W	M	30	India	[99]
	Saraca indica	Rosewood	B	ND	73.6***	India	[100]
	Indigofera linnaei		A	M	75.9	India	[99]
	Trigonella foenum graecum		S	C	185.6	India	[101]
	Trigonella foenum	Fenugreek	W	ND	65	KSA	[102]
	Glycine max	Fenugreek	S	ND	400***	China	[103]
	Sesbania grandiflora		ND	Ac	0.47	China	[104]
	Cassia siamea		B	Al	7	India	[41]
	Senna siamea	Agasti	L	M	>20	India	[105]
	Gliricidia sepium	Cassod Tree	ND	M	97	Cameroon	[27]
	Glycyrrhiza uralensis		ND	E	26.79	Philippine	[106]
	Glycyrrhiza uralensis						

Plant family	Plant species	Local name	Plant part	Extract	IC_{50} (µg/ml)	Region	Ref
	Caesalpinia hymenocarpa		R	ND	>500	China	[107]
		Licorice	R	ND	50	Korea	[108]
		Licorice Krajai	St	A	511.34	Thailand	[109]
Ginkgoaceae	*Ginkgo biloba*		L	Al, A	2143.3*	Iran	[110]
Gnetaceae	*Gnetum gnemon* L.	Melinjo	F,S,L	ND	37.3	Japan	[111]
Graminae	*Bambusa bambos*		L	ND	ND	India	[112]
Hydrangeaceae	*Dichroa febrifuga*	Basak	R, L	ND	19.55	India	[24]
Hypericaceae	*Hypericum perforatum*	St John's Wort	ND	ND	5*	Iran	[113]
Icacinaceae	*Pyrenacantha staudtii*		L	ND	37.36	Nigeria	[53]
Iridaceae	*Crocus sativus*	Saffron	ND	E	ND	Oman	[114]
Juglandaceae	*Carya illinoinensis*	pecan nut	ND	ND	74.11	ND	[115]
Lamiacae	*Leucas Indica*		I	M	7.7	India	[116]
	Melissa officinalis L.		L,St	ND	21.7	Syria	[117]
	Orthosiphon stamineus		L	EA	ND	Iran	[118]
	Perovskia abrotanoides		F	ND	400	Iran	[119]
	Rosmarinus officinalis	Rosemary	L	M,E,A	ND	Spain	[120]
	Calamintha officinalis		L	ND	ND	Iran	[121]
	Origanum vulgare	Basla-ghas	A	E	250	India	[32]
	Hyssopus officinalis	Jufa	A	E	200	India	[32]
	Orthosiphon stamineus		L	ND	28.5	India	[118]
	Mentha aquatic	Mint	L	ND	ND	Italy	[68]
	Lavandula dentate		W	E	39	KSA	[122]
	Ajuga bracteosa	Neelkanthi	A	M	10	India	[123]
	Teucrium sandrasicum		L,I	M	80.7	Turkey	[124]
Lauraceae	*Persea declinata*		B	ND	16.68	Malaysia	[125]
Leguminosae	*Acacia catechu*		F	E	22.8	India	[83]
	Mimosa pudica		L	M	35.52	India	[98]
Liliaceae	*Aloe vera*		L	M	54.97	India	[98]
	Muscari comosum	Lampascioni	Bu	ND	9130	Italy	[126]
Linaceae	*Linum usitatissimum*	Flax	S	ph	ND	ND	[127]
	Linum usitatissimum	Flax	R	E	500	Germany	[128]
Loranthaceae	*Dendrophthoe pentandra*		L	ND	20	Malaysia	[129]
	Dendrophthoe falcata Ettingsh		St	E,A	107,90	India	[130]
Lythraceae		Pomegranate					
	Punica granatum	Pomegranate	F	ND	12.85	ND	[131]
	Punica granatum		F	ND	ND	California	[132]
	Punica granatum	Pomegranate	F	Poly.ph	40	Israel	[130]
	Punica granatum		F	ND	377.88*	Thailand	[133]
	Lagerstroemia speciosa	Pomegranate	L	ND	500	India	[134]
Malvaceae	*Hibiscus cannabinus* L.	Kenaf	S	ND	250	India	[135]
	Grewia nervosa		L	ND	ND	India	[136]
	Malva sylvestris	Mallow	L	ND	ND	Italy	[68]
	Malva sylvestris	Gulkhair	W	E	400	India	[32]
Meliaceae	*Azadirachta indica*	Neem	L	ND	17.8	ND	[137]
	Azadirachta indica	Neem	L	E	350***	UAE	[138]
	Amoora rohituka	Rohera	St	E	41	Bangladesh	[139
	Amoora rohituka	Rohera	St	EA	3.8–6.9	India	[140]
	Dysoxylum caulostachyum		L	EA	78	Indonesia	[82]
	Ekebergia senegalensis		ND	M	13.5	Cameroon	[27]
	Toona sinensis		R	ND	ND	China	[141]
Mimosideae	*Albizia Amara* Roxb.	Munja	L	EA	36.3	India	[142]
Moraceae	*Ficus carica*	Fig	F	ND	62.5*	India	[143]
	Ficus drupacea		St	ND	16.28	Egypt	[144]
	Ficus hispida	Ma Dau Plong	St	M	50	Thailand	[145]
	Broussonetia papyrifera		L,B,F	M	87.5	India	[146]
	Morus alba	White Mulberry	L	ND	9.2	India	[147]
	Morus alba		L,R	ND	50	Korea	[148]
	Artocarpus camansi	White Mulberry	L	E	9.58	Philippine	[106]
	Artocarpus heterophyllus		B	ND	35	India	[41]

Plant family	Plant species	Local name	Plant part	Extract	IC_{50} (µg/ml)	Region	Ref
		Kamansi Kathal					
Moringaceae	*Moringa oleiferna*		S	Ess. Oil	226	KSA	[149]
	Moringa oleiferna		L	E	26.4	India	[83]
Myrsinaceae	*Maesa macrophylla*	Boghati	B,F,L	ND	74.33	India	[24]
Myrtaceae	*Psidium guajava* L.	Red Guava	F	ND	5.96	Brazil	[150]
	Syzygium aromaticum L.	Clove	ND	E, Ess. oil	16.7,17.6	Indonesia	[151]
	Pimenta dioica	Allspice	B		**	USA	[152]
	Calyptranthes tricona		L	ph	100	South Brazil	[153]
	Eugenia aquea		L	ND	ND	Indonesia	[82]
				H	24*		
Nitrariaceae	*Peganum harmala* L.	Espand	S	ND	25***	Iran	[154]
Oleaceae	*Olea europea*	Olive	L	ND	ND	Egypt	[37]
Orchidaceae	*Anoectochilus formosanus*		W	EA	80	Taiwan	[155]
Papavaraceae	*Argemone Mexicana*		L	M	1.35	India	[156]
Papilionaceae	*Ononis hirta*		A	M	27.96	Jordan	[69]
Pedaliaceae	*Sesamum indicum*		S	ND	ND	Taiwan	[157]
Pinaceae	*Pinus radiata*		B	ND	65	South Korea	[158]
Piperaceae	*Piper cubeba*	Tailed pepper	S	M	2.69	Thailand	[13]
	Piper nigrum	Black pepper	F	E	14.4	Brazil	[159]
Plantaginaceae	*Limnophila aromatica*		L	M	>20	India	[105]
Plumbaginaceae	*Plumbago zeylanica*		L	M	200	India	[160]
Poaceae	*Triticum aestivum*		S	A	ND	UAE	[161]
Polygonaceae	*Polygonum odoratum*		L	M	6.01	India	[105]
Portulacaceae	*Portulaca oleracea*	Kulfa	W	E	220	India	[32]
Proteaceae	*Protea elliotii*		ND	M	87	Cameroon	[27]
Pteridaceae	*Pteris vittata*		F	ND	153.9	India	[162]
Ranunculaceae	*Clematis vitalba*	Old Man's Beard	L	ND	ND	India	[68]
	Nigella sativa		S	A, Al	2.72	Egypt	[163]
	Coptidis rhizoma	Huanglian	rh	ND	10**	USA	[164]
Rhamnaceae	*Ziziphus Jujube*		F	ND	500	Iran	[165]
	Frangula		R, rh	ND	20µM***	Iran	[166]
Rosaceae	*Rubus fairholmianus*		R	ND	ND	India	[167]
	Fragaria x ananassa	Strawberry	F	ph	2000*	Italy	[168]
Rubiaceae	*Hedyotis corymbosa*	Pearl grass	W	E	52.33**	Indonesia	[42]
	Galium Aparine	Yogurt herb	ND	ND	503	Turkey	[169]
	Rubia cordifolia	Manjith	R	E	380	India	[32]
	Rubia cordifolia	Manjith	L	M	200	India	[160]
	Psychotria valentonic		L	A	23	Indonesia	[82]
	Gardenia aqualla		ND	M	87	Cameroon	[27]
Rutaceae	*Clausena excavate*	Cherek Hitam	R,SB	ND	30	Malaysia	[170]
	Glycosmis pentaphylla		L	ND	50	India	[171]
	Limonia acidissima		F	ND	272.9	India	[172]
Salicaceae	*Populus sp.*		ND	E	25**	China	[173]
Salvadoraceae	*Salvadora persica*		B	PE	44.3	Egypt	[174]
Sapindaceae	*Nephelium lappaceum* L.		R	ND	25µM	China	[175]
Sapotaceae	*Vitellaria paradoxa*		ND	M	24	Cameroon	[27]
Scrophulariaceae	*Scrophularia oxysepala*		L, St	ND	100	Iran	[176]
	Scrophularia Variegata		A	ND	200**	Iran	[177]
Solanaceae	*Solanum mauritianum*	Bug weed	ND	ND	24.8	India	[178]
	Solanum lycocarpum	Fruit-Of-Wolf	F	Alk	40	Brazil	[179]
	Datura metel	Thorn Apple	St, L	M	62.5	India	[180]
	Solanum lycopersicum	Tomato	F	ND	ND	Iran	[181]
	Solanum nigrum		L	A	ND	India	[182]
	Solanum nigrum		L	ND	100*	Taiwan	[183]
	Withania somnifera		R	ND	ND	Egypt	[184]
	Physalis peruviana		F	ND	NE	Turkey	[185]
	Stemona sessilifolia	Altın çilek	ND	Non-alk	200	China	[186]
Symplocaceae	*Symplocos racemosa*	Lodhra	St	E	500	India	[32]
Taxaceae	*Taxus chinensis*	Pilger, Chinese yew	R,B,L	ND	ND	China	[187]

Plant family	Plant species	Local name	Plant part	Extract	IC_{50} (µg/ml)	Region	Ref
Theaceae	*Camellia sinensis*		L	ph	172.2	China	[188]
	Camellia oleifera		ND	ND	28*	China	[189]
Urticaceae	*Urtica Dioica* L.		A	A	34	Turkey	[190]
Verbenaceae	*Premna odorata*	Alagaw	L,B	E	4.3	Philippine	[106]
Vitaceae	*Cissus populnea*		ND	M	>100	Cameroon	[27]
Zingiberaceae	*Alpinia scabra*	Lengkuas raya	L	H	15.30**	Malaysia	[191]
	Curcuma phaeocaulis		rh	E	75	China	[192]
	Alpinia galangal	Galangal	rh	ND	500	Iran	[193]
	Alpinia offcinarum	Lesser galangal	rh	ND	ND	Korea	[194]
Zygophyllaceae	*Fagonia cretica*		W	A	1000	UK	[195]
	Tribulus terrestris L.		L	ND	15	Bulgaria	[196]

ND: Not Determined; NE: no effect; *: 24h; **: 48h; ***: 72h

Column 4

A: Arial part; B: Bark; Bu: Bulb; F: Fruit; G: Gum; I: Inflorescence; L: Leaves; P: Peel; Pc: Pericarp; Po: Pollen; Pu: Pulp; R: Root; rh: rhizome; S: Seed; St: stem; Sh: Shell; T:Twig; W:Whole plant; Wo: Wood

Column 5

A: Aqueous; Ac: Acetone; Al: Alcoholic; Alk: Alkaloid; C: Chloroform; De: Diethyl ether; Dm: Dichloromethane; E: Ethanolic; EA: Ethyl acetate; H: Hexane; HA: hydroalcoholic; M: Methanolic; PE: petroleum ether; Ph: Phenolic

Table 2. List of plants screened for cytotoxicity in SKBR3 cell line.

Plant family	Plant species	Local name	Plant part	Extract	IC_{50} (µg/ml)	Region	Ref
Acanthaceae	*Thunbergia laurifolia* L.	ND	L	E	106.88	Thailand	[197]
Amaranthaceae	*Spinacia oleracea*	ND	ND	ND	ND	Korea	[198]
Amaryllidaceae	*Allium cepa*	ND	ND	ND	ND	Korea	[198]
Anacardiaceae	*Tapirira guianensis*	Jobillo, Tapaculo	L, B	E	ND	Venezuela	[199]
Annonaceae	*Annona muricata*	Soursop	L	AE	202.33	Kenya	[200]
	Annona muricata	Soursop	S,PU	ND	>100	Venezuela	[202]
	Xylopia aromatica	Fruta de burro	L,B	E	ND	Venezuela	[199]
Apiaceae	*Daucus carota* ssp. *sativus*	Black carrots	S	E	38.74-217.36	Turkey	[202]
Apocynaceae	*Cerbera odollam*	Cerbera mangha	L	A	ND	India	[203]
	Macoubea guianensis	Ba-hee'-a	L,B	E	NE	Venezuela	[199]
	Mandevilla scabra	Clavo huasca	W	E	NE	Venezuela	[199]
Aracaceae	*Phoenix paludosa*	Mangrove date palm	L	H,C,EA,M	75.39**	Sri Lanka	[204]
Arecaceae	*Euterpe precatoria* Mart.	Manaca, Palmito	L,St	E	ND	Venezuela	[199]
Asteraceae	*Silybum marianum*	ND	ND	ND	203.38***	Iran	[205]
	Cichorium intybus	ND	R	M	300***	Iran	[206]
Bignoniaceae	*Jacaranda copaia*	Gualanday	L,B	E	ND	Venezuela	[199]
Boraginaceae	*Heliotropium indicum*	ND	W	E	34.50	Thailand	[197]
Burseraceae	*Commiphora guidottii*	ND	ND	E	70.62	UK	[207]
	Protium heptaphyllum	Currucay	L,T,B	E	NE	Venezuela	[199]
	Protium unifoliolatum	Cara~na	L,B	E	NE	Venezuela	[199]
Clusiaceae	*Garcinia morella* Desr	Gaertn	F	M	2.18***	India	[14]
Combretaceae	*Terminalia chebula* Retz.	Kot Phung Pla	ND	M	13.9-73.2	Thailand	[208]
Compositae	*Chrysanthemum zawadskii* subsp. *Coreanum*	ND	Fl	ND	ND	Korea	[209]
	Chrysanthemum zawadskii var. tenuisectum						
	Rudbeckia laciniata var. hortensis						
Convolvulaceae	*Erycibe elliptilimba*	ND	St	E	ND	Thailand	[210]
Costaceae	*Costus scaber*	Ca~na agria	L,St	E	ND	Venezuela	[199]
Cucurbitaceae	Tubeimu (*Rhizoma Bolbostemmatis*)	ND	W	A	ND	China	[211]

Plant family	Plant species	Local name	Plant part	Extract	IC_{50} (µg/ml)	Region	Ref
	Trichosanthes cucumerina L.	ND	R	Dm, E	120.22 ± 0.08	Thailand	[212]
	Trichosanthes cucumerina L.	ND	F	De	131	Thailand	[212]
Dillenaceae	*Curatella americana* L.	Chaparro sabanero, Curata	L,B	E	ND	Venezuela	[199]
Euphorbiaceae	*Phyllanthus amarus*	ND	W	E	34.25	Thailand	[197]
	Sauropus androgynus	ND	L	M	26.9 – 45.1	China	[213]
	Croton cuneatus Klotzsch	Mangle de rio	L,B	E	ND	Venezuela	[199]
Fabaceae	*Derris timoriensis* (DC.) *Pittier*	ND	St	A	NE	Thailand	[214]
Ginger	*Curcuma longa*	Turmeric	Rh	ND	ND	Korea	[215]
	Curcuma longa	Turmeric	Rh	ND	20µM***	Korea	[216]
Gnetceae	*Gnetum nodiflorum Brongn.*	Tap-kam'	T,L	E	ND	Venezuela	[199]
Guttiferae	*Garcinia mangostana*	Mangosteen	PC	M	16.45	Thailand	[217]
	Garcinia mangostana	Mangosteen	PC	A	54.57	Thailand	[218]
Lamiaceae	*Scutellaria barbata*	ND		A	ND	USA	[219]
	Scutellaria barbata	ND	A	A	ND	USA	[220]
	Scutellaria barbata	ND	A,L,St A	A,Al	ND	USA	[221]
	Scutellaria barbata	ND	St	A	ND	USA	[222]
	Orthosiphon aristatus	ND		A	NE	Thailand	[214]
Lecythidaceae Poiteau	*Eschweilera tenuifolia*	Coco de mono	L,T,B	E	ND	Venezuela	[199]
Malvaceae	*Theobroma cacao*	ND	ND	ND	ND	Spain	[223]
Meliaceae	*Melia azedarach*	ND	F	ND	>100	Japan	[224]
	Azadirachta indica var. siamensis	ND	B,L,R, S	M	8.7- 100	Japan	[225]
Menispermaceae	*Stephania venosa Spreng*	ND	Bu	E	76.50	Thailand	[197]
Moraceae	*Ficus hispida* L.f	ND	F	H,M,EA, Bu,A	H: 19.2 M: 93.2 EA: 25.0 Bu: 100 A: >100	China	[226]
Myrsinaceae	*Ardisia elliptica Thunb*	ND	F	E	103.25	Thailand	[197]
myrtaceae	*Pimenta dioica*	Allspice,	Br	A	≤ 100	USA	[153]
	Pimenta dioica	Allspice	Br	A	≈ 100	USA	[227]
Oleaceae	*Olea europaea*	ND	L	ND	ND	Spain	[228]
	Olea europaea	ND	LF	Ac	ND	Greece	[229]
Passifloraceae	*Passiflora foetida*	ND	A	E	54.75	Thailand	[197]
Phyllanthaceae	*Phyllanthus emblica*	ND	R	A	NE	Thailand	[214]
Polypodiaceae	*Polypodium aureum* L.	Calaguala	L,St	E	NE	Venezuela	[199]
Rhamnaceae	*Ziziphus jujube*	ND	F	C,E,MH	3.70-14.06	Italy	[16]
	Frangula	ND	ND	ND	25 M	Iran	[230]
Rhodomelaceae	*Laurencia*	ND	ND	ND	ND	ND	[231]
Rubiaceae	*Morinda citrifolia* L	ND	F	E	120.00	Thailand	[197]
	Oldenlandia diffusa	ND	W	E	NE	Italy	[232]
	Litosanthes biflora Bl.	ND	St	A	NE	Thailand	[214]
	Psychotria poeppigiani	Labios de fuego	F,L,T	E	NE	Venezuela	[199]
Rutaceae	*Aegle marmelos*	ND	F	E	144.00	Thailand	[197]
	Limonia acidissima	ND	F	E	ND	India	[233]
	Phellodendron amurense	ND	ND	ND	ND	USA	[234]
	Phellodendron amurense						

Plant family	Plant species	Local name	Plant part	Extract	IC_{50} (µg/ml)	Region	Ref
		ND	ND	ND	2.5	USA	[15]
Siparunaceae	*Siparuna guianensis*	Palo de hormiga	L,T	E	ND	Venezuela	[199]
Smilacaceae	*Smilax glabra* Roxb	ND	St	A	NE	Thailand	[214]
	Smilax china Linn	ND	St	A	NE	Thailand	[214]
	Smilax ovalifolia Roxb.	ND	rh	A	NE	Thailand	[214]
Solanaceae	*Withania somnifera*	Ashwagandha	L	M,H	ND	Japan	[235]
Thymelaeaceae	*Daphne Mucronata* Royle	ND	A	Ch,M,A	ND	Iran	[236]
Trapaceae	*Trapa acornis*	ND	Sh	E	ND	India	[237]
Vitaceae	Grape	ND	S	ND	ND	USA	[238]
	Vitis rotundifolia	Vitis rotundifolia	S	A	ND	USA	[239]
Vochysaceaea	*Vochysia ferruginea*	Too- a-ke	L,T,B	E	NE	Venezuela	[199]
	Aconitum carmichaelii Deb	Fuzi	ND	A	ND	China	[211]
	Rhizoma Bolbostemmatis	Tubeimu	ND	A	ND	China	[211]

ND: Not Determined; NE: no effect; *: 24h; **: 48h; ***: 72h

Column 4

A: Arial part; B: Bark; Br: Berry; Bu: Bulb; F: Fruit; G: Gum; I: Inflorescence; L: Leaves; P: Peel; Pc: Pericarp; Po: Pollen; Pu: Pulp; R: Root; rh: rhizome; S: Seed; St: stem; Sh: Shell; T:Twig; W:Whole plant; Wo: Wood.

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