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REVIEW

Targeting epidermal growth factor receptors and downstream signaling pathways in cancer by phytochemicals

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Abstract Epidermal growth factor receptors (EGFR, HER2, HER3) activate signal transduction pathways involved in cancer proliferation, apoptosis, differentiation, metastasis, and angiogenesis. Their overexpression and activation are associated with unfavorable prognosis of cancer patients. Therefore, they are attractive targets for cancer therapy. Due to the development of drug resistance, therapeutic monoclonal antibodies and synthetic small molecule tyrosine kinase inhibitors directed against EGFR family members may fail with fatal consequences for cancer patients. Medicinal plants raised considerable interest during the past years as valuable resources to develop novel treatment therapies targeting epidermal growth factor receptors and their downstream signal transduction pathways. The present review gives an overview of isolated phytochemicals that inhibit these signaling routes. Inhibitors have been described that down-regulate the mRNA or protein expression of EGFR, HER2, or HER3 or inhibit the phosphorylation of these receptors and/or their downstream signaling kinases. Remarkably, a wealth of in vivo experiments complemented in vitro data, indicating that natural products are also active in living animals bringing this research concept closer to clinical applicability. The combination of receptor-inhibiting natural product with standard anticancer drugs frequently caused increased or even synergistic tumor inhibition in vitro and in vivo. It deserves further evaluation, if and how epidermal growth factor receptor-targeting natural products can be integrated into clinical oncology as well as to define their role for more tumor-specific and individualized tumor therapies.

Keywords Drug resistance · Kinase · Molecular docking · Natural products · Signal transduction

Abbreviations

ART	Artesunate
CET	Cephalotaxine
EGFR	Epidermal growth factor receptor
GBM	Glioblastoma multiforme
HER	Human epidermal growth factor receptor
HHT	Homoharringtonine
NSCLC	Non-small cell lung carcinoma
SCLC	Small cell lung carcinoma

Introduction

Chemotherapy regimens derived from results of clinical trials are valuable for determining optimal treatment options for large populations of patients. However, an individual patient's response to chemotherapy can be very different from the predicted response of the average population, and the reasons for this variation are largely unknown. Several clinical and pathological factors have been identified as having prognostic value of treatment outcome and survival of cancer patients, e.g., tumor size, lymph node and distant metastasis, tumor grade, and, more recently, specific molecular biomarkers. These prognostic factors help to classify the standard risk of

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subpopulations of patients with the same tumor entity, but are still unable to predict the response of specific individuals to therapy. Therefore, there is an urgent need for reliable molecular tests to predict the individual patient's risk of death from the disease irrespective of the treatment (prognostic markers) and sensitivity or resistance to chemotherapy (predictive markers). Such tests are necessary to develop individualized treatment schedules in the future. The field of chemotherapy is currently undergoing a paradigm shift from classical cytotoxic chemotherapy towards targeted therapy with the aim to eradicate tumor cells more efficiently with fewer side effects on normal tissue. Proteins encoded by genes carrying tumor-specific mutations serve as preferential targets for the development of novel drugs in cancer therapy.

It is now well accepted that mutations in three main types of genes contribute to carcinogenesis: oncogenes, tumor suppressor genes, and stability genes. Oncogene activation (gain-of-function mutation) results from point mutations, chromosomal translocation, or gene amplification. Without such mutations, tumors cannot grow (tumor addiction). On the other hand, mutations in tumor suppressor genes are loss-of-function mutations, e.g., missense mutations, chromosomal deletions or insertions, or epigenetic silencing, that allow the tumor to grow unchecked by normal cellular control mechanisms. Stability genes or caretakers including DNA repair genes controlling genomic stability and genes responsible for organizing mitotic recombination and chromosomal segregation. Inactivating mutations in these genes are dangerous because they increase the mutational rate in other genes. Out of the large number of potential targets for targeted chemotherapy, we focus on the epidermal growth factor receptor family in the present overview. Growth factor receptors have a tremendous relevance in cancer biology. Therefore, the therapeutic intervention to silence the function of epidermal growth factors and their related signaling pathways represents a highly attractive approach to improve treatment success of solid tumors.

Epidermal growth factor receptors in cancer biology

There are four human epidermal growth factor receptors (EGFR/ERBB1/HER1, HER2/ERBB2/c-neu, HER3, and HER4). After ligand binding, they activate downstream signaling routes, which regulate proliferation, differentiation, apoptosis, metastasis, and angiogenesis. Their 3D structures are represented in Fig. 1. EGFR and HER2 are over-expressed in many solid tumors, which is associated with unresponsiveness to chemo- and radiotherapy as well as short survival times of patients (see below) [1]. The heterodimer structure of EGFR/HER2 is depicted in Fig. 2. Thus far, 10 ligands have been identified, i.e., the epidermal growth factor family (EGF, transforming growth factor-α, β-cellulin, epiregulin, HB-EGF, AR) and the neuregulin family (heregulin, neuregulins) [2, 3]. Upon binding of a ligand to an EGFR monomer, homo-dimerization takes place with a second EGFR molecule or with another HER member. Similarly, HER2 can dimerize with HER3 or HER4 and HER3 with HER4. Ligand binding and dimerization leads to intracellular phosphorylation of HER receptors and thereby activation of the downstream signaling pathways. The existence of 10 ligands of different homo- and heterodimers consisting of four receptors create a considerable flexibility and complexity for signal transduction [2–4]. This complexity is even further increased by varying the duration and strength of receptor signaling, receptor internalization, and recycling as well as rates of phosphorylation and dephosphorylation [5].

Dimerization stimulates intrinsic tyrosine kinase activity of EGFR, which regulates specific signal transduction cascades, e.g., Raf/Mek/Erk, PI3K/PDK1/Akt, PLCγ/PKC, MAPK, and JNK signaling routes. Constitutive EGFR activation as consequence of point mutations or gene amplification causes deregulated cellular processes such as proliferation, invasion, angiogenesis, cell motility, cell adhesion, inhibition of apoptosis, and DNA synthesis. The kinase activity is also associated with autophosphorylation of five tyrosine residues in the C-terminal EGFR domain. Mutations affecting EGFR expression foster carcinogenesis.

The extraordinary relevance of EGFR in tumor biology makes it an exquisite molecular target for tumor therapy. Apart from therapeutic antibodies, several small molecules have been developed as EGFR inhibitors [6]. For example, gefitinib (Iressa®; Astra Zeneca, DE, USA) and erlotinib (Tarceva®; OSI-774, Genentech Inc., CA, USA) are first-generation inhibitors used for the treatment of non-small cell lung cancer and other tumor types [7]. Both quinazolinamines exhibit their inhibitory activity by competing with ATP for the ATP binding pocket of EGFR.

Despite considerable successes with these EGFR tyrosine kinase inhibitors in cancer therapy, resistance against these chemical compounds develop due to the selection of point-mutated EGFR variants [8]. Therefore, there is an urgent need for the identification of novel EGFR tyrosine kinase inhibitors. In recent years, medicinal plants came into the center of interest as resources for novel treatment strategies to target EGFR family members.

Role of epidermal growth factor receptors for drug resistance and patient prognosis

EGFR-expressing cell lines

The connection between EGFR and classical cytotoxic drug resistance has been known for more than two decades. Murine sarcoma 180 (S180) cells selected for resistance towards doxorubicin overexpress EGFR compared to drug-sensitive wild-type S180 cells [9, 10]. As subsequently shown, EGFR

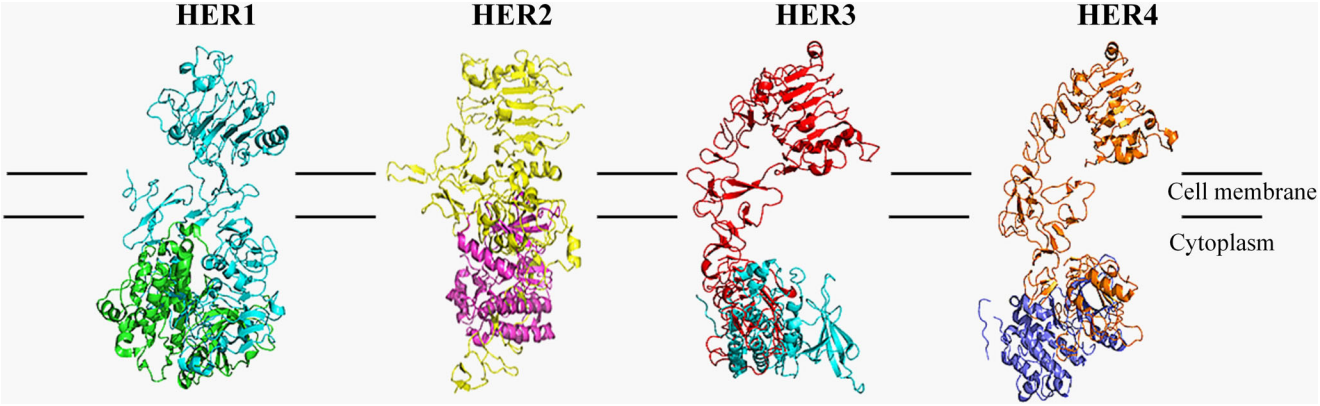


Fig. 1 3D structure of human HER1/EGFR, HER2, HER3, and HER4. Extracellular and cytoplasmic domains of the proteins were retrieved from protein data bank (PDB) database and combined structures were formed with PyMol software

expression also plays a role for drug resistance of tumor cells not previously selected treated with cytostatic drugs. Since kidney carcinomas are frequently unresponsive to chemotherapy, they represent a suitable model to study inherent drug resistance. EGFR expression of human primary cell cultures of renal cell carcinomas of 18 patients subjected to hierarchical cluster analyses showed that the expression of c-ErbB1 and c-ErbB2 was higher in resistant cell cultures compared to sensitive cell cultures [11]. EGFR is involved in drug resistance by affection of apoptosis, DNA repair, or the induction of resistance gene expression [12]. These in vitro results were translated to clinical tumors. Tumors with EGFR expression were significantly more frequent resistant to doxorubicin than EGFR negative or weakly expressing cancers [13, 14].

Glioblastoma multiforme (GBM) is the most aggressive form of adult human brain tumor [15]. Malignant gliomas often show resistance to adjuvant radio- and chemotherapy due to the accumulation of genetic alterations that cause oncogene

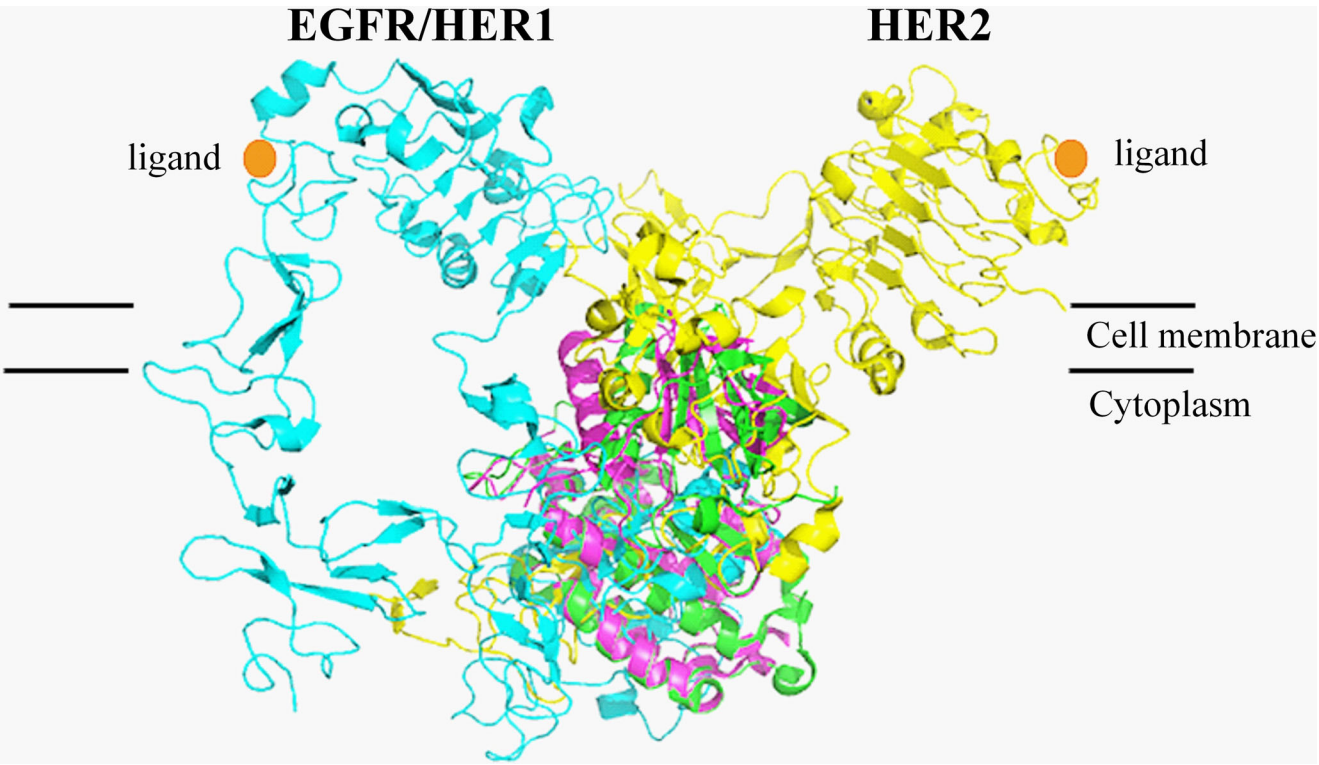


Fig. 2 Heterodimer of human HER1/HER2. Extracellular and cytoplasmic domains of the proteins were retrieved from PDB database and combined structures were formed with PyMol software

Table 1 Phytochemicals with activity against EGFR

Compound	Plant	Tumor type	Effect	Reference
Icariside II (metabolite of icariin)	*Herba epimedii*	A431 lung cancer	Inhibition of STAT3 and MAPK/ERK pathways; activation of PI3K/AKT pathway; induction of apoptosis	Wu et al. 2013 [48]
CS-1 alkaloid		A431 lung cancer	Inhibition of EGF ligand binding to EGFR G1 cell cycle arrest and growth inhibition; inhibition of EGFR internalization; inhibition of translocation of ERK/MAPK translocation to nucleus	Du et al. 2012 [49]
Silibinin	*Silybium marianum*	Breast cancer	Inhibition of EGF ligand-induced CD44 and matrix metalloproteinase-9 expression; inhibition of EGF ligand; induced phosphorylation of EGFR and ERK1/2	Kim et al. 2011 [50]
Honokiol	*Magnolia officinalis*	Head and neck squamous cell carcinoma	Inhibition of AKT and STAT3 growth inhibition and apoptosis; in vitro combination of honokiol and cetuximab significantly enhanced growth inhibition	Leeman-Neill et al. 2010 [51]
11,11′-Dideoxy-verticillin	*Shiraia bambusicola*	MDA-MB-H68 breast cancer; mouse sarcoma 180 and hepatoma 22	Inhibition of EGFR phosphorylation; tumor growth inhibition in vivo	Zhang et al. 2005 [52]
Taspine	*Magnolia spec. Croton lechleri* and others	A431 epidermoid cancer; HEK293/EGFR	Inhibition of EGFR, AKT, and ERK1/2 phosphorylation	Zhang et al. 2011 [53]
Taspine and caulophine	*Radix caulophylli*	A431 epidermoid cancer	EGFR inhibition	Sun et al. 2010 [54]
Oxymatrine and matrin	*Radix sophorae flavescentis*	A431 epidermoid cancer	EGFR inhibition	Wang et al. 2010 [55]
Genistein	*Glycine max*	LNCap and DU+C16145 prostate cancer	Inhibition of EGF-stimulated growth; no effect on EGFR tyrosine autophosphorylation	Peterson and Barnes 1993 [56]
		Five breast cancer lines	Growth inhibition independent of estrogen receptor signaling and EGFR tyrosine kinase activity	Peterson and Barnes 1996 [57]
		HepG2 liver cancer	Inhibition of EGF-induced EGFR degradation and tyrosine phosphorylation	Yang et al. 1996 [58]
		Bladder cancer	Preferential inhibition of cell motility and growth in EGFR-overexpressing cells	Theodoresu et al. 1998 [59]
		MDA-MB231 and MDA-MB-468 estrogen-receptor-negative breast cancer	Inhibition of EGF-stimulated invasion	Shao et al. 1998 [60]
		U20S osteosarcoma	Decrease in EGFR expression	Salvatori et al. 2009 [61]
		Three non-small cell lung cancer lines	Combination of genistein with established tyrosine kinase inhibitors caused enhanced growth inhibition and reduced expression of EGFR and pAKT	Gadgeel et al. 2009 [62]
		BXPC-3, CADAN-3, AsPC-1 prostate cancer	Potentiation of growth inhibition and apoptosis induced by erlotinib	El-Rayes et al. 2006 [63]
		Leiomyoma primary cells	Inhibition of STAT3 phosphorylation, but not EGFR autophosphorylation	Sushan et al. 2007 [64]
		Prostate primary cancer xenograft	Increased lymph node and distant metastasis in vivo; increased proliferation, decreased apoptosis; increased EGFR and Src tyrosine kinase activity	Nakamura et al. 2011 [65]
		LNCap prostate cancer	Decreased expression of pAKT and p70S6K stimulated by EGF	Oh et al. 2010 [66]
				Park et al. 2010 [67]

Table 1 (continued)

Compound	Plant	Tumor type	Effect	Reference
		HSC3 and KB oral squamous cell carcinoma	Combination with cetuximab, inhibited xenograft growth in vivo; down-regulation of pEFR and pAKT in HSC3, but not KB cells	
		MCF-7 breast cancer	Long-term genistein exposure down-regulated PI3K/AKT signaling	Anastasius et al. 2009 [68]
		DU145 prostate cancer	Inhibition of cell growth, inhibition of TGF alpha-induced EGFR and SHC and ERK1/2 activation	Bhatia et al. 2001 [69]
Oridonin	*Rabdosia rubesceus*	A431 epidermoid carcinoma	Inhibition of tyrosine kinase activity; down-regulation of EGFR expression and downstream effector expression (Grb2, Ras, Raf-1, ERK)	Li et al. 2007 [70]
(−) Epigallocatechin-3-gallate	*Camelia sinensis*	A431 epidermoid carcinoma	Inhibition of DNA synthesis; inhibition of EGF-stimulated EGFR autophosphorylation; inhibition of EGF binding to EGFR	Liang et al. 1997 [71]
		DU145 prostate cancer	Inhibition of cell growth; inhibition of TGFα-induced EGFR and SHC activation	Bhatia et al. 2001 [69]
		YCU-N861 and YCU-H891 head and neck squamous cell carcinoma	Inhibition of EGFR phosphorylation; inhibition of STAT3 and ERK phosphorylation; G1 cell cycle arrest, induction of apoptosis; enhanced growth inhibition of 5-fluorouracil	Masuda et al. 2001 [72]
		Cervical carcinoma	Inhibition of EGF-dependent activation of EGFR, ERK1/2, and AKT; induction of apoptosis	Sah et al. 2004 [73]
		Head and neck squamous cell carcinoma xenografts	Synergistic tumor growth inhibition together with erlotinib in vivo; inhibition of pEGFR and pAKT EGFR internalization and ubiquitin degradation	Zhang et al. 2008 [74]
		SW480 colon cancer	EGFR internalization into endosomes; inhibition of EGFR phosphorylation	Adachi et al. 2008 [75]
		SW480 colon cancer	EGFR degradation; EGFR phosphorylation at serine 1046/1047 via activation of p38 MAPK	Adachi et al. 2009 [76]
		Non-small cell lung cancer	Enhanced growth inhibition of erlotinib in vitro and in vivo; inhibition of erlotinib-resistant cells; inhibition of EGFR phosphorylation	Milligan et al. 2009 [77]
		ARO anaplastic thyroid carcinoma	Inhibition of phosphorylation of EGFR, ERK1/2, JNK, and p38; induction of apoptosis; growth inhibition	Lim et al. 2011 [78]
		CAL-27 Head and neck squamous cell carcinoma	Synergistic growth inhibition with gefitinib	Chang et al. 2012 [79]
		CaCo2, Her116, HT29, SW480, and SW837 colon cancer and FHC normal colon cells	Inhibition of EGFR phosphorylation; synergistic growth inhibition with epigallocatechin	Shimizu et al. 2005 [80]
		KYSE150 esophageal squamous cell carcinoma and A431 epidermoid cell carcinoma	Inhibition of EGFR phosphorylation	Hou et al. 2005 [81]
Delfinidin		NC1-H441 and SK-MES-1 non-small cell lung cancer	Inhibition of PI3K activation; inhibition of AKT and MAPK phosphorylation; induction of apoptosis and inhibition of tumor growth in vivo	Pal et al. 2013 [82]
			Inhibition of EGFR phosphorylation	Fridrich et al. 2008 [83]

Table 1 (continued)

Compound	Plant	Tumor type	Effect	Reference
Delphinidin, (−) epigallocatechin-3-gallate, quercetin	*Delphinium consolida*, *Camelia sinensis*, many other species	HT29 colon cancer; A431 epidermoid carcinoma		
Shikonin	*Lithospermum erythrorhizon*	Epidermoid carcinoma	Inhibition of phosphorylation of EGFR, ERK1/2; increasing phosphorylation of JNK1/2	Singh et al. 2003 [84]
Shikonin, β-hydroxy-isovalerylshikonin	*Lithospermum erythrorhizon*	NCI-H522 and DMS114 lung cancer	Inhibition of phosphorylation of EGFR and v-SRC	Hashimoto et al. 2002 [85]
Curcumin	*Curcuma longa*		Disruption of interaction of integrin b	Soung et al. 2011 [86]
		CL1-5, A549, H1975 lung cancer	EGFR ubiquitination and inhibition of EGFR phosphorylation in gefitinib-resistant cells; reduction of xenograft tumors in vivo by combination treatment of curcumin and gefitinib; induction of apoptosis; reduction of gefitinib-induced gastrointestinal side effect by altered MAPK activation.	Lee et al. 2011 [87]
		Non-small cell lung cancer xenografts	Inhibition of EGFR activation and induction of apoptosis in vitro and in vivo in gefitinib resistant tumors; synergistic growth inhibition with gefitinib	Lee et al. 2011 [87]
		Hca-F mouse hepatoma	Inhibition of phosphorylation of EGFR, PI3K, AKT, p38MAPK, and p44/42MAPK	Wang et al. 2011 [88]
		A549 lung cancer and HBE bronchial epithelial cells	Decrease of EGFR downstream signaling of pAKT	Jiang et al. 2014 [89]
		Non-small cell lung cancer xenografts	Down-regulation of EGFR, pEGFR; enhanced cytotoxicity with erlotinib in erlotinib-resistant tumors in vitro and in vivo	Li et al. 2014 [90]
Curcumin, betulinic acid	*Curcuma longa*, *Betula pubescens*, and others	Bladder cancer	Inhibition of EGFR expression induction of autophagy	Chadalapaka et al. 2010 [91]
Demethoxy-curcumin	*Curcuma longa*	PC3 prostate cancer	Sustained EGFR activation AMPK-induced EGFR down-regulation	Hung et al. 2012 [92]
6 Pyrimidine-substituted curcumin analogues	Synthetic derivatives	Colon cancer	Inhibition of cell growth, induction of cell cycle arrest and apoptosis; inhibition of EGFR expression	Qiu et al. 2013 [93]
Mixture of resveratrol, quercetin, and catechin	Diverse plants	Breast cancer	Activation of AMPK, inhibition of AKT and mTOR; enhanced inhibition of gefitinib-resistant cells in vitro and in vivo	Castillo-Pichardo et al. 2012 [94]
Resveratrol	Diverse plants	MDA-MB-231 breast cancer	Inhibition of EGF-mediated cell migration	Lee et al. 2011 [95]
		Prostate cancer	Binding to EGFR, inhibition of phosphorylation of EGFR and AKT	Wang et al. 2010 [96]
		AlPrCa and Pc-3 prostate cancer	Inhibition of EGFR-dependent ERK1/2 activation	Stewart et al. 2004 [97]
Betulinic acid	Diverse plants	Melanoma cells	Induction of phosphorylation of EGFR, AKT, and ERK; weak activation of JNK and p38MAPK	Qiu et al. 2005 [98]
Dihydrocalcones and their glycosides	Apple		Inhibition of EGFR activation	Teller et al. 2013 [99]
Quercetin	Diverse plants	HSC-3, TW206 head and neck squamous cell carcinoma	Inhibition of EGFR and AKT activation; induction of G_2 arrest and apoptosis; growth inhibition in vivo	Huang et al. 2013 [100]

Table 1 (continued)

Compound	Plant	Tumor type	Effect	Reference
		PC-3 prostate cancer	Down-regulation of EGF, EGFR, and p38MAPK	Senthilkumar et al. 2011 [101]
		HeLa cervix cancer	Down-regulation of EGFR expression and activation	Jung et al. 2010 [102]
		Hep2 and CO-K3 laryngeal squamous cancer	Inhibition of EGF-dependent kinases	Raspaglio et al. 2003 [103]
Quercetin, luteolin	Diverse plants	Mia PaCa-2 prostate cancer	Blockage of EGFR signaling pathway	Lee et al. 2004 [104]
Quercetin, luteolin	Diverse plants	Pancreas cancer	Attenuation of EGFR phosphorylation; induction of apoptosis	Lee et al. 2002 [105]
Quercetin, luteolin	Diverse plants	A431 epidermoid cancer	Inhibition of EGFR activation and autophosphorylation	Huang et al. 1999 [106]
Quercetin, apigenin, fisetin, robinetin	Diverse plants	Colorectal cancer	Inhibition of EGFR phosphorylation	Richter et al. 1999 [107]
Deguelin	*Mundulea sericea*	MDA-MB-231, MDA-MB-486, BT-549, and BT-20 breast cancer	Inhibition of EGFR-pAKT/c-MET pERK, NF-kB, and pSTAT3; inhibition of tumor growth in vivo	Mehta et al. 2013 [108]
Proanthocyanidins B1 and B2, isoquercetin	Apple	HT29 colon cancer	Inhibition of EGFR tyrosine kinase activity	Kern et al. 2005 [109]
Proanthocyanidins	Grape seed	SCC1, SCC5, OSC1 9, FaDu head and neck squamous cell carcinoma	Inhibition of EGFR expression; induction of G_1 cell cycle arrest and apoptosis; inhibition of tumor growth in vivo	Prasad and Katiyar 2012 [110]
Luteolin	Diverse plants	MDA-MB-231 breast cancer	Down-regulation of EGFR expression; inhibition of EGFR-induced MAPK activation and phosphorylation of ERK, p38, and AKT; inhibition of tumor growth in vivo	Lee et al. 2012 [111]
7,3′,4′-Trihydroxy-isoflavone	Metabolite of daidzein	JB6 P+ mouse epidermal cells	Inhibition of EGF-induced neoplastic transformation and proliferation; induction of G_1 cell cycle arrest; binding to PI3K and inhibition of its kinase activity; suppression of AKT	Lee et al. 2010 [112]
Artesunate	derivative of artemisinin from *Artemisia annua*	A549 non-small cell lung cancer	Down-regulation of EGFR and AKT; induction of apoptosis and inhibition of tumor growth in vivo	Ma et al. 2011 [113]
Platycodin D	*Platycodon grandiflorum*	MDA-MB-231 breast cancer	Inhibition of ERK, p38MAPK, JNK phosphorylation; down-regulation of EGFR; inhibition of migration, invasion, and adhesion in vitro; tumor growth inhibition in vivo	Chun et al. 2013 [114]
Berberine		HT29 colon cancer	Inhibition of EGF-stimulated EGFR activation; inhibition of tumor growth and induction of G2/M arrest in vivo	Wang et al. 2013 [115]
Capsaicin	Chili pepper	MCF7, T47D, BF474, SKBR3, MDA-MB-231 breast cancer	Down-regulation of EGFR and HER2 expression; inhibition of ERK activation; inhibition of cell migration in vitro; inhibition of tumor growth in vivo	Thoennissen et al. 2010 [116]

activation, e.g., EGFR [16]. In most GBMs, amplification and rearrangement of the *EGFR* gene resulted in mutant receptors, called ΔEGFR (kinase-deficient mutant EGFR) that enhanced tumorigenicity in vivo, and caused cisplatin resistance [17].

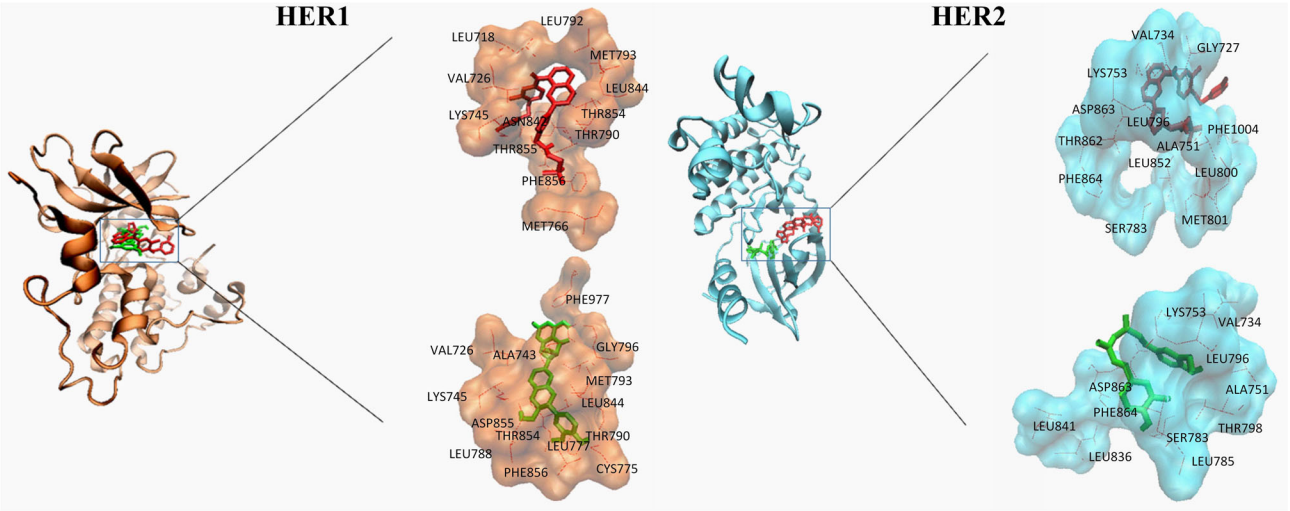
In addition to cisplatin, EGFR also reduced the activity of microtubule poisons, i.e., vincristine and paclitaxel [18]. Combination treatment of human ΔEGFR-expressing GBM cells with EGFR-directed tyrosine kinase inhibitor and cisplatin synergistically induced apoptosis in vitro and in vivo [17, 18].

Furthermore, the combination treatment of a c-Met kinase inhibitor and either an EGFR kinase inhibitor or cisplatin enhanced cytotoxicity of mutant EGFR-expressing GBM cells [19]. Taken together, EGFR expression is associated with drug resistance in vitro making it an exquisite target for novel drugs inhibiting EGFR function. EGFR-mediated resistance is also known for cytotoxic natural products. Two interesting bioactive compounds derived from the Chinese coniferous tree *Cephalotaxus hainanensis* are cephalotaxine (CET) and its ester homoharringtonine (HHT) [20]. Although HHT possessed the highest growth inhibitory activity towards human leukemic cells [21], human ΔEGFR-expressing GBM cells were 14-fold more resistant to HHT than control cells [22]. These findings indicated a causative role of mutation-activated EGFR for cellular resistance towards CET and HHT. Similar results have been obtained for artesunate (ART), which is a semisynthetic derivative of artemisinin, the active principle of *Artemisia annua* L. This herb was traditionally used in Chinese medicine for the treatment of fever and chills. Nowadays, artemisinin is used as antimalarial drug [23]. Artemisinin and its derivative ART also reveal profound anti-cancer activity [24–26]. In sum, drug resistance mediated by EGFR is not restricted to established anticancer drugs but also occurs towards other cytotoxic compounds of natural origin. Hence, EGFR-mediated resistance may represent a general type of cellular defense mechanisms towards a broad range of toxic xenobiotics.

EGFR in clinical tumors

EGFR is expressed in different human tumors, e.g., in cancers of the lung, head and neck, colon, pancreas, breast, ovary, bladder and kidney, and gliomas. EGFR expression correlated is of prognostic significance for cancer patients. Patients with EGFR-overexpressing tumors reveal worse prognosis [27]. To illustrate this, we exemplarily focus on lung cancer in more detail.

Lung cancer is the leading cause of cancer mortality worldwide, and cure rates are less than 15 % [28]. Lung cancers are classified into two histological types: small cell carcinoma and non-small cell carcinoma. The majority of bronchogenic carcinomas can be classified into four histological types: small cell carcinoma, adenocarcinomas, squamous cell lung carcinomas, and large cell carcinomas. The histological features, clinical course, and response to therapy indicate that small cell



	Lowest binding energy (kcal/mol)	Mean binding energy (kcal/mol)	Residues making H-bond	pKi (nM)
Control drug (Lapatinib)	-10.83	-8.98	**MET793**,**PHE856**,**THR854**	11.46
Silibinin	-10.20	-9.54	CYS775,**MET793**,**THR854**	33.15

	Lowest binding energy (kcal/mol)	Mean binding energy (kcal/mol)	Residues making H-bond	pKi (nM)
Control drug (Lapatinib)	-11.13	-11.13	LYS753,**MET801**	6.98
Curcumin	-9.22	-8.46	**ASP863**	175.65

Fig. 3 Molecular docking results for the compounds showing the strongest interaction with HER1/EGFR tyrosine kinase domain (PDB ID = 3W2O) and HER2 tyrosine kinase domain (PDB ID = 3PP0). Residues labeled *bold* at the tables were stated in the literature to reside at the site where the known EGFR inhibitors bind

Table 2 Phytochemicals with activity against HER2 and HER3

Compound	Plant	Tumor type	Effect	Reference
Houttuyninum	*Houttuynia cordata*	MDA-MB-453 breast cancer	Inhibition of HER2 phosphorylation, inhibition of ERK1/2 and AKT activation, dose-dependent cytotoxicity in vitro	Zhou et al. 2012 [117]
		BT474 and N87	Inhibition of HER2 phosphorylation, inhibition of xenograft tumor growth in vivo	Zhou et al. 2012 [117]
11,11′-Dideoxy-verticillin	*Shiraia bambusicola*	SK-OV-3 ovarian cancer	Inhibition of HER2 phosphorylation	Zhang et al. 2005 [52]
ZH-4B		SK-OV-3 ovarian cancer SK-BR-3 breast cancer	Inhibition of HER2 phosphorylation	Guo et al. 2004 [118]
Genistein	*Glycine max*	BT-474 breast cancer	Inhibition of HER2 protein expression phosphorylation and promoter activity through an estrogen-receptor-independent mechanism	Sakla et al. 2007 [119]
		SKOV-3 ovarian cancer	Down-regulation of HER2 mRNA	Li et al. 2004 [120]
		MCF-7 and MCF7 HER2 breast cancer	Inhibition of proliferation and induction of apoptosis	Seo et al. 2011 [121]
(−) Epigallocatechin-3-gallate	*Camelia sinensis*	MCF7 and AU565 breast cancer	Inhibition of HER3 expression after stimulation of HER2 by heregulin-β1	Pan et al. 2007 [122]
		MCF-7 breast cancer	Inhibition of hergulin-β1-induced migration/invasion; inhibition of hergulin-β1-induced HER2/HER3 activation	Kushima et al. 2009 [123]
		NF639, SMF, and BA/F3 2+4 breast cancer	Inhibition of cell growth, inhibition of HER2 phosphorylation	Pianetti et al. 2002 [124]
		Head and neck squamous cell carcinoma and breast carcinoma	Inhibition of HER2 phosphorylation and STAT3 activation	Masuda et al. 2003 [125]
		CaCo2, HCT116, HT29, SW480, and SW837 colon cancer and FHC normal colon cells	Inhibition of HER2 phosphorylation; synergistic growth inhibition with epigallocatechin	Shimizu et al. 2005 [80]
		OE19 esophageal adenocarcinoma	Inhibition of HER2 phosphorylation	Hou et al. 2005 [81]
		HT29 colon cancer	Inhibition of EGFR, HER2, and HER3 phosphorylation; inhibition of ERK and AKT phosphorylation	Shimizu et al. 2005 [126]
Curcumin	*Curcuma longa*	HCT-116 and HAT-29 colon cancer	Inhibition of expression and activation of EGFR, HER2, HER3, and AKT; synergistic growth inhibition with 5-fluorouracil plus oxaliplatin	Patel et al. 2008, 2010 [127, 128]
		MDA-MB-231/HER2 breast cancer	Down-regulation of HER2 expression; inhibition of cell growth and migration, induction of G1 cell cycle arrest and apoptosis	Sun et al. 2012 [129]
Curcumin, resveratrol	*Curcuma longa*, many plants	Breast cancer cells	Enhanced growth inhibition in combination with HER2-targeted immunoliposomes containing trastuzumab	Catania et al. 2013 [130]
Curcumin analogues PGV-0 and PGV-1	Synthetic derivatives	T47D breast cancer	Inhibition of HER2 activity in silico binding to HER2 ATP-binding site; enhanced cytotoxicity in combination with doxorubicin	Meiyanto et al. 2014 [131]
Pterostilbene	Bluberry and grape	Breast cancer	Inhibition of heregulin-β1-mediated cell invasion; inhibition of phosphorylation of p38MAPK and AKT	Pan et al. 2011 [132]
Dihydrocalcones and their glycosides	Apple		Inhibition of HER3 activation	Teller et al. 2013 [99]
Quercetin	Diverse plants	PC-3 and LnCap prostate cancer	Inhibition of HER2 and HER3 expression and autophosphorylation; inhibition of phosphorylation of cRAF, MAPK, ELK-1, and AKT-1	Huynh et al. 2003 [133]

Table 2 (continued)

Compound	Plant	Tumor type	Effect	Reference
Apigenin	Diverse plants	Breast cancer	Inhibition of HER2 autophosphorylation and transphosphorylation; inhibition of AKT kinase activity by preventing the docking of PI3K to HER2/HER3 heterodimers	Way et al. 2004 [134]

lung carcinoma (SCLC) is a separate entity. The behavior of the other three histological subtypes is similar and therefore is referred to as non-small cell lung carcinoma (NSCLC) [29]. NSCLC represent the majority of lung cancers and are usually associated with poor prognosis. While SCLC is drug sensitive, NSCLC are the opposite. Clinical oncology still regards resistance to chemotherapy NSCLC patients as a major problem. As numerous mechanisms are operative in drug-resistant tumors [11, 30, 31], the relative quantitative contributions of each of these resistance mechanisms have to be determined. Hence, understanding the complex genetic network in clinically relevant drug resistance needs more holistic approaches to the entire battery of genes conferring drug resistance.

In 81 human primary squamous cell lung carcinomas, EGFR expression was described as prognostic factor [13]. EGFR expression level was reduced in NSCLC patients with long-term survival [32]. In addition, down-regulation of HER2 expression played an important role in resistant NSCLC [33]. Interestingly, carcinomas of smokers expressed EGFR more frequently than carcinomas of nonsmokers do [34]. The importance of EGFR signaling in lung cancer and its beneficial effects on patient survival led to clinical usage of the EGFR inhibitor erlotinib for the treatment of NSCLC [33].

Taken together, these data clearly speak for an important role of EGFR in drug resistance in vitro as well as in the clinical setting. This is why it appears an exquisite target for novel drugs specifically inhibiting EGFR function and signaling.

HER2, HER3, and HER4 in clinical tumors

HER2 overexpression plays a major role in breast cancer, but it can be also found in other tumor types. HER2 positivity in breast cancers varies from 10 to 40 % [35–38]. The overexpression of *HER2* mRNA and protein is a poor prognostic factor [39, 40] and correlated with poor responsiveness to chemotherapy [36]. While EGFR and HER2 have been intensively studied during the past years, less data are available for HER3 and HER4. The prognostic significance of HER3 has been discussed in a contradictory manner. Some authors reported associations of HER3 expression to poor prognosis in breast cancer patients, while others described HER3 as a favorable prognostic factor [41]. HER4 mediates antiproliferative and differentiation effects [35]. Hence, it is plausible that this receptor represents a favorable prognostic marker in breast cancer patients [41–43].

Since the development of monoclonal antibody C225 to treat EGFR-positive cancers [44], many other therapeutic antibodies and small molecule tyrosine kinase inhibitors against EGFR and HER2 have been developed [45]. In contrast, HER4 does not serve as target for drug development because of its positive prognostic significance. While EGFR- or HER2-overexpressing cancers are adverse prognostic factors if standard cytotoxic chemotherapy is applied, the contrary occurs upon application of EGFR or HER2 inhibitors. Tumors with high EGFR or HER expression are preferentially killed by such targeted antibodies and small molecule inhibitors [37]. This is an instructive example how the specific therapeutic targeting of proteins with worse prognosis can be exploited to improve treatment success rates. Unfortunately, tumors can also develop resistance against EGFR- or HER2-directed antibodies and small molecules, and the search for novel drugs to fight cancer continues.

In this context, the tremendous chemodiversity of phytochemicals comes into play. Novel compounds from natural sources may serve as lead compounds for a new generation of drugs eradicating resistant tumors.

Inhibition of epidermal growth factor signaling by phytochemicals

Natural products as resource for cancer treatment

As pointed out by a survey of the National Cancer Institute, USA, the majority of established cancer drugs are natural products, derivatives of natural products, or drugs mimicking the mode of action of natural products [46]. Searching in nature for novel scaffolds is a promising way to find new chemical tools to bypass and overcome such drug resistance. Novel natural product inhibitors may serve as lead compounds for drug development. A plethora of data in the literature shows that natural products can serve as inhibitors for EGFR-associated signaling molecules such as the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways. This indicates that the identification of novel inhibitors from natural resources is not beyond the scope of expectations.

Table 3 Molecular docking results of selected inhibitors (*white rows*) and phytochemicals (*light gray rows*) against EGFR

Inhibitor	Lowest binding energy (kcal/mol)	Mean binding energy (kcal/mol)	Residues making H-bond	Residues involved in hydrophobic interactions	pKi (nM)
Lapatinib	-10.83	-8.98	MET793,PHE856,THR854	LEU792,THR790,MET793,LEU844,MET766,ASP855,ARG841,ASN842,VAL726,LEU718,MET793,LYS745	11.46
Afatinib	-10.74	-9.31	LYS745,ASP855	MET766,LEU858,VAL726,CYS797,ARG841,LEU844,LEU792,MET793,THR790,PHE856,CYS797,LYS745	13.50
Neratinib	-10.10	-9.12	ASP855	MET766,THR854,PHE723,LYS745,GLY721,ARG841,ALA743,THR790,LEU792,MET793,VAL726,CYS797,LEU844,PHE856,ASN842	39.61
Erlotinib	-9.28	-7.81	MET793,LYS745,ASP855	LEU844,CYS775,VAL726,ALA743,LEU788,LEU858,PHE856,THR854,LEU792,LEU777,ARG776,THR790	156.90
Gefitinib	-8.76	-8.20	ASP855	LEU858,LYS745,VAL726,PHE856,MET766,THR854,ASN842,ALA743,THR790	379.04
Phytochemicals					
Silibinin	-10.20	-9.54	CYS775,MET793,THR854	ARG776,LEU777,PHE856,LEU788,THR790,ALA743,ASP855,LYS745,VAL726,LEU844,GLY796,PHE997	33.15
Betulinic acid	-9.35	-8.86	MET793	ASP855,LEU792,ARG841,LEU844,VAL726,LEU718,SER720,GLY721,CYS797,MET793,GLY796,ALA743	140.19
(-) Epigallo-catechin 3-gallate	-9.24	-7.95	GLY724,MET793,ASP800,CYS797,CYS745,GLY721,ASP855	GLN791,ALA743,THR790,LEU844,VAL726,ASN842	169.14
Demethoxy-curcumin	-9.22	-8.05	LYS745,MET793,PHE856	LEU858,ALA743,VAL726,GLY796,LEU844,LEU792,THR790,THR854,ASP855,CYS775	174.70
Curcumin	-9.17	-7.92	PHE856	LEU792,LEU844,THR790,ALA743,VAL726,ARG776,CYS775,MET793,GLY796,LEU777,LEU788,LYS745,ASP855,LEU858	188.40
Artesunate	-8.59	-7.99	GLY724,CYS745	LEU844,THR854,VAL726,GLY721,ALA743,PHE723,ASP855	508.48
11,11'-dideoxy-verticillin	-8.39	-8.37	SER720	ASP800,CYS797,LEU844,GLY796,GLY719,LEU718,PHE997,MET793,ALA743,VAL726	711.04
Quercetin	-8.38	-7.97	MET793,CYS797,ASP800,LEU792,GLY796	LEU718,ALA743,THR790,GLN791,LEU844,THR854	720.39
β-hydroxy-isovalerylshikonin	-8.37	-7.18	GLY724,LYS745,ARG841,THR854,ASP837	ASP855,LEU844,ASN842,GLY721,GLY724,PHE723,CYS797,VAL726,ALA722	734.03
Oxymatrine	-8.29	-8.15	PHE856	LEU858,LYS745,ASP855,LEU788,THR790,LEU789,LEU777,MET766,THR854	832.22
Proanthocyanidins B2	-8.29	-6.40	PHE723,GLY724,LEU799,SER720	ARG841,ASP837,ASN842,CYS797,ASP800,GLY721,ALA722,VAL726,LYS745	841.73
Luteolin	-8.27	-7.85	MET793,CYS797,ASP800,THR854,LEU792	LEU844,GLY796,GLN791,THR790	862.92
Matrin	-8.23	-8.14	THR790	LEU777,LYS775,PHE850,THR854,ASP855,LEU788,LYS745,LEU858	926.93
Icaviside II, (metabolite of icariin)	-8.19	-6.73	ASP800,MET793,GLN791	ARG841,LYS745,ASN842,LEU718,VAL726,ALA743,PHE997,LEU844,LYS797,THR790,LEU792	995.40
Berberine	-8.13	-7.92	MET793	LEU844,VAL726,ALA743,LEU788,THR790,LEU792,MET766,PHE856,THR854,ASP855,LEU858	1100.00
Shikonin	-8.13	-7.47	THR854	LEU788,THR790,VAL726,LEU858,ASP855,PHE856,LYS745	1100.00
CS-1 alkaloid	-8.00	-7.27	CYS797,ASP800	LYS745,LEU792,MET793,LEU840,VAL726,PHE997,ARG841,ASP855,LEU718,LEU1001	1380.00
Fisetin	-7.98	-7.10	LYS745,LYS775,ASP855	LEU858,VAL726,LEU788,THR790,LEU777,MET766,PHE856,THR854	1420.00
Capsaicin	-7.94	-7.03	PHE856,THR854	LEU858,ASP855,LEU777,MET766,LEU1001,GLY796,MET793,LEU792,LEU844,ALA743,THR790,LEU718	1510.00
Honokiol	-7.92	-7.45	PHE856	ARG776,LEU777,MET766,CYS775,THR790,LYS745,ILE789,ASP855,THR854,LEU788,ALA743,VAL726	1580.00
Delphinidin	-7.89	-7.75	MET793,ASP800,GLY796,THR790	PHE997,LEU718,LEU844,ALA743,CYS797,GLN791	1650.00
Robinetin	-7.79	-7.13	LYS745,THR854,CYS775	ARG776,LEU777,ALA743,LEU788,VAL726,MET766,PHE856,ASP855,LEU858	1940.00
Apigenin	-7.72	-7.53	LYS745,ASP855	MET766,LEU858,VAL726,CYS797,ARG841,LEU844,LEU792,MET793,THR790,PHE856,CYS797,LYS745	2180.00
7,3',4'-Trihydroxy-isoflavone	-7.66	-6.81	LYS745,MET793,ASP855,LYS745	LEU1001,ALA743,THR790,GLY796,LEU844,ALA743,VAL726,PHE997,LEU718	2410.00
Deguelin	-7.66	-6.33	LYS745,ARG841,ASN842,SER720,ASP837,ASP800	ALA722,PHE723,LEU799,CYS797,ASP855,ARG803	2420.00
Isoquercetin	-7.43	-5.84	MET793,ASP800,SER720,LEU718	LEU844,LEU792,GLN791,ALA743,GLY719	3550.00
Catechin	-7.42	-7.42	MET793,ASP855,THR854	GLY796,THR790,ALA743,CYS745,LEU788,LEU844	3660.00
Oridonin	-7.30	-7.20	LYS745,ARG841,THR854	ALA743,LEU844,CYS797,VAL726,ASP855	4360.00
Genistein	-7.30	-7.07	VAL834,GLU762,ARG832	VAL785,GLY857,ARG836,TYR891,LEU833	4470.00
Taspine	-7.14	-7.04	MET793	LEU844,ARG841,ASN842,ASP855,THR854,PHE997,LEU792	5820.00
Resveratrol	-6.64	-6.46	LYS745,THR854,MET793	LEU844,THR790,ALA743,VAL726,LEU792,GLY796,LEU788,ASP855	13580.00
Caulophine	-6.27	-5.79	LYS745,ASP855	ARG841,LEU788,THR790,ALA743,ASN842,LEU844	25160.00
Platycodin D	-3.75	+10.81	PHE723,LYS875,GLY721,ARG841,ASP837,ASP855	LEU788,THR790,LYS745,VAL726,GLY724,SER720,GLY719,THR854,ALA722,LEU844,LEU718	1770000.00

Table 4 Molecular docking results of selected inhibitors (*white rows*) and phytochemicals (*light brown rows*) against HER2

Inhibitor	Lowest binding energy (kcal/mol)	Mean binding energy (kcal/mol)	Residues making H-bond	Residues involved in hydrophobic interactions	pKi (nM)
Lapatinib	-11.13	-11.13	LYS753,MET801	THR862,ASP863,PHE864,SER783,GLY729,GLY727,LEU726,VAL734,ALA 751,GLY804,PHE1004,LYS753,LEU796, LEU800,LEU852,LEU785,ARG784,MET774	6.98
Afatinib	-9.54	-8.16	ASP863,THR862	LEU755,GLU770,LEU785,THR798,LEU852,SER783, PHE864,GLY865	102.08
Neratinib	-8.88	-7.69	ASP863	ARG849,ASN850,CYS805,THR862,LYS753,VAL734, THR796,LEU785,GLY865,GLU770	309.67
Gefitinib	-8.39	-8.00	ASP863	LEU755,GLU770,GLY865,THR862,LYS753,VAL734,ALA751,PHE864,ALA 771,MET774,ILE767,LEU796	703.87
Erlotinib	-7.83	-6.70	MET801,LYS753	LEU800,LEU852,PHE731,ASP863,THR862,LEU796,ALA751,THR798	1810.00
Phytochemicals					
Curcumin	-9.22	-8.46	ASP863	VAL734,ILE752,LYS753,ALA751,LEU796,THR798,PHE864, THR798,LEU785,MET774,VAL773,SER783,VAL839, ARG784,LEU836,TYR835,LEU841	175.65
(-) Epigallocatechin 3-gallate	-8.82	-7.87	LYS753,GLU770,LEU785,GLY865,ASP863	MET774,SER783,LEU796,ALA751,LEU755,VAL734	341.99
Quercetin	-8.17	-7.60	LYS753,THR796,SER783,GLU770,ASP863	LEU785,ARG784,LEU796,LEU755	1030.00
Apigenin	-7.96	-7.42	LYS753,THR798,GLU770,GLY865	LEU785,LEU796,LEU755,ASP863	1470.00
Genistein	-7.91	-7.26	LEU785,ASP863,GLY865,SER783	LEU796,LEU785,MET774,ARG784	1590.00
Pterostilbene	-7.77	-7.59	TYR835	MET774,GLY778,VAL782,THR862,SER783.THR798, ASP863,PHE864,VAL777,MET774,LEU785	2010.00
Resveratrol	-7.75	-7.50	THR798,TYR835	ASP863,PHE864,SER783,LEU785,MET774,GLY778, ALA782,ARG784,TYR835,VAL777	2090.00
11,11'-Dideoxy-verticillin	-6.74	-6.5	ASP808	THR862,ASP863,ASN850,ARG849,LYS753,PHE1004, GLY804,ASP808,CYS805,LEU726	11460.00
Houttyniunum	-5.10	-4.59	THR862,ASP863	PHE864,SER783,LEU785,THR798,ARG784,MET774	181830.00

Inhibitors of EGFR signaling

Phytochemicals from different chemical classes such as flavonoids, terpenoids, and alkaloids have been shown to exert their cytotoxic activity towards cancer cells by affecting EGFR signaling (Table 1). Some specific compounds were intensively investigated such as genistein, curcumin, quercetin, resveratrol, and (−) epigallocatechin-3-gallate. The frequent observation that natural products act in a multifactorial manner [47] applies here as well. As shown in Table 1, phytochemicals inhibited both phosphorylation and expression of EGFR (by ubiquitination and degradation). Furthermore, natural compounds inhibited the phosphorylation of downstream kinases either as consequence of EGFR inhibition or by binding of compounds to corresponding kinase domains of signal transducers. In addition, translocation of kinases (e.g., ERK, MAPK) from the cytosol to the nucleus can be blocked by some compounds. As consequence of silencing EGFR signaling routes, various effects were observed in cancer cells, e.g., induction of cell cycle arrest and apoptosis, inhibition of cell mobility, and inhibition of invasion of metastasis.

It is important to note that several compounds have been shown to exert their effects not only in vitro but also in vivo, e.g., curcumin, (−) epigallocatechin-3-gallate, 11,11′-dideoxyverticillin, quercetin, deguelin, proanthocyanidins, luteolin, artesunate, platycodin D, berberine, capsaicin, and delfinidin. Further evaluation of the compounds mentioned in Table 1 in terms of EGFR inhibition was performed with in silico molecular docking analyses on human EGFR tyrosine kinase domain. Molecular docking analyses in silico on human EGFR tyrosine kinase domain revealed silibinin to interact with comparable binding energies as the known inhibitor, lapatinib with similar docking poses (Fig. 3). Anti-tumor activity in vivo represents a precondition to consider compounds for clinical application. It is also interesting to study the interaction of natural products with anticancer drugs. Phytochemicals caused increased or even synergistic inhibition of tumor growth in combination with established drugs. This has been shown for the combinations of curcumin plus gefitinib/erlotinib, honokiol plus cetuximab, and (−) epigallocatechin-3-gallate plus 5-fluorouracil erlotinib/gefitinib (Table 1). Furthermore, natural products can reduce the side effects of standard anticancer therapy on normal organs as shown by the combination of curcumin and gefitinib, which led to reduced gastrointestinal side effects compared to gefitinib alone in xenograft tumor-bearing mice (Table 1).

Inhibitors of HER2/HER3 signaling

Although the inhibition of other EGFR family members was much less investigated, several studies provided results for the inhibition of HER2 and HER3 and their related downstream signaling routes. As can be seen in Table 2, most evidence has been gathered for (−) epigallocatechin-3-gallate, one of the active ingredients of green tea (*Camelia sinensis*), the flavonoid genistein from soy (*Glycine max*), and curcumin from *Curcuma longa*.

Few publications investigated other compounds such as houttuyninum, 11,11′-dideoxy-verticcillin, ZH-4B, resveratrol, pterostilbene, dihydrocalcones, quercetin, and apigenin. The mechanisms of actions how these phytochemicals affect HER2 and HER3 are comparable with those observed for EGFR. They include inhibition of HER2/HER3 phosphorylation and expression as well as inhibition of downstream signal transducers, e.g., ERK1/2, AKT, STAT3, p38MAPK, cRAF, Elk-1, and PI3K (Table 2). Further evaluation of the compounds mentioned in Table 2 in terms of HER2 inhibition was performed with in silico molecular docking analyses on human HER2 tyrosine kinase domain. Molecular docking analyses in silico on human HER2 tyrosine kinase domain revealed curcumin to interact with comparable binding energies as the known inhibitor, lapatinib with similar docking poses (Fig. 3). The results for the in silico molecular docking analyses on EGFR and HER2 tyrosine kinase domains are represented in Table 3 and Table 4, respectively. The inhibition of HER2/HER3 and related signal transduction pathways led to growth inhibition and induction of apoptosis as well as to the inhibition of human tumor xenograft growth in vivo. Comparable to EGFR inhibition, HER2 and HER3 inhibition by curcumin also caused synergistic growth inhibition with 5-fluorouracil/oxaliplatin (Table 2).

Conclusions and perspectives

The identification of tumor target molecules with prognostic relevance for patients opened avenues for the development of more specific treatment options. Important examples in current cancer biology and pharmacology are epidermal growth factor receptors and specific small molecules inhibiting their signaling in tumors. Nevertheless, resistance can also occur towards targeted therapies and novel drugs attacking these receptors are needed. Natural products have been identified as possible novel drug candidates specifically inhibiting EGFR in tumor cells. An important perspective for EGFR/HER2/HER3 inhibiting natural products is their use for personalized treatment options. The individual testing of the mutational status would allow selecting the right EGFR/HER2/HER3 inhibitor for the right patient. In this respect, natural products may represent valuable tools for the development of personalized therapy in the years to come.

The reliable prediction of resistance development is still a major unresolved issue. Deep sequencing and next-generation sequencing have great potentials in monitoring the development of drug resistance in individual tumors and thus offer a new dimension in personalized medicine. In addition to

monitoring clinical course of tumor diseases upon drug treatment, whole genome sequencing techniques may be useful to measure the modulation of drug resistance by natural compounds. In addition to studies with large numbers of patient samples taken before and after treatment, longitudinal studies monitoring the same patients at the beginning of and during therapy may provide better insight into the individual mechanisms of resistance development in each individual tumor. This kind of research opens avenues for the prediction of individual response of a tumor patient to therapy. It would be of great value for patients to know whether or not a tumor will respond to the proposed therapy [31]. If a tumor is resistant, therapy will only cause toxic effects in normal tissues without effect on the tumor. Then, another more effective regimen could be applied or natural products alleviating the adverse side effects of chemotherapy could be applied.

Conflict of interest There is no conflict of interest.

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