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# The potential role of dietary plant ingredients against mammary cancer: a comprehensive review

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## KEYWORDS

Breast cancer; chemoprevention; dietary supplements; functional foods; molecular mechanisms; phytochemicals

## ABSTRACT

Breast cancer is known as the most devastating cancer in the global female community and is considered as one of the severe health care burdens in both developed and developing countries. In many cases, breast cancer has shown resistance to chemotherapy, radiotherapy and hormonal therapy. Keeping in view these limitations, there is an urgent need to develop safe, readily available and effective breast anticancer treatments. Therefore, the scientists are keen in the extraction of plant-based phytochemicals (organosulfur compounds, betalains, capsaicinoids, terpenes, terpenoids, polyphenols, and flavonoids) and using them as breast anticancer agents. Results of numerous epidemiological investigations have revealed the promising role of phytochemicals in the prevention and treatment of breast cancer. The diverse classes of plant bioactive metabolites regulate different metabolic and molecular processes, which can delay the proliferation of cancers. These phytochemicals possess chemo-preventive properties as they down-regulate the expression of estrogen receptor- $\alpha$ , inhibit the proliferation of cancer cells, and cause cell cycle arrest by inducing apoptotic conditions in tumor cells. This review article discusses the potent role of various plant-based phytochemicals as potential therapeutic agents in the treatment or prevention of breast cancer along with the proposed mechanisms of action.

## Introduction

Breast cancer is a disease associated with uncontrolled proliferation of cells in breast tissue. Majority of breast cancers forms lumps in lobules or ducts connecting lobules to the nipples (ACS 2019). Globally, breast cancer is known to be the second leading causes of death among women (Shareef, Ashraf, and Sarfraz 2016). Various factors, including gender, sedentary lifestyle, diet, alcohol consumption, age, family history, and several reproductive and hormonal factors, are thought to be the leading cause of breast cancer. Nevertheless, it is still unclear to identify any specific factor to be the most responsible in the pathogenesis of mammary cancer (Abdulkareem 2013). In 2012 it was considered as the second most common cancer with identification of 1.7 million new cases (Siegel, Naishadham, and Jemal 2012). In 2019, the National Cancer Institute estimated that one in eight women would produce mammary cancer in her life (Howlader et al. 2019). During January 2019, it was approximated that in the United States, more than 3.8 million women were alive who suffered mammary cancer in their past (ACS 2019). It is identified that mammary cancer is common in postmenopausal women rather than premenopausal. In South-East Asian women, the occurrence of breast cancer is low as compared to other women in Europe and America (Youn and Han 2020). The estimated figures for new cases and deaths in the United States are given in Table 1.

According to an estimate, nearly 12% of women could develop breast cancer during their life (Howlader et al. 2017). On the other hand, nearly 72% and 69% of women will develop breast cancer until the age of 80 who had inherited BRCA1 and BRCA2 mutations, respectively (Kuchenbaecker et al. 2017). BRCA1 and BRCA2 are two predominant human tumor suppressor genes that play an essential role in stabilizing the genetic material of cell by repairing the damaged DNA. Mutation or alteration of any of these genes results in impaired functionality of protein products hence resulting in improper repairing of damaged DNA. Therefore, normal cells are more prone to develop extra genetic alterations resulting in cancer. Women having inherited mutations in BRCA1 and BRCA2 genes have more chances of developing breast cancer compared with women having no inherited mutations of these genes (Friebel, Domchek, and Rebbeck 2014). Nearly 25% of hereditary breast cancer is reported to be due to mutation in BRCA1 and BRCA2 genes (Hawsawi et al. 2019).

**Table 1.** Approximated fresh cases and deaths in the United States during 1997–2017 (Jemal et al. 2004; Siegel, Naishadham, and Jemal 2012; DeSantis et al. 2014; DeSantis et al. 2011; Jemal et al. 2006; Jemal et al. 2008; Jemal et al. 2010; Jemal et al. 2009; Siegel et al. 2014).

Year	Approximated fresh cases			Approximated deaths		
	Both genders	Male	Female	Both genders	Male	Female
1997	181,600	1400	180,200	44,190	290	43,900
1998	180,300	1600	178,700	43,900	400	43,500
1999	176,300	1300	175,000	43,700	400	43,300
2000	184,200	1400	182,800	41,200	400	40,800
2001	193,700	1500	192,200	40,600	400	40,200
2002	205,000	1500	203,500	40,000	400	39,600
2003	212,600	1300	211,300	40,200	400	39,800
2004	217,440	1450	215,990	40,580	470	40,110
2005	212,930	1690	211,240	40,870	460	40,410
2006	214,640	1720	212,920	41,430	460	40,970
2007	180,510	2030	178,480	40,910	450	40,460
2008	184,450	1990	182,460	40,930	450	40,480
2009	194,280	1910	192,370	40,610	440	40,170
2010	209,260	1970	207,090	40,230	390	39,840
2011	232,620	2140	230,480	39,970	450	39,520
2012	229,060	2190	226,870	39,920	410	39,510
2013	234,580	2240	232,340	40,030	410	39,620
2014	235,030	2360	232,670	40,430	430	40,000
2015	234,190	2350	231,840	40,730	440	40,290
2016	249,260	2600	246,660	40,890	440	40,450
2017	255,180	2470	252,710	41,070	460	40,610

Currently, breast cancer is common in Pakistan and considered every ninth woman suffered, and prevalence is 2.5 times greater in Pakistan than other adjacent states like India and Iran (Asif et al. 2014). In Pakistan, the most common cancer developing within Muslim women is mammary cancer. The Confirmation from Karachi cancer registry specifies that the age uniform yearly level of mammary cancer is 69.1 per 100,000, which is the comparable rate to North America as well as Europe (Bhurgri 2004). The evidence from Shaukat Khanum hospital Lahore, Pakistan indicates that in 8 years period, there were presented 3,338 new cases of mammary cancer (Badar et al. 2005). In 2006, the multiple cases of breast cancer in Pakistani families were found 42.8% and 11.9% of BRCA1 and BRCA2 mutations for solitary cases of mammary cancer (Rashid et al. 2006). Among four Asian (China, Pakistan, Thailand, India) countries, highest breast cancer incidence and mortality rates were noticed in Pakistan (Mubarik et al. 2019; Mubarik et al. 2020).

Nowadays, research is focused on the prevention and treatment of cancer. In this context, the emphasis is on fighting cancer by employing anticancer agents that are effective, economical, safe, and have least side effects. Various approaches practised nowadays include radiotherapy, chemotherapy, phototherapy, stem cell transformation, and surgery of tumor. These methods to treat cancer are often associated with severe side effects (Patra, Mukherjee, and Kotcherlakota 2014; Vinogradov and Wei 2012). Most of these side effects include vomiting, nausea, pain, fatigue, gastrointestinal problems, hair loss, and weight alterations (Pearce et al., 2017; Schirmacher, 2019). Another limitation in the continual use of anticancer drugs is the resistance of cancer cells toward these drugs due to mutation. Hence, outcomes of various scientific investigations have revealed the potential of plant-based metabolites as potent anticancer agents owing to their effective and less toxic nature (Singh et al. 2016). In numerous countries, various medicinal plants (>3000) have been studied for their anticancer properties (Tariq et al. 2017; Alves-Silva et al. 2017). These phytochemicals (phenolic acids, flavonoids, terpenoids, polyphenols, etc.) are produced by different parts of plants such as leaves, flowers, roots, seeds, peels, fruits, and barks. These plant-derived anticancer agents have numerous health benefits by inducing anti-oxidative potential, activating DNA-repair mechanisms, and by suppressing cancer cell-activating proteins (Iqbal et al. 2017). This review is focusing on the chemo-preventive potential of plant-based phytochemicals, specifically against breast cancer.

### Symptoms

At the early stage of breast cancer, symptoms are undetectable, that explains the importance of early screening, but these symptoms can occur quickly, nearly in weeks or months. The most frequently, a painless lump is developing. Changes in the size or shape of breast are less common signs but can occur, and breast can become heavy, swelled and painful. The skin of that breast happens to change, its color becomes reddish, or an orange peel appears, and the skin wrinkled or dimpled. The nipple becomes thickened and retracted (Sharma et al. 2010).

### Risk factors

Certain lifestyle factors such as consumption of alcohol and fat-rich diet increase the incidence of breast cancer. Frequent consumption of alcohol increases the concentration of blood estrogen-related hormones and triggers the estrogen-receptor pathways. Alcohol consumption, even in small amount upgrades the risk of mammary cancer because it rises estrogen and androgen level (Singletary and Gapstur 2001). It was observed that the consumption of alcohol in women rises the possibility of mammary cancer, around 7% to 10% per approximately one drink in a day (Liu, Nguyen, and Colditz 2015). The women who have alcohol consumption of 2 to 3 drinks per day increase their risk factor of 20% as compared to nondrinkers. Before first pregnancy alcohol consumption may also significantly affect the risk (Liu, Nguyen, and Colditz 2015). Long-term smoking is also associated with an increased risk of mammary cancer.

**Table 2.** Projected new women mammary cancer cases and deaths by age in the United States during 2019.

Age (y)						
	N	%	N	%	N	%

<40	1180	2	11,870	4	1070	3
40-49	8130	17	37,150	14	3250	9
50-59	12,730	26	61,560	23	7460	18
60-69	14,460	30	74,820	28	9920	24
70-79	8770	18	52,810	20	8910	21
80p	2830	6	30,390	11	11,150	27
	48,100		268,600		41,760	
<i>In situ</i> cases			Invasive cases			Deaths

Total

NAT2 genetic polymorphism identified in smokers might confer an elevated risk of mammary cancer (Kispert and McHowat 2017). It has been reported that smoking addict women before their first pregnancy had a 21% more possibility to develop breast cancer than nonsmoker women (Gaudet et al. 2013). Radiation exposure is also a risk factor in increasing breast cancer, and this was studied during an atomic bomb attack in Japan. After the incident, survivors and females between 10 and 30 years of age were treated through high dosage radiations therapy to the chest (Preston et al. 2002). The breast cancer started to appear about eight years after treated with radiations (Travis et al. 2003).

Around the globe, main risk factors that relate to breast cancer could be characterized as demographic (age, gender), reproductive (age of first menstruations, age of menopause, full-term pregnancy, abortion, and pregnancy characteristics), hereditary (genetic and family history), hormonal (oral contraceptives and HRT-hormone replacement therapies), lifestyle (diet, obesity, alcohol consumption, smoking, and physical activity), and some other factors (air pollution, diabetes, and radiation). Among these, gender and age are major risk factors of breast cancer. This disease is mostly associated with female gender, and in males, the incidence of this cancer is very low (>1%) as compared to other malignancies. Important risk factors of occurrence of breast cancer in old aged men may be any family history of breast cancer, hormonal imbalance, and mutation in human tumor suppressor gene (BRCA2) (Momenimovahed and Salehiniya 2019). Besides gender, the second leading risk factor for breast cancer is age. As the age increases, possibilities of breast cancer increase till the age of menopause, where the rate of breast cancer is maximum. After this age, there is a slight decrease in the rate of breast cancer and remains constant throughout the lifespan (Kim, Yoo, and Goodman 2015). In the United States, nearly 99% and 71% mortalities due to breast cancer were observed in women at an age above forty and sixty, respectively. The approximated new cases and deaths of the female by age due to breast cancer during 2019 are figured out in Table 2.

Among reproductive risk factors, younger age of first menstruations, first pregnancy in late age, and old age menopause are associated with increased risk of breast cancer. Risk of breast cancer decreased up to 5% and 10% with every one-year delay in age of menarche and multi-parity, respectively. At the same time, the risk of breast cancer increases by 3% with every one-year delay in the age of menopause (Horn and Vatten 2017). Use of orally administrated contraceptive pills and estrogen hormone replacement therapies (HRT) in post-menopause are also reported to be linked with an elevated risk of breast cancer. Whereas, frequently exercising postmenopausal women in the age group of 50 to 79 years were reported to have reduced risk of breast cancer (Sun et al. 2017; Momenimovahed and Salehiniya 2019).

### Mammary anticancer effects of dietary phytochemicals

Phytochemicals, from the Greek word “*Phuton*” meaning plants, are chemical compounds that are produced by plants. Phytochemicals are usually mixed up with phytonutrients. Whereas phytochemicals are chemical compounds which may be favorable or may be harmful to human health, phytonutrients are chemical compounds, which have a positive effect on human health. All phytonutrients are phytochemicals, but not all phytochemicals are phytonutrients. Phytochemicals can be highly toxic as illustrated with ricin, found in castor seeds, which is one of the highly toxic and potent phytochemical poisons in the world (Tiwari, Brunton, and Brennan 2013). However, all phytochemicals are not toxic and harmful (Endo et al. 1987). If phytochemicals are protective agents for the plants, various studies reported their protective activities in different Human diseases, especially in cancer prevention.

Additionally, the results of several studies have reported the inhibitory effect of anti-breast cancer plant metabolites on cell cycle phases (Figure 1). Resveratrol from grapes, genistein from soybean, and quercetin from onion are known to be used as mammary anticancer agents (Jang et al. 1997; Murakami, Ashida, and Terao 2008; Nakagawa et al. 2000). Thousands of dietary phytochemicals from fruits, vegetables, grains, leaves, stems, roots of different plants may be designed for handling different infections. In this review, we reported and discussed some chemical compounds, which are extracted from dietary plants and used as mammary anticancer agents displayed in Figure 2. Furthermore, the effect of plant phytochemicals on different mechanistic path- ways involved in modulation of breast cancer is shown in Figure 3.

### Organosulfur compounds

Organosulfur compounds are the subclass of organic com- pounds which contain sulfur. They are present in both animals and plants sources. In plants, they are found in *Allium* species vegetables as well as in plants of *Brassica* and *Eruca* genera. They are reported as biologically active compounds (Goncharov et al. 2016), and some organosulfur dietary compounds are suggested to inhibit breast cancer.

Allicin (1) is an organosulfur compound belonging to the Alliaceae family, obtained from the underground stem of fresh garlic (Block 1985). It was shown to have very healthy and beneficial effects. Allicin would be able to prevent substantial progress in colon, breast and endometrial cancer cells along with many human fibroblast lines. These effects can be attributed to its ability to reduce the level of cellular glutathione transiently (Hirsch et al. 2000). Allicin was reported to inhibit TNF-alpha-induced VCAM-1 protein expression in human breast MCF-7 cancer cell line up to 10 ng/mL, and to reduce tumor cell migration and invasion (Lee et al. 2015).

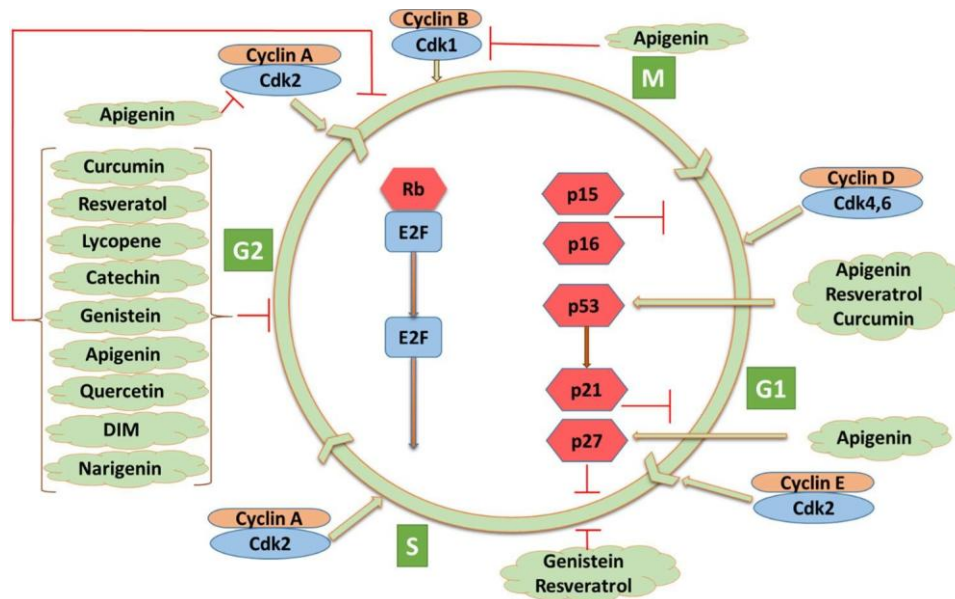


Figure 1. Inhibitory effects of anti-breast cancer plant metabolites on cell cycle phases.

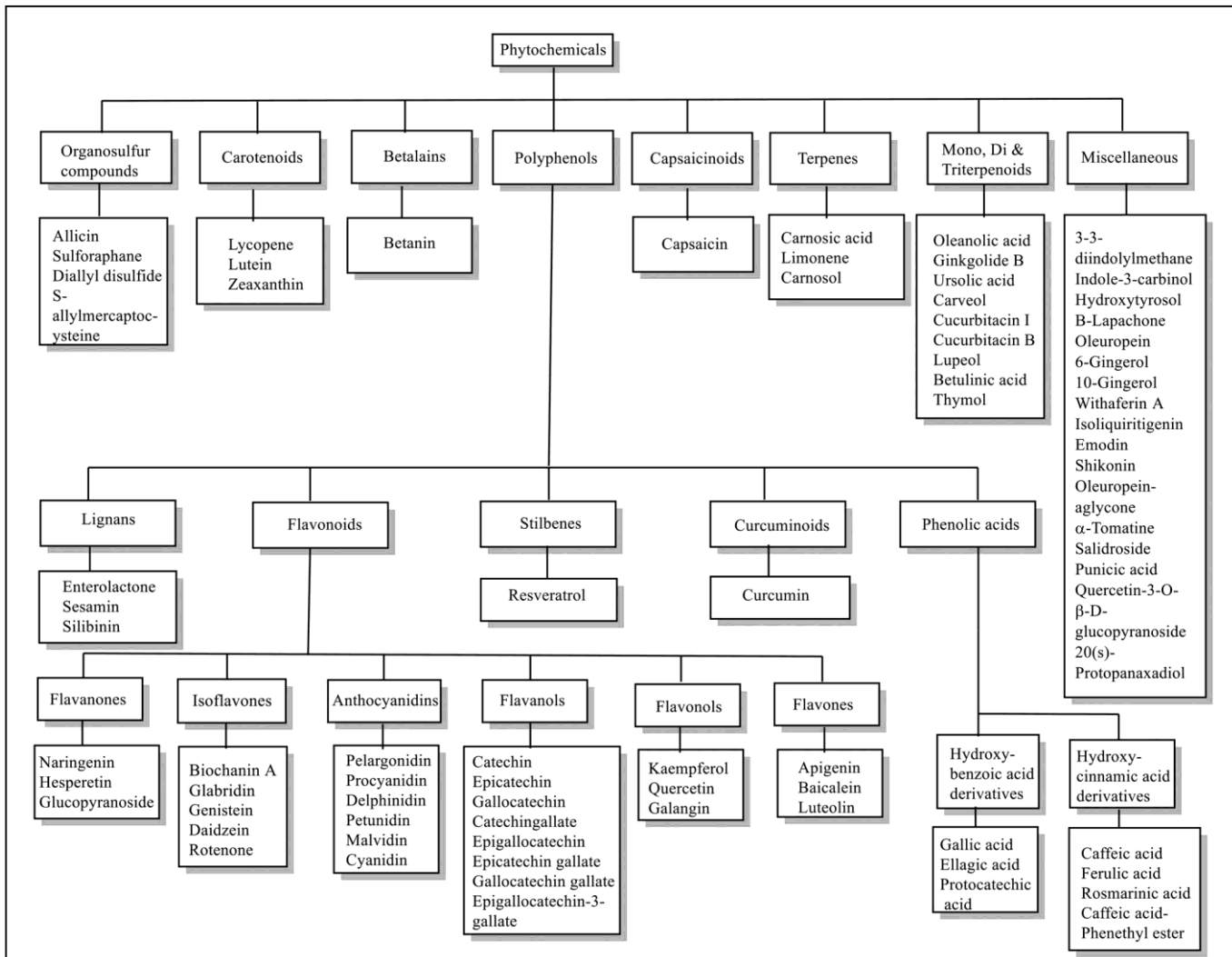


Figure 2. Classification of some dietary phytochemicals used as mammary anticancer agents.

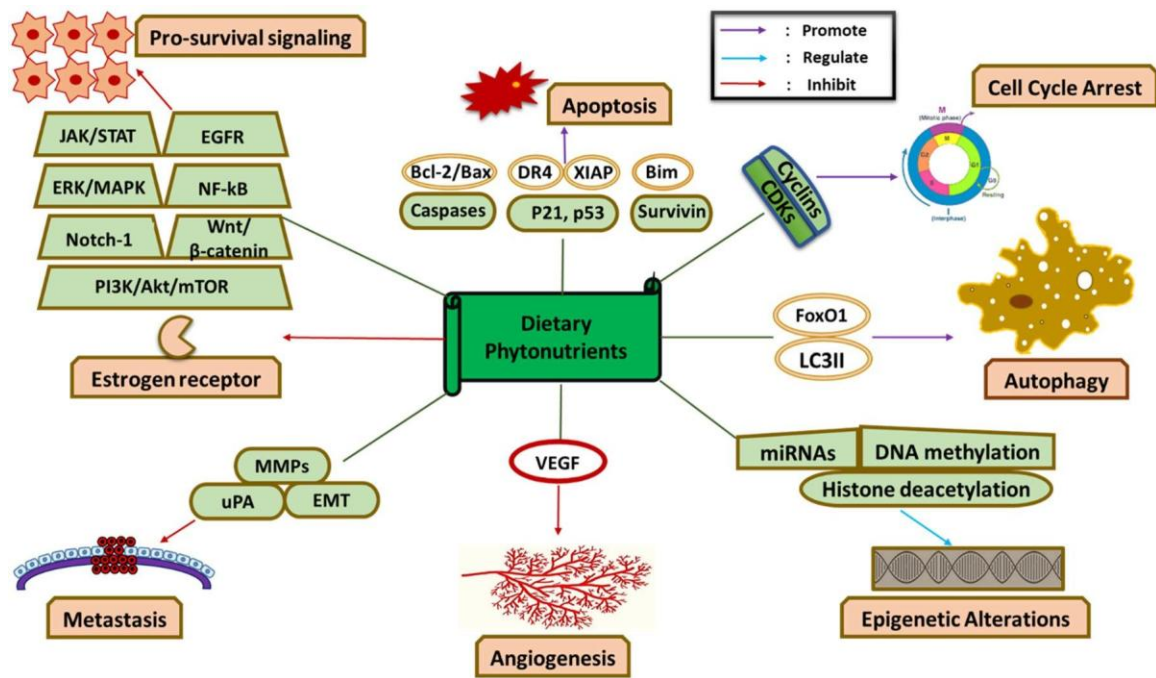


Figure 3. Effects of plant phytochemicals on different mechanistic pathways involved in modulation of breast cancer.

Sulforaphane (2) is an isothiocyanate derivative, present in broccoli and broccoli sprouts. It has been reported as being able to down-regulating Wnt-beta catenin, one of the key pathways that promote self-renewal of breast cancer stem cells (Li et al. 2010). Accumulating studies provide support for the concept that breast carcinogenesis results from the deregulation of self-renewal pathways of normal mammary stem cells (Liu, Nguyen, and Colditz 2015) and might provide a novel approach for breast cancer treatment. Naturally occurring phytochemicals are known to be chemo- preventive metabolites having the potential to either delay, block or reverse the initiation and propagation of cancer. Sulforaphane is one of the most important phytochemical possessing anti-cancer perspectives. Purposely, Hussain and its coworkers reported the chemo-preventive potential of sulforaphane administration individually and in combination with gemcitabine (anti-cancer drug) on the proliferation of breast cancer cells (MCF-7) via modulating the expression of cyclooxygenase-2 (COX-2) and Bcl-2 in a time-dependent manner. The cytotoxic potential of sulforaphane would be due to apoptosis of breast cancer cells in a concentration - and time-dependent manner. The combined treatment of sulforaphane and gemcitabine synergistically caused a growth inhibitory effect on MCF-7 cells with a combination index of less than one. Therefore, the combined use of sulforaphane and gemcitabine not only could enhance the effectiveness of gemcitabine but also reduces toxicity in normal cells (Hussain et al. 2013). Similarly, *in vitro* and *in vivo* investigations have revealed the potential of sulforaphane in suppressing the proliferation of triple-negative breast cancer cells (TNBCs). Sulforaphane inhibits the growth of cancer cells and retards the formation of cancer stem-like cells tumor sphere in TNBC (Castro et al. 2019).

Diallyl disulfide (DADS, 3) is a non-polar organosulfur compound soluble in oil and other non-polar solvents. It has been extracted from underground stems of garlic and also found in other plants of the Alliaceae family. DADS is responsible for strong garlic smell (Nakagawa et al. 2001). Various *in vitro* and *in vivo* models have been studied to assess the antitumor potential of diallyl disulfide. Purposely, Huang et al. (2015) reported that the effect of DADS reduced the viability, elevated apoptotic conditions, and suppressed the metastatic potential in examined TNBC line (*in vitro*). Moreover, DADS dysregulated Bcl-2, downregulated matrix metalloproteinase-9 (MMP-9) and reversed EMT (epithelial-mesenchymal transition) via inhibition of the *b*-catenin signaling pathway. Further, *in vivo* findings also authenticated the anti-cancer perspectives of DADS in experimented MDA-MB-231 xenograft mice. Due to DADS treatment, a significant reduction in size and weight of tumor cells, along with the reduced expression of active *b*-catenin was noticed. Outcomes of this study suggested that the use of DADS might help prevent and treat breast cancer (Huang et al. 2015).

It was also reported that DADS significantly prevented the development of human mammary cancer cells both in estrogen receptor (ER) positive (MCF-7 and KPL-1) and negative (MLK-F and MDA-MB-231) *in vitro* and *in vivo*. Results of MTT-assay revealed  $IC_{50}$  of DADS ranging from 1.8 to 18.1  $\mu$ M post 72 h of incubation. In all four examined cell lines, treatment of DADS reduced the number of viable cells and induced cytotoxicity in a concentration - and time- dependent manner. Likewise, as compared to controls, treatment of DADS (1.8  $\mu$ M) in MDA-MB-231 cells resulted in apoptotic conditions due to Bax protein elevation (142%),

Bcl-XL protein reduction (38%), and caspase-3 up-regulation (438%). DADS was reported to mitigate the cancer cell stimulatory effect of linoleic acid while the synergistic effect was observed when administrated with eicosapentaenoic acid (cancer cell suppressor) (Nakagawa et al. 2001).

S-allylmercaptocysteine (SAMC, 4) is an organosulfur compound, of aged garlic, also present in other *Allium* species vegetables. When tested on the proliferation and viability of diverse cancer cell lines, including erythroleukemia and hormone-dependant cancer cell lines, the two hormones of prostate and mammary responsible cancer cells clearly showed to be more sensitive to the growth-inhibitory influence of thioallyl compounds. The anti-proliferative potential of stable thioallyl compound SAMC has been examined on hormone-responsive breast cancer (MCF-7) cell line. Treatment of SAMC at a dose of >0.1 mM has shown complete growth inhibition of MCF-7 cells, furthermore than 60% suppression was noticed at the SAMC dose of 0.05 mM (Sigounas et al. 1997). Treatment of SAMC has effectively delayed cell growth, caused cell cycle arrest, and induced apoptotic conditions in MCF-7 (ER-positive) and MDA-MB-231 (ER-negative) cell lines. This potential of SAMC was mainly due to activation of caspase-3 and caspase-9, upregulation of p21, p53, and Bax, and downregulation of Bcl-XL and Bcl-2 (Yi et al. 2019).

### Betalains

Betalains are a group of red and yellow aromatic indole derivative pigments, frequently soluble in water. Most of these heteroside compounds have been isolated from plants of the order Caryophyllales, but are also present in *Bougainvillea* and some higher fungi such as *Amanite* (Baldassano et al. 2011). Betalains structures are close to flavonoids; their difference is that betalains react negatively to Erdmann test and migrate as anions even at a low PH of 2.4 (Piattelli, Minale, and Nicolaus 1965). Two categories of betalains are distinguishing according to the color of the pigment, namely betacyanins, which include the reddish to violet pigments and betaxanthins, which are yellow to orange pigments. Mostly betalains are used as coloring agents. Betanin (5) is the most abundant betacyanins pigment, mostly present in pokeberries and beetroots, isolated the first time in 1918 (Schudel 1918). Betanin contains nitrogen, which sets it apart from anthocyanins (Schudel 1918). It is reported that betanin acts against oxidative stress (Tesoriere et al. 2009) and that it can also significantly reduces the growth of several cancer cell lines such as breast, prostate (Kapadia et al. 2013) as well as colon, liver, skin cancer cells (Lechner et al. 2010). The 25 mM betanin dose was reported as an IC<sub>50</sub> value against MCF-7 breast cancer cells. At low concentration, purified betanin and its isomer isobetanin revealed cytotoxic activity against tumor cells expressing functional p53 and very little or negligible effects against normal cells. In p53, wild-type tumor cells, betanin/ isobetanin extracts showed inducing apoptosis and autophagy. Moreover, betanin enriched extracts prevent some p53-mutated tumor cells development, without inducing apoptosis (Nowacki et al. 2015).

### Capsaicinoids

Chili peppers contain the group of phytochemicals called capsaicinoids, which are responsible for the spiciness of the peppers (Tremblay, Arguin, and Panahi 2016). Capsaicinoids mostly contain homocapsaicin, nordihydrocapsaicin, dihydrocapsaicin and homodihydrocapsaicin. They are biologically active compounds that showed acting as anticancer, anti-obesity, anti-inflammation and antioxidant agents (Luo, Peng, and Li 2011). Capsaicin (6), is a capsaicinoid, identified as being the alkaloid *trans*-8-methyl-*N*-vanillyl-6-nonenamide, a vanilloid receptor agonist. It constitutes the major pungent principle found in chili peppers of the *Capsicum* plants genus (Monseesorn et al. 1982). It prevents hunger, reduces in fullness and energy expenditure and fat oxidation (Tremblay, Arguin, and Panahi 2016) and has excellent growth-inhibitory effects against various tumor cells. It was demonstrated to be associated with cell-cycle arrest and apoptosis in the breast cancer cells. *In vitro* and *in vivo* investigations on breast cancer cells, including both ER-positive (BT-474, MCF-7, and T47D) and-negative (MDA-MB231, and SKBR-3) cancer cell lines, showed that capsaicin played an essential role as a novel moderator of EGFR/HER-2 pathway with a prospective starring role in the therapy and the blocking of the human mammary tumor (Thoennissen et al. 2010).

### Terpenes

Terpenes are a diverse class of hydrocarbon molecules comprising of isoprene units (5-carbons) and known as the largest type of plant secondary metabolites (Tidgewell, Clark, and Gerwick 2010). Two main representants, namely limonene and carnosic acid, are recognized as breast anticancer agents. Carnosic acid (7), a phenolic diterpene found in numerous Labiaceae plants, especially in leaves of the Mediterranean half-shrub rosemary, revealed anti-mammary tumor properties (Yesil-Celiktas et al. 2010). Alone or combined with curcumin, it may be useful to prevent and treat ER-negative breast cancer (Einbond et al. 2012). Furthermore, carnosol (8), the major oxidized metabolite of carnosic acid, which acts as an antioxidant agent, also showed anticancer activities (Lo et al. 2002) with IC<sub>50</sub> values of 83 mM at 24 h and 25 mM at 48 h (Al Dhaheri et al. 2014). Further investigation on its mechanism of action revealed that it arrested at G2 phase of the cell cycle the development of invasive triple-negative MDA-MB-231 breast cancer cell line and induced ROS-dependent apoptosis as well as beclin1-independent autophagy (Al Dhaheri et al. 2014).

D-limonene (9), a monocyclic monoterpene, was found in various fruits such as lemons, oranges, mandarins and grapes. Although it may use as flavor and also in perfumes, foods and soaps because of its pleasant smell (Sun 2007), it is also recognized as an anticancer agent in different types of cancers. Limonene showed acting as an anti-mammary agent during different phases of the cell cycle such as initiation, promotion and progression phases, also had chemotherapeutic activities against rodent models with mammary malignancy (Crowell 1997). As it is well-tolerated, showing minimal toxicity in preclinical studies, it entered in phase-I of the clinical trials in patients with advanced cancer (Vigushin et al. 1998). A limited phase II evaluation followed this promising study in breast cancer.

### Terpenoids

Terpenoids are modified terpenes, also derived from isoprene units, but most of them present multi-cyclic structures with oxygen containing functional groups. In plants, terpenoids play diverse functional roles such as hormones, structural components of membranes, electron carrier and photosynthetic pigments. Furthermore, they can be involved in communication and defense, as attractants for pollinators and seed dispersers, competitive phytotoxins, antibiotics, and herbivore repellents as well as toxins (McGarvey and Croteau 1995). They are also found in almost all living organisms; some of them being biologically active and recognized as able to fight against malaria, inflammation, cancers and other diseases (Mbaveng, Hamm, and Kuete 2014).

### Carotenoids

Carotenoids are more than 1,100 colored pigments from yellow-orange to red colors, of tetraterpenoids family, that can be found in

photosynthetic bacteria, algae and plants. According to the presence or absence of oxygen in their structure, they are categorized into two classes: carotenes, which are oxygen-lacking carotenoids, as illustrated with beta-carotene, lycopene, and xanthophylls, which are the oxygenated carotenoids such as lutein, and zeaxanthin (Misawa 2010). Carotenoids give orange, red and yellow color to the plants but some red plants have no carotenoids. Around 40 to 50 of carotenoids of the human diet are provided by vegetables and fruits. The most common dietary carotenoids are alpha-, beta-carotenoids, lycopene and lutein. Some of them are recognized acting as breast anti-cancer agent, as illustrated with lycopene (10), a phytochemical carotenoid found in tomatoes, strawberries, cherries, papayas and carrots, but which has no provitamin-A function (Upadhyay 2018). However, it was evidenced that a large extent of lycopene reduces lungs, stomach, prostate, oral cavity, colon and mammary cancers with IC<sub>50</sub> values in the range of 1–2 mM (Levy et al. 1995; Giovannucci 1999).

Additionally, lycopene revealed to inhibit insulin-like

growth factor-1-stimulated growth, which is autocrine / paracrine regulators of breast cancer cell growth. Hence, this action of lycopene might lead to new fronts in research focusing on the effect of lycopene treatment on regulation of endometrial cancer and other tumors. Lutein (11) is a xanthophyll family carotenoid, also recognized as anti-mammary agent. It is found in egg yolks, yellow carrots and vegetables of green leaves like kales and spinaches; this two latter having the highest amount of lutein. Its anti-mammary activity was investigated in female BALB/c mice, which were fed with 0.002% to 0.2% lutein. The results showed that the lowest volume of breast tumor had been observed with mice fed with 0.002% dietary lutein. Authors also indicated that at this dose, dietary lutein acted by selectively modulating apoptosis, and by inhibiting angiogenesis (Chew et al. 2003). Zeaxanthin (12), is a constitutional lutein isomer with, as the only difference, the location of a double bond in one of the ionone rings; each having a variety of different stereoisomers (Krinsky, Landrum, and Bone 2003). In the eye, lutein and zeaxanthin constitute macular pigments of the yellow region near the center of the retina, forming a very efficient filter for blue light, and high protection to healthy cells of eyes (Krinsky, Landrum, and Bone 2003).

### Triterpenoids

Some triterpenoids, such as oleanolic acid (13) and its iso-merursolic acid (14), have been reported to possess mammary anticancerous properties. Both are pentacyclic triterpenoid compounds, present in a free acidic form in Nature, and widely spread in plants kingdom, especially in the species *Olea europaea*, *Wrightia tomentosa*, *Rosa woodsii* and *Prosopis glandulosa*. They revealed similar and diverse pharmaceutical activities such as anti-inflammatory, hepato-protective, anti-oxidant properties and anticancer effects (Jesus et al. 2015). Oleanolic acid, the active component of *Wrightia tomentosa*, showed inhibitory activity against MCF-7 and MDA-MB-231 mammary tumor cell lines with IC<sub>50</sub> values of 7.5 and 7 mg/mL, respectively. This proliferation inhibition and the observed pro-apoptotic effects revealed to be due to induction of apoptosis pathway (Chakravarti et al. 2012). Ursolic acid is also present in many other plants such as basil, cranberries, blueberries, elderflowers, rosemary and others. Ursolic acid showed its ability to induce apoptosis and to modulate glucocorticoid receptor and activator protein-1 in MCF-7 cells (IC<sub>50</sub> value of 0.4 mM) (Kassi et al. 2009).

Similarly, various plants of Cucurbitaceae family contain a diversified class of triterpenoids known as Cucurbitacins (Chen et al. 2005). It has been found that tyrosine-phosphorylated signal transducer and activator of transcription 3 (STAT3) has a vital role in human tumor malignancies. Cucurbitacin I (15) has reported suppressing the propagation of MDA-MB-468 (human breast carcinoma) cells line due to inhibition of phosphor-STAT3 and induction of apoptotic conditions (Blaskovich et al. 2003). Anticancer effect of Cucurbitacin B (16), another triterpenoid presents in family Cucurbitaceae, has been studied against six different human cancer cell lines (MDA-MB-231, MCF-7, BT474, MDA-MB-453, T47D, and ZR-75-1). Moreover, it showed that the proliferation of these human cancer cells suppressed because of the disruption of microtubules and F-actin (Wakimoto et al. 2008).

Lupeol (17) is a pentacyclic lupine-type triterpene (a phytosterol family, also named fagarsterol, clerodol, lupenol), mainly found in strawberries, green peppers, olives, white cabbages, grapes and mangos. Lupeol offers a broad spectrum of pharmaceutical activities, especially in anti-inflammatory diseases. In particular, lupeol showed reducing the prostaglandin E2 (PGE2) manufacturing in A23187-stimulated macrophages (Fernandez et al. 2001). It also showed anti-tumor activities against diverse cancers, including against MCF-7 breast cancer cell line, for which an IC<sub>50</sub> value of 50 mM was reported (Balapure and Wadegaonkar 2014). Lupeol stimulates the decoying effect of RA4 DNA sequence and in MDA-MB-231 ER $\alpha$ -negative mammary cancer cells was risen the level of ER $\alpha$  gene expression (Lambertini et al. 2005). A study on its mechanism of action was provided, showing its multi-target functionalities with a great anti-inflammatory potential targeting key molecular pathways which involve nuclear factor kappa B (NF $\kappa$ B), cFLIP phosphatidylinositol-3-kinase (PI3K)/Akt and Wnt/ $\beta$ -catenin in a variety of cells (Saleem 2009). Due to its therapeutic effect at doses which exhibited no toxicity to normal cells and tissues, preclinical studies have been undergone in order to evaluate its chemopreventive activity, especially in cancers.

Betulinic acid (3 $\beta$ -hydroxy-lup-20(29)-en-28-oic acid)

(18) is a pentacyclic triterpene, extracted from birch trees. It revealed *in vitro* and *in vivo* potential anticancer effects, especially against breast cancers (Mertens-Talcott et al. 2013; Potze et al. 2014). Additionally, ionic derivatives of betulinic acid with water solubility improvement revealed higher cyto-toxicity against MCF-7 breast cancer cell line. Significantly, the derivative (19) showed an IC<sub>50</sub> value of 25  $\mu$ M, which is around four-fold lower than that of betulinic acid (Suresh et al. 2012). Investigation of betulinic acid mechanism of action revealed a high complexity. Induction of apoptosis in cells p53 independent cells was shown. However, in very resistant triple-negative breast cancer cells (ER, progesterone receptor and HER2-negative), betulinic acid revealed to target Sp transcription factors. As Sp-specificity proteins are overexpressed in cancers and take part in the proliferation and angiogenic phenotype affiliated with tumor cancer cell lines, this result suggests a high potential of betulinic acid in clinical trials. Recent studies showed that it could attenuate migration and invasion of highly aggressive breast cancer cells *via* aerobic glycolysis inhibition. It also revealed a novel regulatory pathway between GRP78 and glycolytic metabolism in cancer cells (Zheng et al. 2019).

### Diterpenoids

Ginkgolides are diterpenes comprising of twenty-carbon atom skeleton and are abundantly present in Ginkgo biloba tree. Investigations on ginkgolide B (20) from the fruits of *Ginkgo biloba* revealed that the expression and localization of peripheral-type benzodiazepine receptor (PBR) correlated with human breast cancer cell proliferation and aggressive phenotype expression. Studies showed that although it did not affect the proliferation of non-aggressive MCF-7 cell lines, ginkgolide B revealed inhibitory activity against the highly aggressive MDA-MB-231. This latter, in opposite to MCF-7 cells, are rich in peripheral-type benzodiazepine receptors (Papadopoulos et al. 2000). These results suggested that the modulation of PBR expression could be used to control tumor growth (Papadopoulos et al. 2000). It has been reported that treatment of MCF-7 cells with ginkgolide B resulted in apoptosis due to induction of ROS (reactive oxygen species) production and elevation in the intracellular content of nitric oxide (NO) as compared to the untreated control group (Chan 2007).

### Monoterpenoids

Carveol (21), extracted from celery, also showed *in vivo* anticancer activity against mammary cancer MCF-7 and MDA-MB-231 cell lines with



IC<sub>50</sub> values of 1.2 and 1.0 mM, respectively (Patel and Thakkar 2014). Thymol (22) is another monoterpene abundantly present in fruits of *Trachyspermum ammi*. Thymol has been reported possessing cytotoxic potential along with the effect on apoptotic gene expression in numerous malignancies. Thymol revealed anti-cancer properties against MCF-7 cell line with IC<sub>50</sub> values as 54 mg/mL (48 h) and 62 (72 h) mg/mL. It further induced apoptotic conditions in MCF-7 cells by affecting the p21 and p53 gene expression (Seresht et al. 2019).

### Polyphenols

Polyphenols, with more than 10,000 compounds, represent a broad chemical class found in vegetables, fruits, cereals and some beverages (Lason and Leskiewicz 2013). In plants, they are involved in the UV protection and defense against pathogens. In Humans, they are recognized as having potential health benefits, mainly due to their antioxidant properties. They provide significant protection against the development of diverse chronic pathologies including cancer, but also diabetes, cardiovascular diseases and aging. A majority of various polyphenols has been reported acting as breast anticancer agents. Polyphenols are classified into four sub-classes, according to the number of phenol rings they contain in their structure: lignans, stilbenes, curcuminoids, phenolic acids, and flavonoids.

### Lignans

Lignans are diphenolic compounds, found in fiber-rich plants such as vegetables, grains, nuts, seeds as well as different beverages (Yoder et al. 2015). Flax and sesame seeds, which provide enterolactone and sesamin, respectively, have been mainly studied. Both are known natural antioxidants with potential health efficacy, mostly as mammary anti-cancer agents, due to their structural similarity to 17-*b*-estradiol, being able to act as estrogenic and antiestrogenic compounds.

Flaxseeds of genus *Linum* in the Linaceae family are a rich source secoisolariciresinol diglucoside (Kitts et al. 1999), which is converted by a consortium of intestinal bacteria into active mammalian lignans, namely enterodiols and enterolactone (Tour'e and Xueming 2010). Enterolactone

(23) showed an IC<sub>50</sub> value of 82 mM at 24 h against MCF-7 cell lines (Danbara et al. 2005). It showed reducing the growth of hormone-sensitive breast cancer, and it was suggested to be ER-mediated due to observed lignan binding to ER (Saarinen et al. 2000). Sesamin (24) is the most abundant lignan found in sesame seeds. It was reported to arrest the growth in the G1 phase of the cell cycle of human MCF-7 cell lines. This growth inhibition activity was correlated with down-regulation of cyclin D1 protein expression, a proto-oncogene that is overexpressed in many human cancers, through activation of proteasome degradation of cyclin D1 protein (Yokota et al. 2007).

Silibinin (25), from milk thistle *Silybum marianum* L., is known as a hepatoprotective agent in traditional phytotherapy. It showed to induce apoptosis in human breast cancer MCF-7 cells by down-regulated the expression of the ER alpha (ER $\alpha$ ) through up-regulation of caspase 6 (Zheng et al. 2015). Furthermore, in triple-negative mammary cancer cell line MDA-MB-231, its action revealed to be connected with Wnt/*b*-catenin signaling inhibitory activity by suppressing lipoprotein receptor-related protein-6 (LRP6) expression at the transcription level (Lu et al. 2012). LRP6 is an essential co-receptor for the Wnt/*b*-catenin-signaling pathway, known for playing an important role in breast cancer development and progression. Silibinin also showed down-regulating the potent tumor promotor 12-*O*-tetradecanoyl phorbol-13-acetate-induced MMP-9 expression by controlling COX-2 expression in mammary cancer cells MCF-7 and MDA-MB231 (Kim et al. 2009). Furthermore, its synergistic effects, when it is combined with paclitaxel in both wild-type and drug-resistant MDA-MB-435 and MCF-7 breast cancer cells, were correlated with a significant increase in the level of the pro-apoptotic protein BAX and a significant decrease in the level of the anti-apoptotic proteins, Bcl2 and survivin. These results have proposed silibinin as a useful drug in breast cancers prevention and treatment (Molavi et al. 2017).

### Stilbenes

The most known stilbene, 3, 5, 4<sup>0</sup>-trihydroxystilbene, is resveratrol (26), first discovered by Michio Takaoka, in the grapes of *Veratrum grandiflorum* (Takaoka 1940). Later, it was reported in 1977 by Langcake from grapevines leaves, as a phytoalexin, being produced in response to pathogen or environmental damages (Langcake and Pryce 1977). Although mainly present in the red grape peel, it is also found in blueberries, raspberries and peanuts. *Cis*- or *trans*- configuration of resveratrol can be found as well as their glycosylated forms (Le Corre et al. 2005). Resveratrol, in its *trans*-configuration, was reported as a breast anti-cancer agent. It showed an IC<sub>50</sub> value of 25 mM against MCF-7 breast cancer cells stably transfected with CYP19 (MCF-7 aro) (Wang et al. 2006). Due to its structural similarity to the estrogen agent diethylstilbestrol, it is considered as a phytoestrogen, able to act as either estrogen agonist or antagonist agent. Such compounds have generated tremendous interest because of their potential use in hormone replacement therapy and cancer prevention. Estrogen, which is synthesized from cholesterol, is catalyzed at the final reaction by the enzyme named aromatase CYP19. Inhibitors of aromatase have been recently developed for their potential chemo-prevention and therapy activity. From 1997, resveratrol's inhibitory involvement in the different tumor events, namely initiation, promotion and progression was demonstrated in mice breast cancers, suggesting it's useful as a potential chemo-preventive agent in breast cancer (Jang et al. 1997). Later, the phytoestrogenic activity of resveratrol was demonstrated by its potential to bind and to initiate alpha- and beta-ERs control transcription of estrogen-responsive target genes. Resveratrol revealed inhibitory activity against breast cancer cell growth in both ER-positive and -negative cell lines by an apoptotic mechanism (Nakagawa et al. 2001).

### Curcuminoids

Curcuminoids are the yellow pigments found in turmeric, the rhizome of *Curcuma longa* L. of the Zingiberaceae family. Curcumin (27), the major compound extracted from turmeric rhizome, traditionally used in Indian culinary curries, is well known for its antioxidant and anti-inflammatory properties (Maheshwari et al. 2006). It also revealed anticancer activities, especially toward human breast cancer, revealing to be more efficient against MCF-7 cell line than against the human mammary epithelial cells MCF-10A with IC<sub>50</sub> values of 29 and 55 mg/mL at 24 h, respectively (Ramachandran et al. 2005). Its antiproliferative effects are estrogen-dependent in MCF-7 ER-positive cells. Additionally, its significant *in vitro* anti-invasive effects revealed not to be estrogen-dependent in the MDA-MB-231 ER-negative breast cancer cells (Shao et al. 2002). It showed to induce apoptosis in mammary cancer cells by its influence on numerous signaling pathways, suggesting its potential use for prevention and treatment of mammary cancer (Duvoix et al. 2005).

### Phenolic acids

Phenolic acids are largely distributed in plants, vegetables and fruits. They play a significant role in the growing and reproduction, but their primary role is to protect damaged plants against pathogens (Sahelian 2018). They also showed remarkable potential against different types of diseases, including cancer. According to the number of phenolic cores in their structure, phenolic acids are classified into hydroxy-benzoic acids and hydroxy-cinnamic acids.

*Hydroxy-benzoic acids*. Hydroxy-benzoic acids such as gallic acid, ellagic acid and protocatechuic acid showed acting as mammary anticancer

agents. Gallic acid (28) also known as 3, 4, 5-trihydroxybenzoic acid is found in different fruits, especially in gallnuts, and also in tea leaves. Its broad biological activities include anti-inflammatory, antiallergic and anti-carcinogenic properties. Gallic acid is also studied for its antitumor effects, especially in reducing the growth of MCF-7 human breast cancer cell in a dose dependent manner (Hsu et al. 2011). Authors explored its mechanisms of action, showing that it acted at the G2/M phase, resulting in an increase of the kinase inhibitor proteins p27<sup>Kip1</sup> and p21<sup>Cip1</sup> by suppressing Skp2-mediated polyubiquitination.

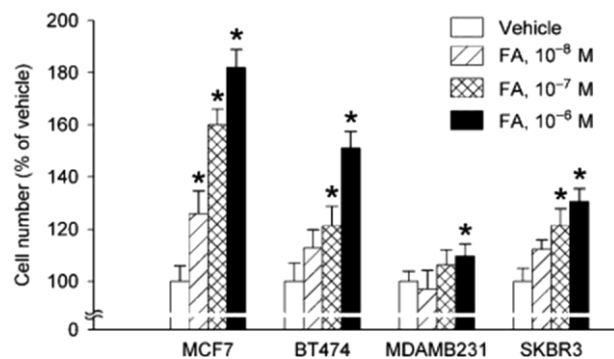


Figure 4. Effects of Ferulic Acid in four human mammary tumor cell lines (Chang et al. 2006). Reproduced with copyright permission from John Wiley and Sons.

Protocatechuic acid (29) also known as 3, 4-dihydroxybenzoic acid is found in numerous medicinal plants, also in fruits, especially gooseberries, grapes and nuts. Protocatechuic acid showed to inhibit the proliferation of T47D breast cancer cell line, revealing a potent inhibitory activity with an IC<sub>50</sub> value of 2 × 10<sup>-11</sup> M (Kampa et al. 2004). Ellagic acid (30) is a dimeric derivative of gallic acid, widely distributed in plants, red fruits such as grapes and pomegranates (Khalil et al. 2018; Khalil et al. 2017), berries including raspberries, strawberries, blackberries, cranberries, and some nuts such as pecans and walnuts. In plants, it is present in vacuoles as hydrolyzable, water-soluble ellagitannins, but can also be present in free form (Brat 2008). It was reported as an anticancer agent, suppressing MDA-MB-231 breast cancer growth by inhibiting angiogenesis. Exploring its mechanism of action revealed that it acted by suppressing VEGFR-2 tyrosine kinase activity, an essential target in the strategy of cancer therapy, with an IC<sub>50</sub> of ~25.8 nM and by blocking its signaling pathway (Wang, Oo Khor, et al. 2012).

**Hydroxy-cinnamic acids.** Hydroxy-cinnamic acids are prenylpropanoids, present in different plants and seeds of fruits, vegetables and cereals and also in tea, cocoa, and wine. They are bio-synthesized through the shikimate pathway, starting from tyrosine or phenylalanine, the two precursor molecules of these class of compounds. These phenolic constituents revealed effective anti-inflammatory and antioxidant properties (El-Seedi et al. 2012). Caffeic acid and ferulic acid are the two hydroxy-cinnamic acids, which showed mammary anti-cancer properties.

Caffeic acid (31) or dihydroxy-cinnamic acid, naturally present in coffee, but also fruits, grains and vegetables, is known for its antioxidant, anti-proliferative and anti-inflammatory properties in normal cells (Kanimozhi and Prasad 2015). When tested against the proliferation of the hormone-sensitive T47D breast cancer cell line, it showed to be a potent inhibitor agent with an IC<sub>50</sub> value of 2.17 nM through pro-oxidant properties (Kampa et al. 2004). This activity revealed oxidative DNA damage and its downstream signaling induced apoptotic cancer cell death. Rosmarinic acid (32) is another caffeic acid ester, which was isolated from *Salvia rosmarinus*. It was reported that this compound prevented mammary cancer cell proliferation by minimizing COX-2 expression, antagonizing the extracellular signal-regulated protein kinase 1/2 (ERK 1/2) activation and AP-1 activation (Scheckel, Degner, and Romagnolo 2008). It was also reported that rosmarinic acid showed to abolish interleukin-8 in the pathway of the NF- $\kappa$ B and thus to hinder bone metastasis from mammary carcinoma (Wang, Wang, et al. 2012). One derivative, namely caffeic acid phenethyl ester (33), the active compound of the honeybee, showed to hinder NF- $\kappa$ B induced apoptosis via Fas signal activation in MCF-7 cell lines (Watabe et al. 2004). Another derivative, ferulic acid (34), found in leaves and seeds of different plants both in its free form and in covalently conjugated form, plays a broad role in the hardness of cell wall and synthesis of important organic constituents.

Ferulic acid is biologically active as antimicrobial, antioxidant, anti-allergic, hepatoprotective, anti-inflammatory, anti-carcinogenic and antithrombotic agent (Kumar and Pruthi 2014). It showed anticancer activity against different breast cancer cell lines, especially against MCF-7 cancer cell line, at a concentration of 10<sup>-6</sup> M presented in Figure 4 (Chang et al. 2006). The anti-proliferative activity of ferulic acid on T47D was reported with an IC<sub>50</sub> value of 2.3 nM (Kampa et al. 2004).

### Flavonoids

Flavonoids constitute a broad family of benzo-*c*-pyrone derivatives with more than 6,000 identified compounds, so far; most of them in the free state but also as their respective glycosides. They are found ubiquitously in plants, producing yellow or red pigments for flower coloration, and in vegetables and fruits. They are also recognized as having pharmacological properties, due to their anti-oxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic reported properties (Kesarkar et al. 2009). Their activity showed to be associated with their chemical nature, their degree of hydroxylation, polymerization, conjugation, and substitution (Kumar and Pandey 2013). They are classified into different subclasses, namely flavanones, isoflavones, flavones, flavonols, flavanols, and anthocyanidins. Their synthesis was reported to follow the pathway of phenylpropanoids.

**Flavanones.** Flavanones are one of the main sub-classes of flavonoids, mainly found in *Citrus* plants (Rutaceae family). They are mostly present in fresh fruits, industrially processed or hand-squeezed *Citrus* juices, mostly obtained from sour oranges, limes, lemons, mandarins, grapefruits and tangerines (Barreca et al. 2017). Naringenin and hesperetin are both major flavanones in their aglycone forms, which showed anti-cancer mammary activities. Naringenin (35) is one of the most important water-insoluble flavanone, obtained from the hydrolysis of its corresponding glycoside naringin (Orhan et al. 2015). The Naringenin and its glycosylated form (naringin) mostly found in *Citrus* species. Both, mostly found in grapefruits, are mainly known for their antioxidant activities. Accordingly, hesperetin (36) is the aglycone form of hesperidin. Both are mostly found in oranges (Roohbakhsh et al. 2014). Naringenin and hesperetin revealed inhibitory effects on growth and proliferation of human mammary tumor cell line MDA-MB-435 with an identical IC<sub>50</sub> value of 18 mg/mL. When tested in mixture, they showed an IC<sub>50</sub> value of 22.5 mg/mL (So et al. 1996). Hesperetin showed to block the proliferation and to arrest cell cycle at G1-phase in human breast cancer cells MCF-7, leading to apoptosis. Cyclins CDK4 and p21Cip1 have been suggested to be involved in the mechanism of action (E. J. Choi 2007). Quercetin-3-*O*-*b*-D-glucopyranoside (37) is one of the major constituents of apple peels, accounting for 82%. It has been proven to be responsible for antioxidant effects and antiproliferative activity against breast cancer MCF-7 cell line, with an EC<sub>50</sub> value of 23.9 ± 3.9 mM (He and Liu 2008).

**Isoflavones.** Isoflavones are considered as phytoestrogens, being able to exert pseudo-hormonal activity by binding to ERs in mammals. They revealed antioxidant, antimicrobial, anti-inflammatory activities, and they showed a significant role in the inhibition of hormone-related cancer such as breast cancers. Their benefits in the diet have been unveiled through studies showing that the ratio of breast and prostate cancer in Asian people was lower in comparison to those of Western people. These results were attributed to a higher presence of isoflavones in Asian diets (around 15–47 and 0.15–17 mg/day for Asian and Western diets, respectively) (Yu et al. 2016). Biochanin A, Glabridin, genistein, daidzein and rotenone are main isoflavones having mammary anti-cancer perspectives. Glabridin (38) is the main isoflavone present in *Glycyrrhiza glabra* licorice roots (Simmler, Pauli, and Chen 2013). Glabridin and their derivatives inhibited the growth of mammary cancer cell lines; the hydroxyl groups in glabridin playing a significant role in the proliferation-inducing activity and binding to the human ER.

Structure-activity relationships revealed that glabridin was three or four times more active, with an IC<sub>50</sub> value of 5 mM than its derivatives 2<sup>0</sup>-O-methylglabridin and 4<sup>0</sup>-O-methyl- glabridin (Tamir et al. 2000). Biochanin A (39), whose the primary sources are peanuts, red clovers and soya's (Yoon et al. 2012), revealed a wide range of biological activities, including antioxidant, anti-inflammatory, anti-carcinogenic and anticancer applications. It is reported to inhibit the mammary tumor growth in a xenograft model; showing a tumor size expressively smaller than in the control group at the dose of 15 mg/kg (Moon et al. 2008). Genistein (40) is found in soy, in the stem of fava beans (Kaufman et al. 1997). It showed to be an antioxidant agent, and to have weak estrogenic and antiestrogenic properties, to inhibit topoisomerase II and angiogenesis, and to induce cell differentiation. *In vitro* studies revealed that in the treatment with genistein, the expression of the epidermal growth factor (EGF) receptor mass was shortly up-regulated in mammary glands of immature rats. It could be due to the mechanism responsible for the increased cell proliferation seen at that age, which could prevent the development of mammary cancer in adults. Authors speculate that Asian women are preserved of breast cancer because they have an early consumption of soy-derived foods containing genistein, confirming its essential benefits for the welfares of cancer chemo-protective activity (Lamartiniere 2000). Daidzein (41) is also an Isoflavone extracted from dried fruits, vegetables and nuts. However, Zante currants and raisins are considered the two wealthiest sources, which contain both genistein and daidzein. Both have estrogenic activity in Humans, acting as anticancer agents in human breast, prostate, bowels and other cancer cell lines (Liggins et al. 2000). However, although being structurally similar, they did not share the same mechanism of action. Genistein showed inhibitory cell proliferation with an IC<sub>50</sub> value of 8.8 μM in MDA-MB-468 cells, involving G2/M arrest and apoptosis (Balabhadrapathruni et al. 2000). The induced apoptosis in breast cancer cell lines MDA-MB-231 was associated with the inhibition of cyclin B1 and the induction of p21 (Choi et al. 1998). Daidzein induced inhibition growth of MCF-7 cells at a concentration greater than 25 mM (Jin et al. 2010), leading to apoptosis through the mitochondrial caspase- dependent cell death pathway. Rotenone (42) is a natural pesticide isoflavone, mostly present in the seeds, stems, roots and leaves of *Fabaceae* plants. Rotenone was found highly active against MCF-7 breast cancer cell line, inducing apoptosis. This compound, involving ROS generation, showed to activate c-jun N-terminal kinase and p38 mitogen-activated protein kinases (p38 MAP) and to inactivate the ERK 1=2 (Deng, Huang, and Lin 2010).

**Flavones.** Flavones represent a subclass of flavonoids structurally related to the parent flavone 2-phenyl-1-benzopyran- 4-one. They have been proven to have a key role in plant adaption to the terrestrial environment, such as protection from UV radiations. Flavones revealed broad biological activities including antioxidant, anti-inflammatory, anti-microbial and anti-cancer activities (Jiang, Doseff, and Grotewold 2016). Three flavones members, namely apigenin, baicalein and luteolin, showed mammary anticancer activities. Apigenin (43) also known as 4<sup>0</sup>, 5, 7-trihydroxyflavone, a secondary plant metabolite, present in some fruits such as grapefruits, oranges, and in vegetables including parsley, onions, wheat sprouts and also in tea, chamomile, as well as in red wine. Apigenin is found in natural sources in the form of apigenin-7-O-glucoside and various acylated derivatives but also as a dimer, named biapigenin, mostly in *Hypericum perforatum* buds and flowers (Shukla and Gupta 2010). Apigenin has wide biological applications. It plays a role in scavenging free radicals as antioxidant agent, anti- mutagenic, anti-inflammatory, antiviral, anticancer and purgative activities (Salehi et al. 2019). It has a significant role in various cancers, including cervical, colon, hematologic, lungs, ovarian, prostate, skin, thyroid, endometrial, gastric, liver and breast cancers. Apigenin has been proven to have a significant role in inhibition MCF-7, T47D, MDA-MB231, MDA-MB-453 and MDA-MB-468 breast cancer cell lines proliferation (Shukla and Gupta 2010). However, its inhibitory effects revealed to be mediated by targeting different signal transduction pathway. In MCF-7 and MDA-MB-468 breast carcinoma cells, IC<sub>50</sub> values were determined as being 7.8 and 8.9 mg/mL, respectively. However, although inhibition of ERK MAP kinase phosphorylation was recognized as a mechanism of action in MCF-7 cells, activation of ERK MAP kinase phosphorylation was observed in MDA-MB- 468 cancer cell line (Yin et al. 2001). Luteolin (44) is one of the most common flavonoids belong to this sub-class. It was reported in many plant families such as Apiaceae, Asteraceae, Gentianaceae, Lamiaceae, Ranunculaceae, namely from *Angelica keiskei*, *Apium graveolens*, *Petroselinum crispum*, *Cajanus cajan* and several other plants. It showed antimicrobial, antioxidant, anticancer, activities (Lopez- Lazaro 2009). Luteolin has been proven suppressing the growth of MDA-MB-231 ER negative breast cancer tumor both *in vitro* and *in vivo*. Luteolin has proven to exert its antitumor activity through an inhibitory effect on epidermal growth factor receptor-mediated pathway (Lee, Oh, and Sung 2012). Baicalein (45) (5, 6, 7-trihydroxyflavone) is the aglycone form of baicalin; both being the main components found in Chinese traditional medicine plant *Scutellaria bai- calensis* Georgi (Lamiaceae family). Much attention has been given to both compounds due to their anti-inflammatory activities. They have been proven interested in food industries, cosmetics and pharmaceutical applications, including in cancers, mainly due to its protective effect against mitochondrial dysfunction (De Oliveira et al. 2015). Baicalein was also isolated from the Asian medicinal plant *Oroxylum indicum*. It is an isomer of genistein, which is recognized as the leading cancer chemopreventive flavonoid found in soy- derived foods. However, they revealed differential action on ER transactivation and apoptosis in MCF-7 breast cancer cells (Po et al. 2002). Genistein has been proven to exert a biphasic effect on the proliferation and death of MCF-7 cells, showing estrogenic activity to transactivate ERα at low concentrations. In opposite, baicalein did not display this biphasic effect and showed to inhibit E2-induced migration, adhesion and invasion through interfering with the G protein-coupled ER 30 (GPR30) signaling pathway (Shang et al. 2015).

**Flavonols.** Flavonols are one of the wide sub-class of flavonoids, having the common skeleton of 15 carbon atoms arranged in three rings. They are mostly present in fruits and vegetables such as apples, red grapefruits, sweet cherries, beans, broccoli, pear, onion, white currants and others (Harnly et al. 2006). They have wide biological activities, and three of them, namely kaempferol, quercetin and galangin, displayed mammary anti-cancer activities. Kaempferol (46) is found in beans, kales, chives, onions and apples (Bhagwat, Haytowitz, and Holden 2014). The effect of kaempferol was examined in MDA-MB-453 human mammary tumor cells and revealed that after treated with 50 mM of kaempferol for 24 h, apoptosis was induced *via* modulation of the p53 path- way (Choi and Ahn 2008). Kaempferol, having both estrogenic and antiestrogenic activity, showed a biphasic response on the estrogen activity, depending on E<sub>2</sub> concentration. It has been proven stopping the focus formation induced by E<sub>2</sub>, to block the malignant transformation, which is caused by estrogens. It might regulate the level of estrogenic activity in the body and have potent effects in blocking estrogens disparity diseases (Oh, Kim, and Chung 2006). Quercetin (47) is mainly present in onions, cranberries, apples and pears (Bhagwat, Haytowitz, and Holden 2014). Quercetin revealed to hinder cell proliferation of MDA-MB-468 breast carcinoma cells with an IC<sub>50</sub> value of 7 mg/mL and activity being some- what specific for p53 (Avila et al. 1994). It was reported that quercetin inhibited the growth of MCF-7 human breast can- cer cell line through two different mechanisms, by blocking cell cycle development through transient M phase accumulation and then G2 arrest of the cell cycle, and by inducing apoptosis (Choi et al. 2001). Galangin (48) is found in high

concentrations in *Alpinia officinarum* roots, used as a spice and as a well-known medicinal herb in Asia. It showed to hinder the proliferation of MCF-7 breast carcinoma cells at two levels, by direct inhibition of CYP1A1 enzyme activity and by hindering CYP1A1 transcription caused by AhR ligands (Ciolino and Yeh 1999).

**Flavanols.** Flavanols are a sub-class of flavonoids, which possess flavan-3-ol core, that is mostly found in green teas, especially in the green tea plant *Camellia sinensis*, but also in cocoa beans as well as in diverse fruits such as apples, peaches, grapefruits, bananas, blackberries, strawberries, red currants (De Pascual-Teresa, Moreno, and Garc'ia-Viguera 2010). Flavanols in their monomer form are called catechins and due to their two chiral carbons, exist as four diastereoisomers for each compound. Catechin (49) is the simplest flavan-3-ol, found commonly in different fruits such as apples, grape seeds and strawberries and red wine, green tea. Its broad biological properties include antioxidative, anti-hypertensive, anti-inflammatory, anti-proliferative, anti-thrombogenic, anti-hyperlipidemic activities (Zanwar et al. 2013). Epigallocatechin (50) is a flavanol with an inhibitory effect against MDA-MB231 breast cancer cell line. Epicatechin (51) is odorless white color ingredient mostly present in grapes, cocoa powder, green and black tea. It is a potent antioxidant agent (Bonetti, Brombo, and Zuliani 2017). Gallocatechin (52), Catechingallate (53), Gallocatechin gallate (54) and Epicatechin gallate (55) are compounds that belong to this group that showed to suppress MDA-MB231 breast cancer cell line. The most abundant catechin is ( ) epigallocatechin-3-gallate (EGCG) (56), accounted for 50 to 80% of green tea. EGCG is known for its potent antioxidant activity as well as anti-inflammatory and immunomodulatory properties. It has been proven to inhibit cell proliferation by decreasing the tumor vessel density in different cancer cell lines and breast cancer-xenograft models (Sartippour et al. 2001). Much attention has been paid to angiogenesis inhibitory activity since EGCG showed targeting specifically tumor angiogenesis and not normal tissues (Nagle, Ferreira, and Zhou 2006). Epigallocatechin-3-gallate is a major component of green tea. This compound has many biological activities, mainly as an antioxidant and anticancer agent. It also upgrades cardiovascular health and weight loss and secures the skin damage from radiations (Nagle, Ferreira, and Zhou 2006). In breast cancer, EGCG showed to potentiate radiotherapy efficacy (Gu et al. 2013; Sartippour et al. 2001; Zhang et al. 2012) and has been proposed as an adjuvant in cancer therapy (Yiannakopoulou 2014). Its anticancer effects have proven to be mediated by blocking HIF-1 $\alpha$  and NF $\kappa$ B pathways.

**Anthocyanidins.** Anthocyanidins are the aglycone forms of anthocyanins. They are colored water-soluble pigments, present in fruits and vegetables, which are responsible for colors in diverse seeds, fruits, leaves, flowers. They are famous for their antioxidant activities, and they display antimicrobial, anti-inflammatory activities (Khoo et al. 2017). According to the different substituents on the flavylium-B ring, the most common anthocyanidins are pentameric procyanidin (57), pelargonidin (58), delphinidin (59), petunidin (60), malvidin (61) and cyanidin (62). The most efficient anthocyanidin is malvidin, which showed an inhibitory effect of MCF-7 cell growth of 74.7% at 200 mg/mL, revealing an IC<sub>50</sub> value of 32.2 mM (Zhang, Vareed, and Nair 2005). Procyanidins are condensed flavan-3-ols compounds, formed from ( ) epicatechin and ( ) catechin. They are mostly present in apples, grape seeds and grape skins, cinnamon, cocoa beans and chocolate. They are famous for their potential health benefits, especially in preventing coronary and heart diseases (Hammerstone, Lazarus, and Schmitz 2000), pentameric procyanidin, isolated from *Theobroma cacao*, was investigated against diverse human breast cancer cell lines, including MDA-MB-231, MDA-MB-436, MDA-MB-468, SKBR-3 and MCF-7 cells. Interestingly, it was observed that pentameric procyanidin inhibited the growth of all these breast cancer cells. Furthermore, a selective activity was observed against these human breast cancer cell lines as normal human mammary epithelial cells (MCF-10) remained resistant to this anthocyanin (Ramljak et al. 2005).

#### Miscellaneous compounds

The steroid sapogenin 20(S)-protopanaxadiol (63), also named 20(S)-PP and present in *Panax ginseng* and *Panax pseudoginseng* showed inhibitory activity against ERs in human mammary cancer MCF-7 cell lines both *in vitro* and *in vivo*. It was suggested that 20(S)-PP inhibited cell proliferation with an IC<sub>50</sub> value of 26.3 mM and estrogen-stimulated gene expression in mammary cancer cells (Yu et al. 2007). More recently, it was shown that its potential mechanism might be attributed to the phosphatidylinositol 3-kinase/ Protein kinase B/Mammalian (PI3K/AKT/mTOR) signal pathway, mediating apoptosis of human breast cancer MCF-7 cells (Zhang et al. 2018). Compounds, changing PI3K/ AKT/mTOR signaling pathway, have attracted great attention to scientists as they selectively target tumor cells, especially breast cancer cells, leaving normal tissues alive. Currently, a Chinese medicine named the "Yijinsheng Capsule," developed from 20(S)-PPD, is in phase 3 of clinical trials as radiotherapy and chemotherapy assisting agent. Indole-3-carbinol (I3C, 64) is a compound formed from glucobrassicin mostly present in vegetables like broccoli, Brussels sprouts, cabbages, cauliflowers and kales. It was studied that I3C inhibited tumor growth in breast, liver, lungs and cervix (Weng et al. 2008). I3C was investigated on both estrogen-dependent MCF-7 and estrogen non-dependent MDA-MB-231 breast cancer cell lines, and it showed inhibiting the growth of MCF-7 significantly with the induction of P-450 system, but a minimal effect was observed against MDA-MB-231 (Tiwari et al. 1994). The 3,3'-Diindolylmethane (DIM, 65) is a stable condensation product of indole-3-carbinol (I3C). Both compounds are found in Brassica vegetables (Le et al. 2003). DIM is reported as a chemo-preventing agent against various types of cancers, especially against human breast cancers. It has shown to inhibit the breast cancer cells growth *in vitro* and *in vivo* via induction of cell cycle arrest in G2/M phase. Studies on both estrogen-dependent MCF-7 cell line and on the more aggressive estrogen-independent MDA-MB-468 cell lines revealed different mechanisms of action. Treatment of MCF-7 cells with DIM, (60 mM) led to down-regulation of Cdc25A, which was mediated by an enhanced expression of miR-21. However, no change in miR-21 expression was observed in the ER-negative MDA-MB-468 breast cancer cell lines (Jin 2011). Hydroxytyrosol or dihydroxyphenylethanol (66) is the phytochemical mostly present in fruit and leaf of the olive tree (*Olea europaeae* L). Its concentration in olive oil depends on the variety and maturation of olives. The healthy benefits of olive oil are worldwide recognized through the famous traditional Mediterranean diet. Main biological activities of hydroxytyrosol are due to the strong antioxidant and anti-inflammatory properties, being able to act as a chemoprotective agent in cardiovascular diseases, cancers, and several other diseases including HIV (Vilaplana-Perez et al. 2014). Hydroxytyrosol is considered as the most powerful antioxidant agent with an oxygen radical absorbance capacity value of 68,576, which is 15 times higher than that of green tea and 3 times higher than that of Coenzyme Q10 (Richards 2019). Oleuropein (67) is another compound extracted from olive fruits, its concentration was reported up to 140 mg/g olives, but the amounts decrease as the fruits ripen. It is responsible for the bitter taste of olives. Oleuropein has wide biological activities such as it act as antioxidant, anti-inflammatory, anti-cancer, anti-microbial, anti-viral and anti-atherogenic agent (Haris Omar 2010). Hydroxytyrosol and oleuropein showed cell proliferation inhibition at the dose of 50 and 200 mg/mL, respectively. Both induced cell apoptosis in estrogen-dependent MCF-7 breast cancer cells (Han et al. 2009). Oleuropein aglycone (68) revealed to induce apoptosis in breast cancer cells, showing a 2-fold apoptotic effect in MCF-7 overexpressing HER2- than in MCF-7 cells, and highlighting the pivotal role of the proto-oncogene HER2 in protective effects and progression of human breast cancer (Menendez et al. 2007). 6-Gingerol (69) is the predominant compound responsible for the pungent taste of ginger rhizome (*Zingiber officinale* Rosc.). It is worldwide used for its spicy and flavoring properties in numerous dishes and beverages. In addition to antioxidant activities, it revealed anti-inflammatory, anti-diabetic and anti-cancer effects (Mashhadi et al. 2013). Its potential benefit for the prevention of breast cancer was studied, and

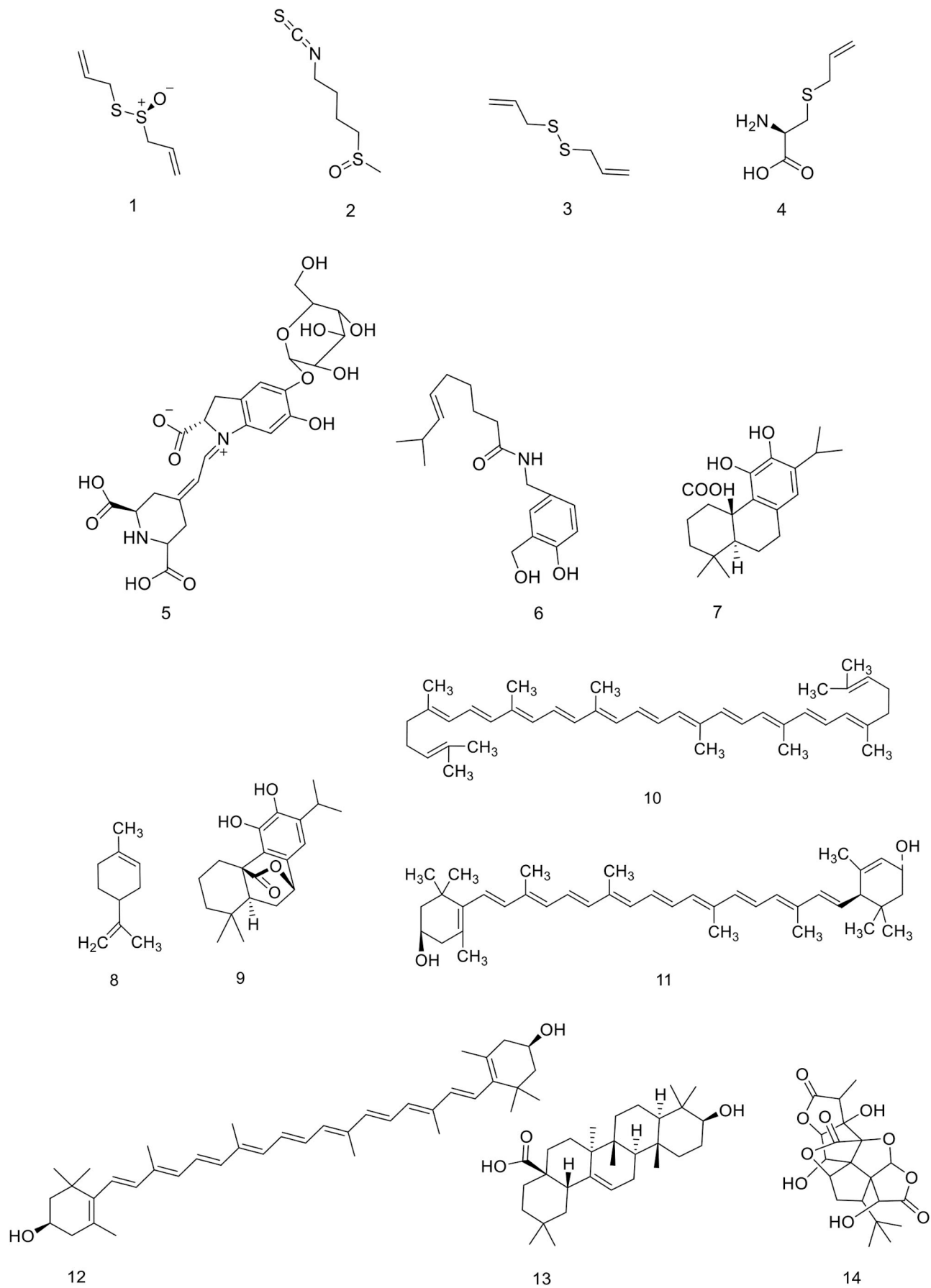


Figure 5. Chemical structures of dietary plants compounds showing mammary anticancer effects.

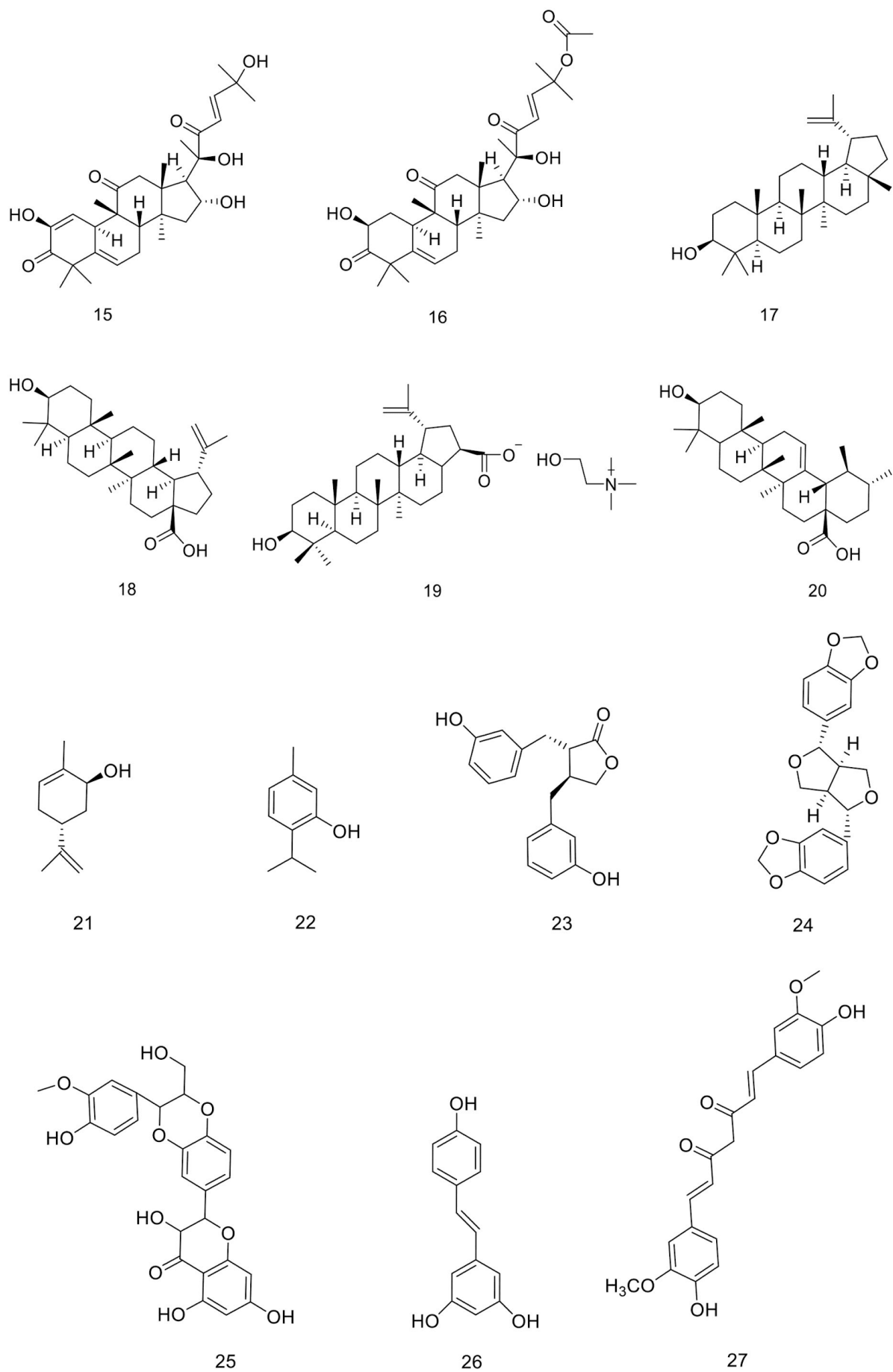
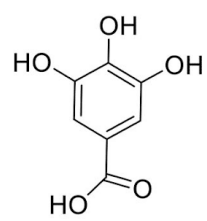
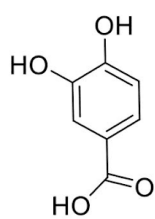


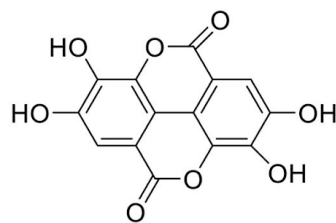
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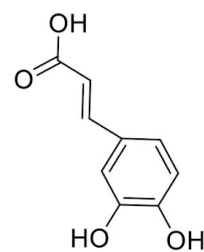
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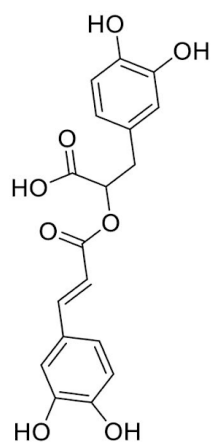
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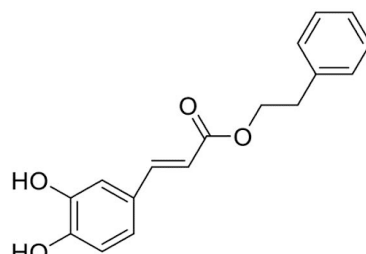
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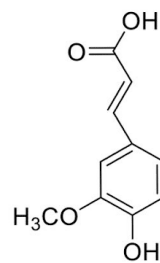
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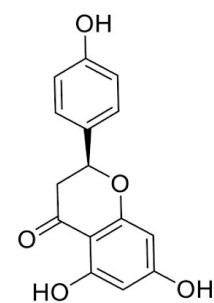
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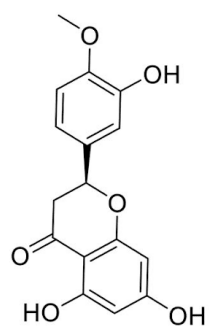
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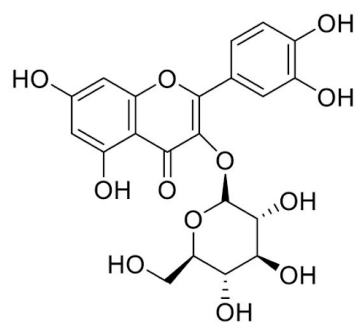
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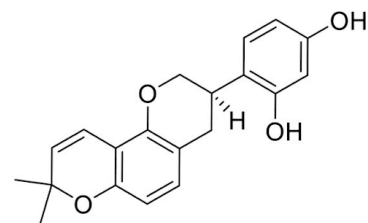
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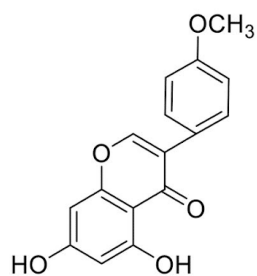
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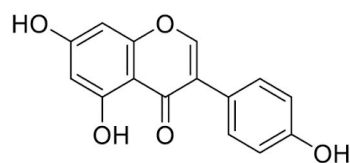
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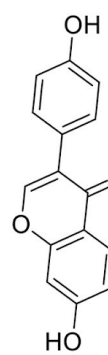
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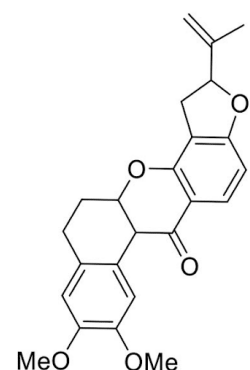
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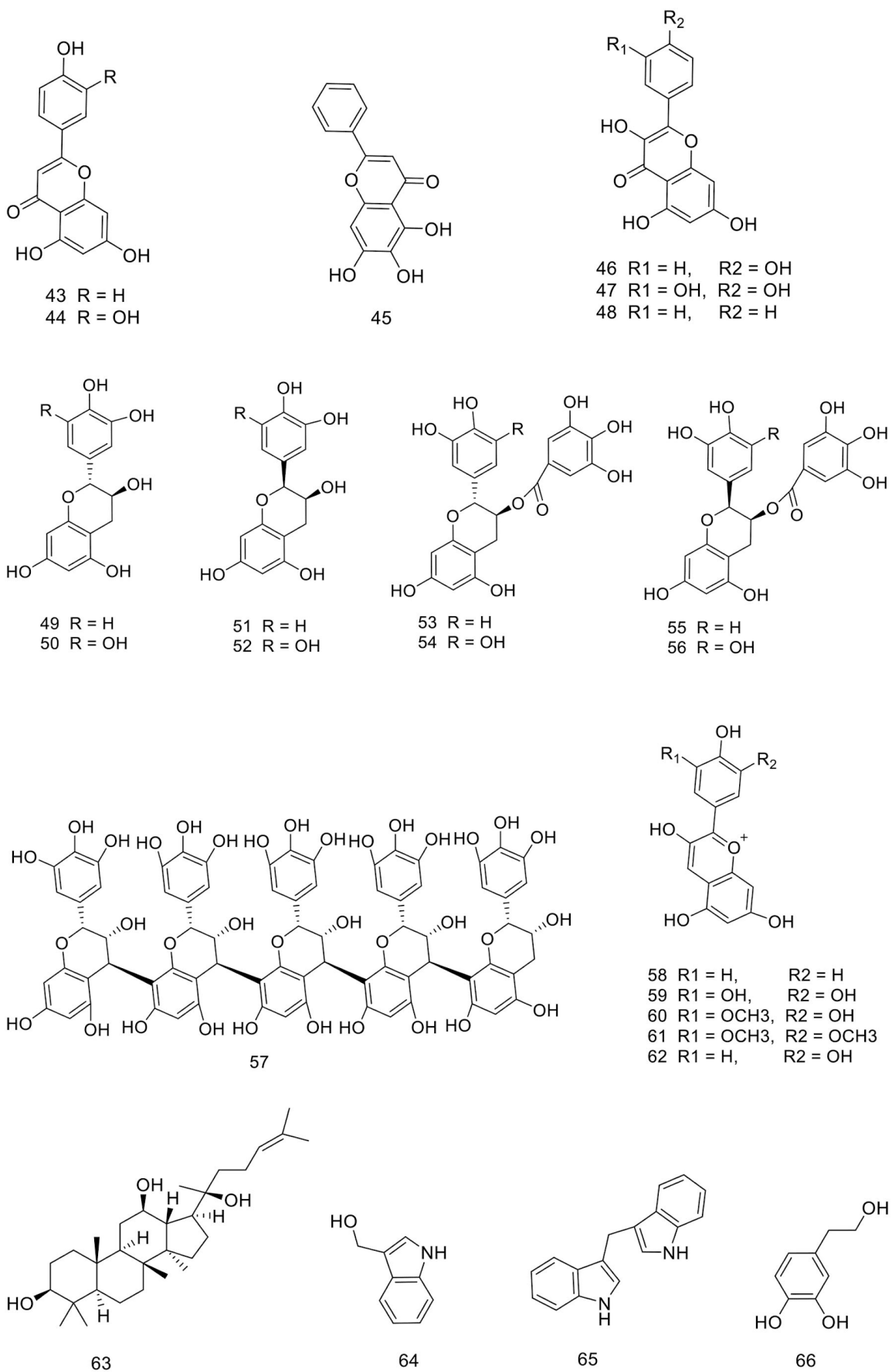


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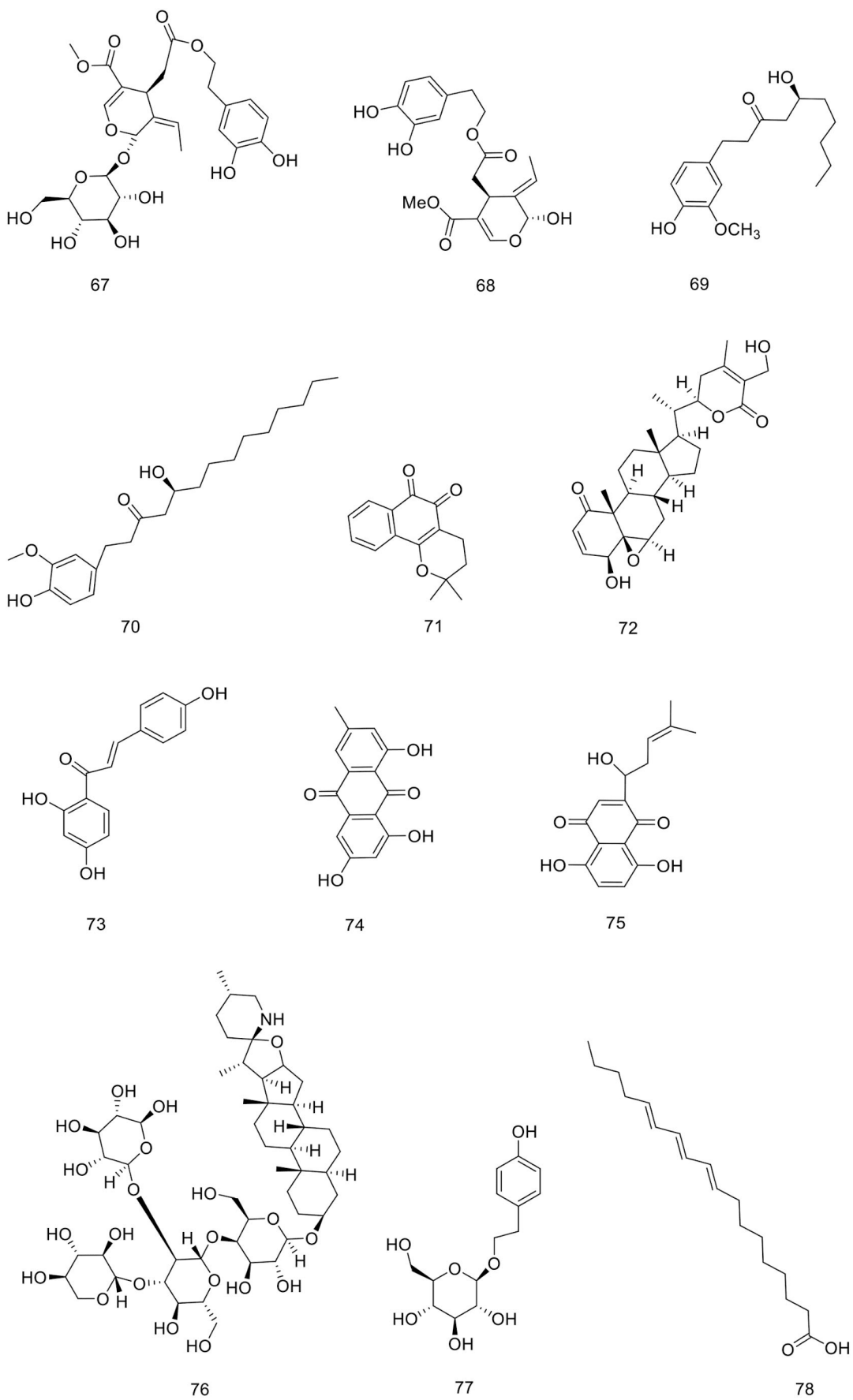


Figure 5. Continued.

it showed the ability to inhibit cell adhesion, invasion, motility in MDA-MB-231 breast cancer cells through inhibition of activities and expression of MMP-2 and MMP-9, the extracellular matrix degrading enzymes (Lee et al. 2008). Mechanism of action of 10-gingerol (70), another gingerols derivative, was investigated since it showed inhibition of cell proliferation and invasion of breast cancer cells. Results demonstrated that it significantly suppressed the expression of Epidermal Growth Factor Receptor in estrogen-receptor negative MDA-MB-231 cells and ER-positive MCF-7 cells (Joo et al. 2016).

Beta-Lapachone (71) is a poorly soluble *o*-naphthoquinone compound containing aromatic ring combined to quinone subunits. It was firstly isolated from the tree *Handroanthus impetiginosus* and was also found in many plants. Its structure is highly reactive, and it displayed anti-inflammatory and anti-cancer properties. Beta-lapachone has been proven to induce apoptotic or necrosis in various human cancer cells through mitochondrial cytochrome C-caspase pathway (Li et al. 1999). Furthermore, it showed to react with the enzyme NAD(P)H quinone oxidoreductase (NQO1), a multifunctional antioxidant enzyme, then super-oxides production. The expression of NQO1 is highly expressed in diverse cancers, indicating a pivotal role in cancer development. Beta-lapachone was also reported to induce cell death in MDA-MB-231 cells in an NQO1-dependent manner (Pardee, Li, and Li 2002; Kim and Cho 2018). Withaferin A (72), a C-28-steroidal lactone isolated from diverse *Solanaceae* plants such as *Iochroma arborescens*, *Withania somnifera*, is well known in ayurvedic medicine for its cardioprotective, anti-inflammatory, antiangiogenesis, and anti-tumor properties. Investigation of its mechanism of action against MCF-7 and MDA-MB-231 breast cancer cell lines revealed that it silences HER2/PR/ESR-dependent gene manifestation programs to suppress aggressive triple-negative breast cancer in favor of luminal BC hallmarks, improving the therapeutic sensitivity (vel Szic et al. 2017). Isoliquiritigenin (73) is a dietary compound of licorice root plants, especially from *Glycyrrhiza glabra*, which is used as a sweet flavoring. Isoliquiritigenin displayed a wide range of biological activities including anti-inflammatory, antimicrobial, antioxidative, anticancer, immunomodulatory, cardioprotective, and hepatoprotective activities. In breast cancer, isoliquiritigenin has been proven to inhibit angiogenesis by suppressing the vascular endothelial growth factor and the vascular endothelial growth factor receptor-2 VEGF/VEGF-2 pathways via promoting HIF-1 $\alpha$  proteasome degradation (Peng et al. 2015). In mammary carcinogenesis, isoliquiritigenin showed inhibition of breast cancer stem cells through the DNA methyltransferase DNMT1-mediated Wnt inhibitory factor 1 demethylation, encouraging development of WF1 for breast cancer prevention (Wang et al. 2015). Emodin (74) is an anthraquinone found in barks and roots of numerous plants including *Rheum officinale* and *Polygonum cuspidatum* and molds and lichens, and it is used as a laxative. Emodin was reported as a tyrosine kinase inhibitor, inhibiting the growth of HER-2/neu overexpressing tumors and enhancing survival in athymic mice (Zhang et al. 1999). It also showed to induce apoptosis in human breast cancer cells BCap-37 through disruption of the mitochondrial signaling pathway (Huang, Chen, and Shi 2008). Shikonin (75) is a naphthoquinone pigment, found in the roots of the Chinese herbal plant *Lithospermum erythrorhizon*. Shikonin is known as an anti-inflammatory, antigonadotropic, anti-HIV agent. Investigations on its antiestrogen activity showed that it inhibited the growth of breast-tumor ER $\alpha$ -positive cells (Yao and Zhou 2010). Although it has proven to inhibit the activities DNA topoisomerases, suppressing the activity of pyruvate kinase M2 (PKM2) was also reported. Additionally, in combination with taxol, it showed to target Akt/p70S6K and ERKs (Li et al. 2014).  $\alpha$ -Tomatine (76) is a steroidal glycoalkaloid, present in the leaves, and roots of tomatoes and mainly known for its antiviral, anti-microbial and anti-inflammatory properties.  $\alpha$ -Tomatine showed inhibition of MCF-7 breast cancer cell proliferation, with an EC<sub>50</sub> value of 7.17 mM after 72 h. Investigation on its mechanism of action revealed that it did not induce apoptosis, but a disruptive membrane effect might be involved due to its binding with membrane cholesterol (Sucha et al. 2013).

Salidroside (77) is a glucoside of tyrosol and extracted from plants of the genus *Rhodiola*, especially from the Chinese medicinal herb *R. rosea*. It showed antiviral, cardio-vascular and neuroprotective effects. Its inhibitory activity against human breast cancer cell line was studied on ER-positive MCF-7 and ER-negative MDA-MB-231 breast cancer cells, showing that cell-cycle arrest leads to apoptosis by suppressing anti-apoptotic proteins and might involve the mitochondrial pathway (Hu et al. 2010). Punicic acid (78) is a polyunsaturated fatty acid having omega-5 long-chain; mainly occurring in *Punica granatum* pomegranate seed oil (Shabbir et al. 2017). As most of the fatty acids having a long chain, it showed anti-cancer activity and revealed 92% and 96% inhibition of proliferation against ER-negative MDA-MB-231 and ER-positive MDA-ER $\alpha$ -7 human cancer cells at 40 mM, respectively (Grossmann et al. 2010). Chemical structures of dietary plants compounds showing mammary anticancer effects are shown in Figure 5.

## Conclusions

Results of various *in vitro* and *in vivo* studies have demonstrated the potential of dietary phytochemicals in prevention and treatment of breast cancer. Several mechanistic studies have also confirmed the significance of plant phytochemicals against breast cancer. According to epidemiological studies, consumption of these dietary plant biologically active ingredients present in different fruits and vegetables is reported to be inversely associated with the risk of breast cancer. These naturally occurring plant-based phytochemicals possess potential breast anticancer perspectives *via* inducing apoptotic conditions, resulting in cell cycle arrest, down-regulating anti-apoptotic factors and inhibiting proliferation and metastasis of cancer cells. They help in the treatment of breast cancer through elevating the concentration of anti-oxidative enzymes, scavenging reactive oxygen species, and regulation of cell signaling pathways. Scientists are more focused on extraction, isolation and identification of the diverse class of phytochemicals from naturally occurring plants so that a better knowledge regarding their mode of action and toxicity could be understood. Additionally, pre-clinical and epidemiological trials must be carried out to optimize their potencies, metabolism, bioavailability, drug-nutrient interaction, and a better understanding of their pharmacokinetics. Conclusively, the various concentration of natural plant phytochemicals has been investigated as promising breast anticancer agents. Nevertheless, further clinical studies must be conducted to validate the suitable dose of administration of each phytochemical to be used in the treatment and prevention of breast cancer.

## Conflict of interest

All the authors declare that there is no conflict of interest.

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