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Natural Products as Aromatase Inhibitors

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Abstract

With the clinical success of several synthetic aromatase inhibitors (AIs) in the treatment of postmenopausal estrogen receptor-positive breast cancer, researchers have also been investigating also the potential of natural products as AIs. Natural products from terrestrial and marine organisms provide a chemically diverse array of compounds not always available through current synthetic chemistry techniques. Natural products that have been used traditionally for nutritional or medicinal purposes (e.g., botanical dietary supplements) may also afford AIs with reduced side effects. A thorough review of the literature regarding natural product extracts and secondary metabolites of plant, microbial, and marine origin that have been shown to exhibit aromatase inhibitory activity is presented herein.

Keywords

aromatase inhibitors; natural products; breast cancer; botanical dietary supplements

BREAST CANCER

Worldwide breast cancer estimates included over one million incident cases and almost 400,000 deaths in the year 2000 [1,2]. In the United States, over 178,000 women were expected to be diagnosed with breast cancer in 2007 with over 40,000 deaths occurring from the disease [3]. In developed countries, mortality from breast cancer has recently begun to decline, primarily due to earlier detection and improved treatments [4,5]. Breast cancer is thought to be a result of inherited genetic predisposition (e.g., mutations in genes such as *BRCA*-1, *BRCA*-2, *p53*, *PTEN/MMAC1*, and/or *ATM*) and/or environmental factors (e.g., radiation exposure, dietary factors, alcohol consumption, hormonal exposure) [2,6,7]. Numerous genetic mutations are necessary for breast cancer development and progression including the acquisition of the capabilities for self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis, known collectively as the "hallmarks of cancer" [8].

Numerous molecular targets have been identified as playing a significant role in breast cancer development and progression. Estrogens and the estrogen receptors (ERs) are widely

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recognized to play an important role in the development and progression of breast cancer, making estrogens and the ERs widely studied molecular targets [9–12]. Two of the endogenous estrogens found in humans include estradiol and estrone. In pre-menopausal women, estrogens are produced primarily through conversion of androgens in the ovaries while estrogen production in postmenopausal women occurs in only peripheral tissues [13,14]. Estrogens have various effects throughout the body, including positive effects on the brain, bone, heart, liver, and vagina, with negative effects such as increased risk of breast and uterine cancers with prolonged estrogen exposure [10,15,16]. Estrogens exhibit their effects through binding to one of two variants of ERs, ERα or ERβ [17,18]. Upon binding of estrogen, the ER dimerizes and binds to the estrogen-response element (ERE), causing transcription of estrogen dependent genes [19]. Estrogens influence breast cancer development and progression by various methods including stimulation of cell proliferation through the ERα pathway, direct increases in rates of genetic mutations, or effects on the DNA repair system [12,20–22].

Modulation of estrogen exposure as a treatment for breast cancer began as early as the late nineteenth century when complete ovariectomy was noticed to have favorable effects on cancerous progression [23]. While ovarian ablation (through surgery, irradiation, or medication) is still utilized clinically for some pre-menopausal breast cancer patients [19,24], extensive research has been performed to modify estrogen exposure pharmacologically. Modulation of estrogens and ERs can be accomplished by inhibiting ER binding, by downregulating ERs, or by decreasing estrogen production [24–26]. Tamoxifen (Nolvadex®), a selective estrogen receptor modulator (SERM) that works by blocking the binding of estrogen to the ER, has been considered the treatment of choice for estrogen abatement for the last twenty-five years [27,28]. However, tamoxifen acts as both an ER antagonist and agonist in various tissues and thus results in significant side-effects such as increased risk of endometrial cancer and thromboembolism [26]. This partial antagonist/agonist activity is also thought to lead to the development of drug resistance and eventual treatment failure for patients using tamoxifen [29,30]. Other SERMs, including raloxifene (Evista®, approved in United States for osteoporosis), and toremifene (Fareston®, approved in the United States to treat breast cancer) are in development to overcome these side effects and still maintain efficacy in breast cancer treatment [31–33]. Fulvestrant (Faslodex®) is a clinically approved estrogen receptor down-regulator currently used as second-line therapy in the treatment of postmenopausal metastatic breast cancer [34,35]. An important target to decrease estrogen production involves aromatase inhibition, which has found clinical utility in postmenopausal women with breast cancer.

AROMATASE INHIBITION AND BREAST CANCER

Aromatase is a cytochrome P450 enzyme and is responsible for catalyzing the biosynthesis of estrogens (estrone and estradiol) from androgens (androstenedione and testosterone) (Fig. 1) [36,37]. The aromatase enzyme is encoded by the aromatase gene *CYP*19 for which the expression is regulated by tissue-specific promoters, implying that aromatase expression is regulated differently in various tissues [38–41]. Aromatase has been found in numerous tissues throughout the body including breast, skin, brain, adipose, muscle, and bone [36,37,42]. The concentration of estrogens has been shown to be as much as twenty-fold higher in breast cancer tissues than in the circulating plasma, suggesting locally increased aromatase expression for estrogen biosynthesis near or within the cancerous tissues [13,43]. Inhibition of the aromatase enzyme has been shown to reduce estrogen production throughout the body to nearly undetectable levels and is proving to have significant affect on the development and progression of hormone-responsive breast cancers. As such, aromatase inhibitors (AIs) can be utilized as either anticancer agents or for cancer chemoprevention

[44–47]. However, the use of AIs for cancer chemotherapy or chemoprevention is limited to postmenopausal women or premenopausal women who have undergone ovarian ablation.

Aromatase inhibitors can be classified as either steroidal or nonsteroidal. Steroidal AIs (also known as Type I inhibitors) include competitive inhibitors and irreversible inhibitors, which covalently bind aromatase, producing enzyme inactivation. Nonsteroidal AIs (Type II inhibitors) reversibly bind the enzyme through interaction of a heteroatom on the inhibitor with the aromatase heme iron [42,48,49]. AIs have been clinically available since the introduction of aminoglutethimide (**1**, AG) in the late 1970's (Fig. 2) [42,50]. However, AG did not completely inhibit aromatase, resulting in decreased efficacy, nor did AG selectively inhibit aromatase, causing considerable side effects [50]. Second-generation AIs (Fig. 2) include formestane (**5**), which was administered through intramuscular injection [19], and vorozole, both having various limiting side-effects [51]. Three third-generation AIs are currently in clinical use, namely, anastrozole (**2**, Arimidex®), letrozole (**3**, Femara®), and exemestane (**6**, Aromasin®) (Fig. 2) [19,42,45,46,49,52]. These agents have shown nearly complete estrogen suppression and are highly selective for aromatase.

When compared with currently existing breast cancer therapies, aromatase inhibitors generally exhibit significantly improved efficacy with fewer side effects [53–55]. Current studies on synthetic AIs generally focus on combination treatment [56–58], resistance mechanisms [59–64], and/or improving their safety profile by reducing side effects [55,65–67].

Although synthetic AIs show a better side effect profile than tamoxifen, serious side effects still occur, generally related to estrogen deprivation [68–72]. Synthetic AIs may cause decreased bone mineral density, osteoporosis, and increases in musculoskeletal disorders [55,65,66,73–75]. Synthetic AIs also can result in increased cardiovascular events as well as altering the lipid profiles of patients [67,74,76]. Synthetic AIs can also affect cognition, decreasing the protective effects of estrogens on memory loss with aging [40,77]. Several quality of life side effects are also often seen with the use of synthetic AIs including diarrhea, vaginal dryness, diminished libido, and dyspareunia [54,78,79]. Some of the side effects of synthetic AIs can be partially alleviated using available therapies, including osteoporosis treatments and cholesterol-lowering medicines.

Even with the improved efficacy of AIs or other endocrine therapies, postmenopausal breast cancer patients eventually develop resistance to AIs causing relapse of the disease [59–64,80]. Generally, resistance involves tumor regrowth after 12–18 months of treatment and stable disease. Several mechanisms are thought to be involved in resistance to synthetic AIs including circumventing normal cellular pathways, enhancing sensitivity to existing estrogens, and/or redistributing estrogen receptors to extra-nuclear sites [59–64]. Several clinical trials are currently exploring the use of combination therapies with synthetic AIs and other compounds [e.g., epidermal growth factor receptor (EGFR) inhibitor gefitinib, HER-2/neu inhibitor trastuzumab, estrogen receptor degrader fulvestrant, and selective estrogen receptor modulators toremifene and raloxifene], hoping to extend the length of stable disease and reduce resistance mechanisms to synthetic AIs.

Two new aromatase inhibitors and one dietary supplement are currently undergoing clinical trials as single agent AIs (http://www.clinicaltrials.gov/). Atamestane (**7**, Fig. 2) is currently in two phase III clinical trials, including a recently completed study of atamestane with toremifene as compared with letrozole for advanced breast cancer and a study of toremifene with or without atamestane versus letrozole in women with metastatic breast cancer. In preclinical experiments, atamestane with or without toremifene was found to have fewer side-effects than letrozole, with favorable effects on bone, serum, and uterine markers [81].

Testolactone (**4**, Teslac®, Fig. 2) is considered a first generation AI and is currently approved for use in the United States for treatment of advanced breast cancer [82]. The AI activity of testolactone is thought to be competitive and irreversible, similar to other steroidal AIs. Testolactone is undergoing clinical trials for conditions other than breast cancer, including the recently completed study for the treatment of LHRH (lutenizing hormone-releasing hormone) resistant precocious puberty in girls (phase II), another recently completed study for the treatment of boys with precocious puberty (phase II), and as part of an ongoing study of a three drug combination therapy for children with congenital adrenal hyperplasia (phase I) [83,84]. Phase I clinical trials have begun on the botanical dietary supplement IH636 grape seed extract for the prevention of breast cancer in postmenopausal women who are at increased risk of developing breast cancer. The IH636 extract has a high concentration of proanthocyanidins and has been shown to inhibit aromatase using *in vitro* and *in vivo* models [85,86].

Even with the growing number of clinically used AIs including anastrozole, letrozole, exemestane, and other compounds in development there remains a need for improved AIs, due to the development of resistance to AIs and because of the side-effects associated with currently utilized compounds. New aromatase inhibitors could offer increased clinical efficacy and less severe side-effects. Although still theoretical, selective aromatase modulators (SAMs) may be found based on the evidence for tissue-specific promoters of aromatase expression [19,41,50]. Transcriptional regulation of aromatase is performed by several tissue-specific promoters, with normal breast adipose tissue utilizing PI.4 (major), PI.3 (minor), and PII (minor) promoters [46,87]. Promotors PI.3 and PII both direct aromatase expression in breast cancer tissues, while other tissues utilize various promoters to regulate aromatase expression (PI.1 – placenta; PI.4 – skin; PI.5 – fetal tissues; PI.6 – bone; PI.7 – vacular endothelial; PII – ovary and testis; PIf – brain) [46,87–89]. This tissue-specific regulation of aromatase expression by different promoters provides a possible mechanism for inhibiting aromatase expression in breast cancer tissues while continuing aromatase expression in peripheral tissues. For example, if PI.3 and PII could be downregulated in breast cancer tissues then there may be some minor side-effects in the ovary or testes, and the adipose tissue but the common side-effects of current AIs on the bone, brain, and cardiovascular system may be alleviated. Several researchers have been examining upstream targets that specifically influence promoters important in aromatase expression in breast cancer (e.g., COX-2 enzyme inhibitors that decrease aromatase expression involving PII and PI.4 [87] and liver receptor homologue (LRH)-1 modulators that decrease PII activity [90]).

NATURAL PRODUCTS AS AROMATASE INHIBITORS

With the clinical success of several synthetic aromatase inhibitors (AIs) for the treatment of postmenopausal breast cancer, researchers have been investigating the potential of natural products as AIs. Natural products have a long history of medicinal use in both traditional and modern societies, and have been utilized as herbal remedies, purified compounds, and as starting materials for combinatorial chemistry. Terrestrial flora and fauna, marine organisms, bacteria, fungi, and other microbes, provide a chemically diverse array of compounds not available through current synthetic chemistry techniques [e.g., 91–100]. Natural products that have been used traditionally for nutritional or medicinal purposes (for example, botanical dietary supplements and ethnobotanically utilized species) may also provide AIs with reduced side effects. Reduced side effects may be the result of compounds within the natural product matrix that inhibit aromatase while other compounds within the matrix alleviate some of the side effects of estrogen deprivation (e.g., phytoestrogens). As such, natural product AIs may be important for the translation of AIs from their current clinical uses as chemotherapeutic agents to future clinical uses in breast cancer chemoprevention.

New natural product AIs may be clinically useful for treating postmenopausal breast cancer and may also act as chemopreventive agents for preventing secondary recurrence of breast cancer.

Natural product AIs may also be important in the search for more potent AIs. Natural product compounds that significantly inhibit aromatase may be utilized to direct synthetic modification of natural product scaffolds to enhance aromatase inhibition. Furthermore, natural product AIs could also be used to explore regulation of aromatase through other pathways and receptors {e.g., modulation of liver receptor homologue-1 (LRH-1) an orphan receptor that regulates aromatase in adipose tissue, testis, and granulose cells as well as contribute to over-expression of aromatase in breast cancer patients [90,101]}. Natural product AIs could also be useful in the search for selective aromatase modulators (SAMs). Although still theoretical, selective aromatase modulators (SAMs) may be found based on the evidence for tissue-specific promoters of aromatase expression [19,41,50,102,103]. New natural product AIs could offer increased clinical efficacy and decreased side effects. Finally, screening for new natural product aromatase inhibitors may provide improved leads for future drug development.

The next sections of this article will detail natural product AIs that have been reported in the literature up to January 2008, beginning with a description of natural product extracts tested followed by a review of natural product compounds that have been tested.

NATURAL PRODUCT EXTRACTS TESTED FOR AROMATASE INHIBITION

Numerous natural product extracts have been tested for their ability to inhibit aromatase. Extracts evaluated have been produced mainly from edible plants and edible fungi, but have also included botanical dietary supplements, spices, teas, coffee, cycads, cigarettes and tobacco, traditional indigenous medicines, wine, and beer. Preparation of natural product extracts has rarely followed a standardized extract preparation method and in some cases this information has not been included in literature reports. Aromatase inhibition assays have varied widely, with the most common being a noncellular tritiated water release assay using microsomes from different sources, most commonly from human placentas. Although less frequent, cellular and *in vivo* aromatase inhibition assays have been utilized to test natural product extracts. In some cases other assays may be utilized to test for aromatase inhibition. Some studies did not report the assay utilized to determine aromatase inhibition activity. Assay results are presented in numerous forms [e.g., % inhibition, percent control activity (PCA), units/100 g], thus complicating the comparison of levels of aromatase inhibition activity from one sample to another. For the purposes of this review, the most active extracts in the microsomal assay will be discussed followed by discussion of the results of cellular and *in vivo* studies.

The most active natural product extracts from testing in the microsomal aromatase inhibition assay, reported as % inhibition, comprise the ethyl acetate partition of *Dioon spinulosum* Dyer ex Eichl. [104], the ethyl acetate partition of *Encephalartos ferox* Bertol. f. [104], a 75% methanol reflux extract of *Riedelia* Meisn. sp. [105], a 75% methanol reflux extract of *Viscum album* L. [105], the methanol partition of *Cycas rumphii* Miq. [104], the methanol and ethyl acetate partitions of *Cycas revoluta* Thunb. [104], a 75% methanol reflux extract of *Alpinia purpurata* K. Schum. [105], and a 75% methanol reflux extract of *Coccothrinax* Sarg. sp. [105]. The natural product extracts that were most active in the microsomal aromatase inhibition assay reported as PCA included five red wine varieties (*Vitis* L. sp.) from various wineries, with the most active being Cabernet Sauvignon from Tanglewood (France) [86,106,107]. The hexane partition of the leaves of *Brassaiopsis glomerulata* (Blume) Regel (Araliaceae) was found to be active in microsomes [108]. The methanol and

chloroform extracts of *Garcinia mangostana* L. (Clusiaceae) (mangosteen) were also strongly inhibitory against aromatase in microsomes [109].

When results were reported as μg/mL, the most active extracts in the microsomal assay included a water reflux extract of *Euonymus alatus* (Thunb.) Sielbold ("gui-jun woo" in Korean folk medicine), a dichloromethane partition of *Isodon excisus* Kudo var. *coreanus* [110], a water reflux extract of *Scutellaria barbata* D. Don [111], and a polyphenol-enhanced extract of green tea (*Camellia sinensis* Kuntze) [112]. Another study reported results in units/100 g wet weight (one unit was defined as the dose required for 50% inhibition) and found tea (*C. sinensis*), coffee (*Coffea* L. sp.), cocoa (*Theobroma cacao* L.), collards (*Brassica oleracea* L.), and tomato leaves (*Lycopersicon esculentum* Mill.) to strongly inhibit aromatase using a microsomal assay [113]. Interestingly, this study also reported that cigarette smoke (obtained using methylene chloride and aqueous traps) and tobacco leaves (70% ethanol extract; *Nicotiana tabacum* L.) also potently inhibited aromatase, as reported in cigarette equivalents [113].

The *Euonymus alatus* (Thunb.) Sielbold and *Scutellaria barabata* D. Don extracts mentioned above were subjected to further testing in both myometrial and leiomyonal cells with the extracts found to have stronger aromatase inhibition activity in leiomyonal cells [111]. Other active natural product extracts tested in cellular aromatase assays included xanthohumol-rich stout beer in choriocarcinoma-derived JAR cells [114], a water extract of grape seed extract (*Vitis* L. sp.) in MCF-7aro cells [85], a water reflux extract of white button mushrooms [*Agaricus bisporus* (J. Lange) Imbach] in MCF-7aro cells [115], red clover flowers (*Trifolium pratense* L.) in a MCF-7 cell dual assay for aromatase inhibition and estrogenicity [116], mangosteen (*Garcinia mangostana* L.) in SK-BR-3 cells [109], and *Brassaiopsis glomerulata* (Blume) Regel in SK-BR-3 cells [108]. The red clover flowers were found to inhibit aromatase at low concentrations and were also estrogenic at high concentrations.

One of the red wines [Pinot noir from Hacienda (Sonoma, CA); *Vitis* L. sp.] with demonstrated activity in the microsomal assay was further tested *in vivo* using an aromatase-transfected MCF-7 breast cancer xenograft mouse model and found to be active [86,106,107]. The grape seed extract (*Vitis* L. sp.) that exhibited aromatase inhibition in MCF-7aro cells was further tested using an *in vivo* MCF-7aro xenograft mouse model and found to reduce tumor weight [85]. This study also ascertained that grape seed extract suppressed exon I.3-, exon PII-, and exon I.6-containing aromatase mRNAs in MCF-7 and SK-BR-3 cells, which is interesting since promoters I.3 and II are important promoters for aromatase expression in breast cancer [87,102,117]. Furthermore, it was also found reported in this same study that grape seed extract down-regulated the transcription factors cyclic AMP-responsive element binding protein-1 (CREB-1) and glucocorticoid receptor (GR), which are up-regulators of aromatase gene expression [85]. Researchers at the City of Hope Comprehensive Cancer Center's Beckman Research Institute at Duarte, California, have begun recruiting patients for a Phase I clinical trial of IH636 grape seed proanthocyanidin extract in preventing breast cancer in postmenopausal women at risk of developing breast cancer (http://clinicaltrials.gov/ct/show/NCT00100893?order=59). The study lists aromatase inhibition as one of the possible mechanisms of action of grape seed extract.

Numerous other natural product extracts have been reported as "active" but actually, most of these exhibit only marginal to weak inhibition of aromatase (see Table 1).

NATURAL PRODUCT COMPOUNDS TESTED FOR AROMATASE INHIBITION

Quite a large number of small-molecule natural product secondary metabolites, of various compound classes, have been evaluated for their ability to inhibit the aromatase enzyme. As

with the natural product extracts reported in the literature, purified natural products have been tested in a variety of aromatase inhibition assays, with the most common being a noncellular tritiated water release assay using microsomes from different sources, typically from human placentas. Cellular and *in vivo* aromatase inhibition assays have been utilized to biologically evaluate some of the natural product compounds reported in the literature. Again, assay results have been presented in the literature in numerous forms, complicating the direct comparison of aromatase inhibition potency from compound to compound. For the purposes of this review, compounds are considered strongly active if their IC_{50} in microsomes was less than 5 μM and/or if their IC_{50} in cells was less than 10 μM, moderately active if their IC_{50} in microsomes was less than 10 μM and/or if their IC_{50} in cells was less than 20 μM, weakly active if their IC_{50} in microsomes was less than 25 μM and/or if their IC_{50} in cells was less than 50 μM, and inactive if their IC_{50} in microsomes was greater than 25 μM and/or if their IC_{50} in cells was greater than 50 μM. Natural product compounds are discussed according to compound class organized by the group most frequently tested for aromatase inhibition, beginning with flavonoids, followed by other classes listed alphabetically. Up to January 2008, 282 natural product compounds had been reported to be tested for aromatase inhibition in the literature, with 125 flavonoids, 36 terpenoids, 19 peptides, 18 lignans, 16 xanthones, 15 fatty acids, 10 alkaloids, and 43 miscellaneous compounds having been evaluated.

The various types of flavonoids previously tested for aromatase inhibition have comprised 37 flavones, 20 flavanones, 19 chalcones, 10 isoflavans, nine catechins, eight isoflavanones, six isoflavones, five pterocarpans, four rotenoids, two anthocyanins, two flavanols, two homoisoflavonoids, and one coumestan. Of the flavonoids tested, flavones have been tested most often and have been the most active (Table 2, Fig. 3). Chrysin (5,7,4'-trihydroxy-3',5'-dimethoxyflavone, **11**) has shown strong aromatase inhibition in microsomes [118–124], JEG-3 cells [125], Arom+HEK 293 cells [125], human preadipocyte cells [126], H295R adrenocortical carcinoma cells [127], and in a MCF-7 dual assay for aromatase inhibition and estrogenicity (chrysin was also estrogenic at high concentrations) [116]. Chrysin (**11**) did not show activity using trout ovarian aromatase [128] or in endometrial cells [118].

Apigenin (5,7,4'-trihydroxyflavone, **8**) and quercetin (3,5,7,3',4'-pentahydroxyflavone, **37**) have been tested numerous times for aromatase inhibition. Apigenin (**8**) was found to be strongly active in microsomes [121–124], JEG-3 cells [125], Arom+HEK 293 cells [125], and granulose-luteal cells [129]. However, this flavone was found to be only moderately active in H295R adrenocortical carcinoma cells [127] and was not active using trout ovarian aromatase [128]. The pentahydroxylated flavone, quercetin (**37**), present in numerous plant species but reported in the aromatase literature as being isolated from *Epilobium capense* [130] and *Morinda citrifolia* L. (noni) [131], was found to be moderately active in two microsomal studies [120,122] but only weakly active in another microsomal study [130]. Quercetin (**37**) was not active in granulose-luteal cells [129], JEG-3 cells [125], H295R adrenocortical carcinoma cells [127], human preadipocyte cells [126], or using trout ovarian aromatase [128].

Reports of activity for unsubstituted flavone (**19**), a natural product derivative, have ranged from moderately active (8 μM IC_{50}) [122] to inactive (375.0 μM IC_{50}) [128] in microsomes. Flavone (**19**) was found to be weakly active in human preadipocyte cells [126] but inactive in JEG-3 cells [125], H295R adrenocortical carcinoma cells [127], and using trout ovarian aromatase [128].

7-Hydroxyflavone (**26**) has been tested several times and has shown strong aromatase inhibition in most microsomal assay testing [123,124,132]. 7-Hydroxyflavone (**26**) also exhibited strong activity in JEG-3 cells [125] and H295R adrenocortical carcinoma cells

[127] but was not active using trout ovarian aromatase [128]. Luteolin (5,7,3',4'-tetrahydroxyflavone, **31**) has shown strong activity in microsomal testing [120,121,133] and cellular testing with JEG-3 cells [125]. Luteolin (**31**) was only moderately active in preadipose cells [134]. 7,8-Dihydroxyflavone (**16**) was tested four times and has shown strong to moderate activity in microsomal testing [121,123].

Of the flavones tested three or less times, those with strong activity include 6-hydroxyflavone (**25**) in JEG-3 cells [125], 7,4'-dihydroxyflavone (**15**) in microsomes [132], 7-methoxyflavone (**32**) in microsomes [123,124] but not in H295R adrenocortical carcinoma cells [127], and isolicoflavonol (3,5,7-trihydroxy-3'-prenylflavone, **27**, isolated from *Broussonetia papyrifera*) in microsomes [135]. Moderately active flavones included broussoflavonol F (3,5,7-trihydroxy-8,3'-diprenylflavone, **10**, isolated from *B. papyrifera* Vent.) in microsomes [135], galangin (3,5,7-trihydroxyflavone, **20**) in JEG-3 cells [125], kaempferol (3,5,7,4'-tetrahydroxyflavone, **29**) in JEG-3 cells [125], 5,7,4'-trihydroxy-3'-methoxyflavone (**44**) in microsomes [136], and rutin (5,7,3',4'-tetrahydroxyflavone 3-diglucoside, **39**, isolated from *Vitis* L. sp.) [107].

When comparing aromatase inhibitory activity within the flavone compound class, several trends become apparent. Hydroxyl groups at positions 5, 7, and 4' generally increase aromatase inhibition activity [e.g., as in apigenin (**8**), luteolin (**31**), chrysin (**11**), and isolicoflavonol (**27**)], although hydroxylation at these positions is not always enough to provide strong aromatase inhibition [e.g., morin (**33**), quercetin (**37**)]. Methoxylation generally decreases aromatase inhibition activity [e.g., 7-hydroxyflavone (**26**) was more active than 7-methoxyflavone (**32**), apigenin (**8**) was more active than prunetin (**36**), and kaempferol (**29**) was more active than kaempferide (**28**)] except in the case of chrysin (**11**), which has two methoxyl groups and is one of the most active flavones tested thus far. Substitution at the C-3 position generally reduces activity [e.g., 3-hydroxyflavone (**21**), morin (**33**), quercetin (**37**), myricetin (**34**) and robinetin (**38**), which were all inactive or only weakly active], while prenylation seems to increase activity, as exemplified by isolicoflavonol (**27**) and broussoflavonol F (**10**).

Twenty flavanones have been tested for aromatase inhibition in the literature (Table 3, Fig. 4). Of these, naringenin (5,7,4'-flavanone, **59**) has been tested most often and has shown strong to moderate aromatase inhibition activity in microsomal testing [118,119,123,124]. This substance was found to be active in JEG-3 cells [125], Arom+HEK 293 cells [125], and inhibited aromatase at low concentrations in a MCF-7 dual assay for aromatase inhibition and estrogenicity [naringenin (**59**) was also estrogenic at high concentrations] [116]. Naringenin (**59**) was less active in H295R adenocortical carcinoma cells [127]. The (2*S*) stereoisomer of naringenin (**59**, isolated from *Broussonetia papyrifera* Vent.) [135] was less active than naringenin (**59**) when no stereochemistry was indicated.

Unsubstituted flavanone (**52**), a natural product derivative, was found to range from having moderate aromatase inhibition [121,122,132,133,137] to being inactive [128] in microsomal biological evaluations. Flavanone (**52**) was inactive using trout ovarian aromatase [128]. 7-Hydroxyflavanone (**56**) and 7-methoxyflavanone (**58**) were both found to be aromatase inhibitors in microsomes [133,137,138], with 7-hydroxyflavanone (**56**) exhibiting more potent activity than 7-methoxyflavanone (**58**). 7-Hydroxyflavanone (**56**) was also active in H295R cells but 7-methoxyflavanone was inactive [127]. Hesperetin (5,7,3'-trihydroxy-4'-methoxyflavanone, **53**) [121,133] and eriodictyol (5,7,3',4'-tetrahydroxyflavanone, **50**) [133] were each tested twice in microsomal aromatase assays and found to be strongly active. 8-Prenylnaringenin (**62**, isolated from *Humulus lupulus* L.) was one of the most active natural product compounds tested for aromatase inhibition in both microsomes and cell assays [114,139].

Of the flavanones tested only once, (2*S*)-2',4'-dihydroxy-2”-(1-hydroxy-1-methylethyl)dihydrofuro[2,3-*h*]flavanone (**49**, isolated from *Broussonetia papyrifera* Vent.) [135], (2*S*)-abyssinone II (**45**, isolated from *B. papyrifera*), (2*S*)-5,7,2',4'-tetrahydroxyflavanone (**63**, isolated from *B. papyrifera*), (2*S*)-euchrenone a7 (**51**, isolated from *B. papyrifera*), 7,8-dihydroxyflavanone (**48**) [124], and naringin (**60**) [121] were found to be potent aromatase inhibitors using microsomal assays. Pinostrobin (5-hydroxy-7-methoxyflavanone, **61**) [125] was found to be active in JEG-3 cells [125].

When comparing the activity within the flavanone compound class, several trends are noticeable. Hydroxyl groups at positions 7 and 4' generally increases aromatase inhibition [e.g., eriodictyol (**50**), (2*S*)-abyssinone II (**45**), and (2*S*)-euchrenone a7 (**51**)]. Methoxylation, however, decreases activity [e.g., 7-hydroxyflavanone (**56**) was more active than 7-methoxyflavanone (**58**)]. Prenylation generally caused substantial increases in aromatase activity [e.g., 8-prenylnaringenin (**62**), (2*S*)-abyssinone II (**45**), and (2*S*)-euchrenone a7 (**51**)] except in the case of isoxanthohumol (**57**).

Nineteen chalcones have been tested for their ability to inhibit aromatase (Table 4, Fig. 5). 3'-[γ-Hydroxymethyl-(*E*)-γ-methylallyl]-2,4,2',4'-tetrahydroxychalcone 11'-*O*-coumarate (**75**, isolated from *Broussonetia papyrifera* Vent.) [135], naringenin chalcone (4,2',4',6'-tetrahydroxychalcone, **78**) [133], eriodictyol chalcone (3,4,2',4',6'-pentahydroxychalcone, **68**) [133], and 2,4,2',4'-tetrahydroxy-3'-prenylchalcone (**82**, isolated from *B. papyrifera*) were the most active of the chalcones tested in microsomal assays. Butein (3,4,2',4'-tetrahydroxychalcone, **65**) was active in MCF-7aro cells [140], while xanthohumol (4,4',6'-trihydroxy-2'-methoxy-5'-prenylchalcone, **83**, isolated from *Humulus lupulus* L.) was active in SK-BR-3 cells [139]. Isoliquiritigenin (4,2',4'- trihydroxychalcone, **77**) isolated from licorice (*Glycyrrhiza glabra* L.) [141] and tonka bean (*Dipteryx odorata* Willd.) [142], was found to be inactive in microsomes [133,143] but strongly active in SK-BR-3 cells [143]. Isogemichalcone C (**76**) was also moderately active in a microsomal assay [135].

A couple of trends are discernible when comparing the aromatase inhibitory activity of structures within the chalcone compound class. Hydroxyl groups at positions 4, 2', and 4' have generally provided compounds with a greater degree of aromatase inhibition. The 1,2 double bond is necessary for activity [e.g., phloretin (**80**) was inactive while naringenin chalcone (**78**) was active]. In addition, methoxylation generally reduces activity [e.g., eriodictyol chalcone (**68**) was considerably more active than hesperetin chalcone (**69**); 3'-[γ-hydroxymethyl-(*E*)-γ-methylallyl]-2,4,2',4'-tetrahydroxychalcone 11'-*O*-coumarate (**75**) was more active than isogemichalcone C (**76**)].

Ten isoflavans were tested with four isoflavans found to be weakly active (Table 5, Fig. 6). 4'-*O*-Methylglabridin (**90**), isolated from licorice (*Glycyrrhiza glabra* L.), leiocin (**87**), isolated from *Berchemia discolor* Hemsl. [144], leiocinol (**88**), isolated from *B. discolor*, and methylequol (**89**) [145] were all weakly active in the microsomal assay.

Nine catechins were reported as being tested for their ability to inhibit aromatase (Table 6, Fig. 7). Epigallocatechin gallate [EGCG, **99**, isolated from *Camellia sinensis* Kuntze (green tea)], has been tested four times with results ranging from weakly active [146], when steroechemistry was not reported, to inactive for the (−) stereoisomer [112], in microsomal testing. However, an epidemiological study inferring aromatase inhibition through changes in estradiol levels demonstrated that estradiol levels were lower for people with higher EGCG (**99**) intake [147]. Furthermore, EGCG (**99**) has been tested using an *in vivo* Swiss-Webster mouse model measuring ovarian aromatase activity and was found to inhibit aromatase activity by 56% at 25 and 12.5 mg/kg [148]. Theaflavin (**101**) and theaflavin-3,3'-gallate (**102**), both isolated from *Camellia sinensis* Kuntze (black tea), were found to

strongly inhibit aromatase in microsomes [146]. (−)-Gallocatechin gallate (**100**), isolated from *C. sinensis* (green tea), was found to weakly inhibit aromatse in microsomes [112]. All other catechins tested were found to be inactive.

Aromatase inhibition testing has been reported for eight isoflavanones (**103–110**, Table 7, Fig. 8), with all isoflavanones found to be inactive in microsome testing [132,143].

From the literature, six isoflavones were tested for aromatase inhibition (Table 8, Fig. 9). The isoflavone biochanin A (5,7-dihydroxy-4'-methoxyisoflavone, **111**) was reported as either moderately active [121] or inactive [119,123,149] in microsomal assays but was strongly active in JEG-3 cells [125] and inactive in granulose-luteal cells [129], human preadipocyte cells [126], and against trout ovarian aromatase [128]. However, biochanin A (**111**) did inhibit aromatase at low concentrations using a MCF-7 dual assay for aromatase inhibition and estrogenicity and was estrogenic at high concentrations [116]. None of the other isoflavones inhibited aromatase.

Sixteen miscellaneous flavonoids were tested for their ability to inhibit aromatase (Table 9, Fig. 10). The coumestan, coumestrol (**119**), has been tested five times for aromatase activity and results have ranged from weakly active [123] in microsomal testing to moderately active in preadipose cells [134]. The only other miscellaneous flavonoid found to be active was a rotenoid, rotenone (**132**, a commercially available insecticide and a potent respiratory toxin), which was found to be strongly active in H295R adrenocortical carcinoma cells [127]. None of the flavanols, homoisoflavonoids, or pterocarpans were found to be active.

From the literature, ten alkaloids have been reported as being tested for aromatase inhibition (Table 10, Fig. 11). Five of these alkaloids were isolated from *Nicotiana tabacum* L. [113,150], with the others from *Hydrastis canadensis* L. (goldenseal), and *Piper* L. sp. [143]. None were found to inhibit aromatase.

Fifteen fatty acids have been tested for aromatase inhibition (Table 11, Fig. 12). Using the categories delineated above, one of the fatty acids, (10*E*,12*Z*)-9-oxo-10,12-octadecadienoic acid (**154**) isolated from *Urtica dioica* L. (stinging nettle) showed moderate aromatase inhibitory activity [151]. Two other fatty acids, (10*E*,12*Z*)-9-hydroxy-10,12-octadecadienoic acid (**149**) and docosapentaenoic acid (**146**) [152], showed weak aromatase inhibitory activity in microsomal testing [151]. However, though several unsaturated fatty acids exhibited strong aromatase inhibitiory activity during initial screening they were found to be inactive in cellular aromatase testing [152]. In bioassay-guided studies on natural product extracts for aromatase inhibition activity, fatty acids may be regarded as “interfering” substances, since they are active in noncellular, enzyme-based aromatase assays but do not inhibit aromatase in secondary cellular testing [152].

In previous literature reports, eighteen lignans were evaluated for aromatase inhibition (Table 12, Fig. 13). The mammalian lignans enterodiol (**166**) and enterolactone (**167**) were each tested three times, as was nordihydroguaiaretic acid (**172**). Enterolactone (**167**) was moderately active in microsomes and strongly active using Arom+HEK 293 cells [153]. Nordihydroguaiaretic acid (**172**) was weakly active in micromal testing [145], although this compound was also found to be inactive in microsomes by another group [154]. Of the other lignans tested, 4,4'-dihydroxyenterolactone (**164**) was moderately active and 4,4'-enterolactone (**165**) was weakly active in microsomal aromatase testing [145]. All other lignans tested were inactive, although nectandrin B (**171**), isolated from *Myristica argentea* Warb. [154], and secoisolariciresinol (**173**) isolated from *Urtica dioica* L. (stinging nettle) [155] were both previously reported as active compounds.

From the literature, nineteen natural product peptides were tested for aromatase inhibition (Table 13, Fig. 14). Sixteen peptides were isolated from an unidentified soil bacterium and were similar in structure, varying only in two side chains and two residues [156]. Most of these peptides from bacteria were inactive in microsomes, with SNA-60-367-6 (**186**) and -11 (**190**) being weakly active [156]. No cellular testing was done on these compounds. *N*-Benzoyl-L-phenylalanine methyl ester (**177**), isolated from *Brassaiopsis glomerulata* L., was found to be weakly active in SK-BR-3 cells [108].

A total of 36 terpenoids have been tested for aromatase inhibition, including ten diterpenoids, ten steroids, seven triterpenoids, five isoprenoids, two sesquiterpenoids, and two withanolides (Table 14, Fig. 15). Of the terpenoids tested, diterpenoids and steroids have been tested most often but were only found to be weakly inhibitory or inactive. The most active of the diterpenoids using recombinant yeast microsomes was the ring C-aromatized compound, standishinal (**203**), isolated from *Thuja standishii* Carrière [157]. Inflexin (**198**), an *ent*-kaurane diterpenoid, isolated from *Isodon excisus* Kudo var. *coreanus*, was also active in micromal aromatase testing [110]. These two diterpenes show little similarity, making structural comparisons within the diterpenoid class difficult. Ten steroids isolated from *Aglaia ponapensis* Kaneh. [158], *Albizia falcataria* (L.) Fosberg, and *Brassaiopsis glomerulata* (Blume) Regel [108] were found to be inactive in microsomal aromatase testing.

Of the seven triterpenoids ursolic acid (**227**), isolated from *Isodon excisus* Kudo var. *coreanus* [110] and *Urtica dioica* L. [155], was tested in microsomes and found to be moderately inhibitory once [110], but otherwise inactive. Another of the triterpenoids tested, aglaiaglabretol B (**223**) isolated from *Aglaia crassinervia* Kurz ex Hiern [159], was moderately active against SK-BR-3 cells [143]. However, aglaiaglabretol B (**223**) was also found to be cytotoxic during previous work [159], limiting the potential use of this compound as an aromatase inhibitor.

Of the five isoprenoids (−)-dehydrololiolide (**205**), isolated from *Brassaiopsis glomerulata* (Blume) Regel, moderately inhibited aromatase in SK-BR-3 cells [108]. The other four isoprenoids were inactive.

A sesquiterpene lactone, 11βH,13-dihydro-10-*epi*-8-deoxycumambrin (**211**), isolated from *Stevia yaconensis* Hieron. var. *subeglandulosa* [160], was found to be strongly active using microsomal aromatase testing [161]. Though the other sesquiterpene lactone 10-*epi*-8-deoxycumambrin B (**210**) was found to be moderately active in microsomes it was found to be cytotoxic in further testing [161]. The former was moderately active as an aromatase inhibitor in JEG-3 choriocarcinoma cells and was not cytotoxic [161].

The two withanolides, isolated from *Physalis philadelphica* Lam. (tomatillo, an edible fruit similar to tomato often used in salsa) [162], were found to be inactive against aromatase in microsome testing [143].

Sixteen xanthones were tested for aromatase inhibition in microsomes (Table 15, Fig. 16). Twelve xanthones were isolated from *Garcinia mangostana* L. (mangosteen) [163]. γ-Mangostin (**276**) and garcinone D (**270**), were found to be strongly active in microsomes and α-mangostin (**275**) and garcinone E (**271**) were found to be moderately active. The other xanthones from *G. mangostana* L. were inactive. Four xanthones were isolated from a marine fungus, *Monodictys putredinis* [164], and were found to be inactive in microsomal testing.

There have been 43 miscellaneous natural product compounds tested for aromatase inhibition in the literature (Table 16, Fig. 17). Fourteen benzenoids were tested, with

TAN-931 (**269**) isolated from the bacterium *Penicillium funiculosum* No. 8974 [165], being weakly active in microsomes. TAN-931 (**269**) was further tested *in vivo* using Sprague-Dawley rats and was found to reduce estradiol levels presumably, although not definitively, through aromatase inhibition [165]. All other benzenoids were inactive.

Seven anthraquinones have been tested, six of which were isolated from *Morinda citrifolia* L. (noni), a widely used botanical dietary supplement [166,167]. None of the anthraquinones isolated from *M. citrifolia* was found to be active in microsomal aromatase testing. Benzanthraquinone I (**249**), isolated from the bacteria *Streptomyces* S-11106, exhibited strong aromatase inhibitory activity in microsomes [168].

The stilbenoid, resveratrol (**286**), isolated from *Vitis* L. sp. [107], was reported to strongly inhibit aromatase in microsomes [107], to moderately inhibit aromatase in another microsomal test [136], and to be inactive when tested a third time [143]. One of the miscellaneous compounds, albanol A (**281**) isolated from *Broussonetia papyrifera* Vent. [135], was found to moderately inhibit aromatase in microsomes. All other miscellaneous compounds, including all alkanols, aromatic hydrocarbons, benzofurans, chlorophylls, diarylheptanoids, dioxadispiroketals, spiroketones, and tannins, were found to be inactive against aromatase.

CONCLUSIONS

Numerous natural product extracts, from plant, fungal, and microbial terrestrial and marine sources, have been evaluated for aromatase inhibition using various noncellular, cell-based, and *in vivo* assays. Some of the more active extracts included those of *Agaricus bisporus* (Lange) Imbach (white button mushrooms) [115] and *Vitis* L. sp. (grape and/or wine) [86,106,107], among others. Some aromatase activity-guided fractionation has been performed on *Vitis* sp. extracts, resulting in the isolation of various procyanidin dimers that have yet to be fully characterized [86]. Interestingly, several types of extracts and partitions of *A. bisporus* and a sample of *Vitis* sp. (grape) were subsequently tested for their ability to inhibit aromatase in microsomes and found to be inactive [143]. Several factors could be involved in the discrepancies between the literature results, including variations in the species collected, timing of collections, purity of materials extracted, preparation of extracts, and assay methodology.

Several other extracts were determined to inhibit aromatase in microsomes including from *Brassaiopsis glomerulata* (Blume) Regel [108] and *Garcinia mangostana* L. (mangosteen) [109], with both of these species having undergone activity-guided purification resulting in the isolation of compounds with AI activity. Extracts of several cycads were also found to be potent AIs [104] but, to date, their bioassay-guided fractionation has not been performed. Another active extract that has not undergone fractionation is *Euonymus alatus* [111]. Active compounds isolated from these extracts may provide potent AIs and possible leads for further development.

Nearly 300 natural product compounds have been evaluated for their ability to inhibit aromatase, in noncellular, cell-based, and *in vivo* aromatase inhibition assays. Flavonoids have been tested most frequently and generally found to be the most active class of natural product AI compounds. Some of the more active flavonoids included apigenin (**8**), chrysin (**11**), 7-hydroxyflavone (**26**), isolicoflavonol (**27**), (2*S*)-abyssinone II (**45**), (2*S*)-2',4'-dihydroxy-2”-(1-hydroxy-1-methylethyl)dihydrofuro[2,3-*h*]flavanone (**49**), eriodictyol (**50**), 8-prenylnaringenin (**62**), 3'-[γ-hydroxymethyl-(*E*)-γ-methylallyl]-2,4,2',4'-tetrahydroxychalcone 11'-*O*-coumarate (**75**), isoliquiritigenin (**77**), and rotenone (**132**). Other very active AI compounds included the xanthone, γ-mangostin (**239**), the

sesquiterpene lactone, 11βH,13-dihydro-10-*epi*-8-deoxycumambrin (**211**), and the anthraquinone, benzanthraquinone I (**249**).

Since natural product drug discovery efforts frequently utilize non-cellular screening assays, several of the compounds reported to be active in non-cellular assays should be avoided by future AI drug discovery endeavors. This is exemplified by the unsaturated fatty acids, which are commonly found in natural product extracts and have been shown to interfere with non-cellular AI assays [152]. Several flavonoids have also been found to be active in non-cellular screening and inactive in cell-based assays. In natural product AI screening efforts it is recommended that extracts active in non-cellular bioassays be dereplicated for the presence of known aromatase inhibitors prior to expensive and time-consuming bioassay-guided fractionation.

All of the most active compounds were of the flavonoid or xanthone compound classes, with the exception of the active sesquiterpene lactone and the active anthraquinone. The ability of flavonoids to inhibit aromatase has been well established [169,170] and some flavonoids have continued into *in vivo* studies with various results [125,148]. Interestingly, Saarinen et al. [125] have shown that apigenin (**8**), chrysin (**11**), and naringenin (**59**) were all inactive using an *in vivo* AI mouse model. The AI activity of flavonoids needs further *in vivo* testing to substantiate the extensive and potent *in vitro* results. Various AI mouse models are currently available or in development, including a transgenic model that overexpresses aromatase [171], an aromatase-knockout mouse model [172], and a MCF-7 xenograft model [173].

Several natural product compounds have already undergone synthetic modifications to further enhance AI activity. Two separate syntheses have been performed on the strongly active flavone (2*S*)-abyssinone II (**45**) [174,175] and several analogues have been found to be more active than the natural compound. Synthesis of 7,8-benzoflavanones has provided several leads with potent AI activity [176]. Ursolic acid (**227**) derivatives were synthesized with resulting compounds having lower activity than the natural product [177]. The diterpenoid, standishinal (**203**), and several synthetic derivatives were subjected to AI testing with the most active compounds having a *cis*-configuration on the A/B ring [178]. Synthetic xanthones have only recently been tested for their ability to inhibit aromatase [48,179,180] with extremely potent AI activity in the nanomolar range. However, very few natural product or synthetic compounds have undergone extensive evaluation using additional *in vitro* or *in vivo* and preclinical models.

This review highlights several compound classes that may act as aromatase inhibitors (e.g., flavones, flavanones, chalcones, and xanthones) and other structural classes that are less active. These scaffolds may be utilized to direct synthetic modification of natural product scaffolds to enhance aromatase inhibition. New natural products or natural product analogues that inhibit aromatase may be clinically useful for treating postmenopausal breast cancer. Aromatase inhibitors may also act as chemopreventive agents for preventing secondary recurrence of breast cancer. Furthermore, AIs from edible plant materials may eventually be appropriate for primary prevention of breast cancer in postmenopausal women (e.g., lower toxicity due to history of human consumption). Botanical dietary supplements or foods that are ingested regularly and act as AIs may have a role in breast cancer chemoprevention or chemotherapy for postmenopausal women.

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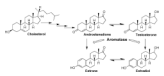


Fig. (1).
Conversion of cholesterol to androstenedione and testosterone, followed by aromatase catalyzed conversion to estrone and estradiol, respectively.

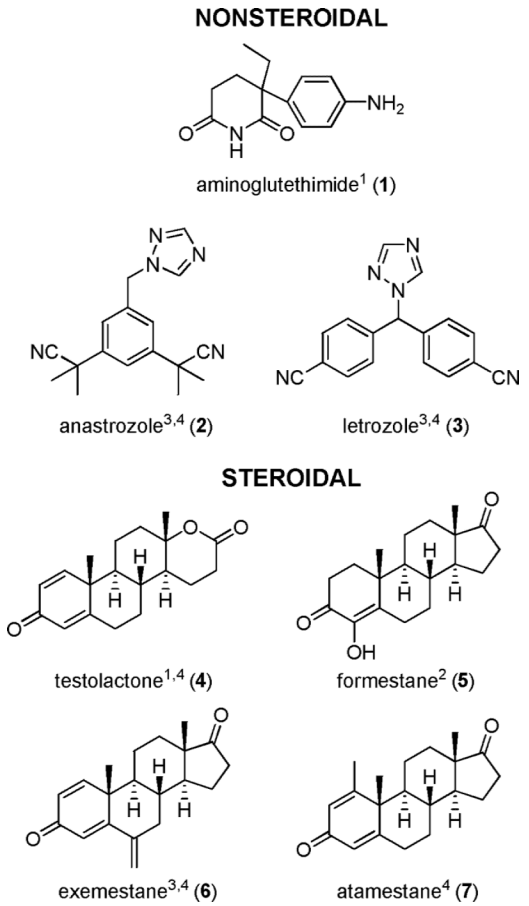
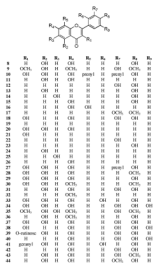


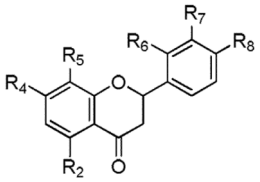
Fig. (2).

Examples of first[1], second[2], and third[3] generation AIs, including AIs currently in clinical trials[4]. All three third generation compounds are currently approved for clinical use.

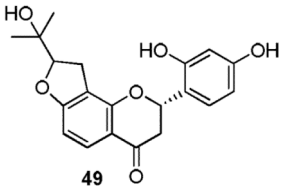


	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
6	H	OH	H	OH	H	H	OH	H
9	OCH_3	OH	H	OCH_3	H	H	OH	OCH_3	H
10	H	OH	H	OH	H	H	H	H	H
11	H	OH	H	OH	H	H	H	H	H
12	H	H	H	H	H	H	OH	OH	H
13	H	OH	H	H	H	H	H	OH	H
14	H	OH	H	H	H	H	H	OH	H
15	H	H	OH	H	H	H	H	OH	H
16	H	H	H	OH	H	H	H	H	H
17	H	H	H	H	H	H	OCH_3	OCH_3	H
18	H	H	H	OH	H	H	OH	OH	H
19	H	H	H	OH	H	H	H	H	H
20	OH	OH	H	OH	H	H	H	H	H
21	OH	H	H	H	H	H	H	H	H
22	H	H	H	H	H	H	OH	H	H
23	H	H	H	H	H	H	H	H	H
24	H	OH	H	H	H	H	H	H	H
25	H	H	OH	H	H	H	H	H	H
26	H	H	H	OH	H	H	H	H	H
27	OH	OH	H	OH	H	H	prenyl	OH	H
28	OH	OH	H	OH	H	H	H	OH	H
29	OH	OH	H	OH	H	H	H	OH	H
30	OH	OH	H	OCH_3	H	H	H	OCH_3	H
31	H	OH	H	OH	H	H	OH	OH	H
32	H	H	H	OCH_3	H	H	H	H	H
33	OH	OH	H	OH	H	H	OH	OH	H
34	OH	OH	H	OH	H	H	OH	OH	OH
35	OCH_3	OH	OH	OCH_3	H	H	OH	OCH_3	H
36	H	OH	H	OCH_3	H	H	H	OH	H
37	H	OH	H	OH	H	H	OH	OH	H
38	OH	OH	H	OH	H	H	OH	OH	OH
39	O-sulfonic	OH	H	OH	H	H	OH	OH	H
40	H	H	H	OH	H	H	OH	OH	OH
41	prenyl	OH	H	OH	H	H	OH	OH	H
42	H	OH	H	OH	H	H	OH	OH	H
43	H	OH	H	OH	H	H	OH	OCH_3	H
44	H	OH	H	OH	H	H	OCH_3	OH	H

Fig. (3).
Structures of natural product flavones tested for aromatase inhibition.

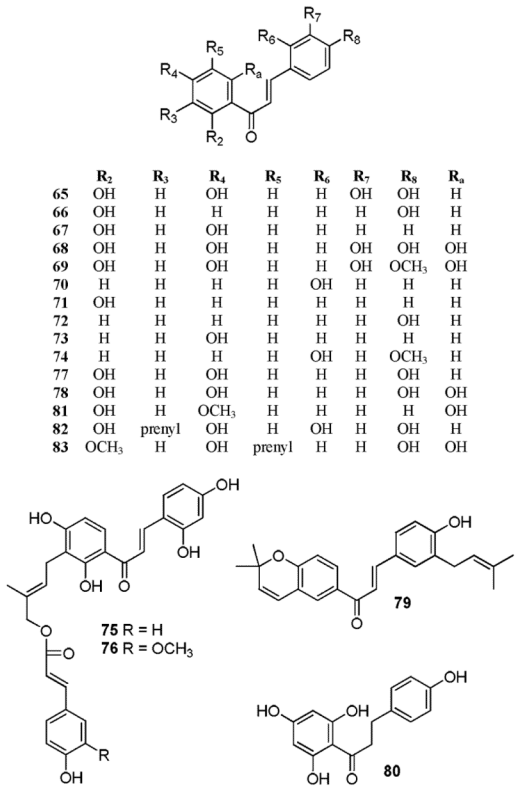


		R_2	R_4	R_5	R_6	R_7	R_8
45	2*S*	H	OH	H	H	prenyl	OH
46		H	H	H	H	OH	OH
47		OH	OH	H	H	H	H
48		H	OH	OH	H	H	H
50		OH	OH	H	H	OH	OH
51	2*S*	H	OH	prenyl	OH	H	OH
52		H	H	H	H	H	H
53		OH	OH	H	H	OH	OCH_3
54		OH	O-rutinoside	H	H	OH	OCH_3
55		H	H	H	H	H	OH
56		H	OH	H	H	H	H
57		OCH_3	OH	prenyl	H	H	OH
58		H	OCH_3	H	H	H	H
59	2*S*	OH	OH	H	H	H	OH
60	2*S*	OH	O-rutinose	H	H	H	OH
61		OH	OCH_3	H	H	H	H
62		OH	OH	prenyl	H	H	OH
63	2*S*	OH	OH	H	OH	H	OH
64		OH	OH	H	H	OCH_3	OH



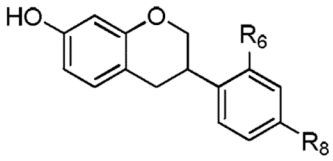
49

Fig. (4).
Structures of natural product flavanones tested for aromatase inhibition.

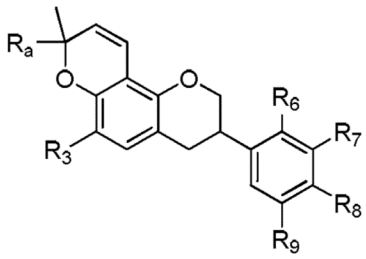


	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_a
65	OH	H	OH	H	H	OH	OH	H
66	OH	H	H	H	H	H	OH	H
67	OH	H	OH	H	H	H	H	H
68	OH	H	OH	H	H	OH	OH	OH
69	OH	H	OH	H	H	OH	OCH_3	OH
70	H	H	H	H	OH	H	H	H
71	OH	H	H	H	H	H	H	H
72	H	H	H	H	H	H	OH	H
73	H	H	OH	H	H	H	H	H
74	H	H	H	H	OH	H	OCH_3	H
77	OH	H	OH	H	H	H	OH	H
78	OH	H	OH	H	H	H	OH	OH
81	OH	H	OCH_3	H	H	H	H	OH
82	OH	prenyl	OH	H	OH	H	OH	H
83	OCH_3	H	OH	prenyl	H	H	OH	OH

Fig. (5).
Structures of natural product chalcones tested for aromatase inhibition.

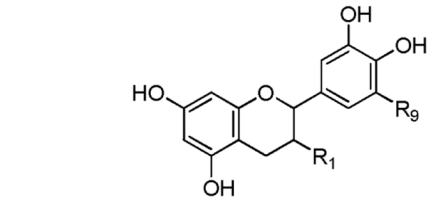


	R_6	R_8
84	H	OH
89	H	OCH_3
93	OCH_3	OCH_3



		R_3	R_6	R_7	R_8	R_9	R_a
85	3*S*	H	OH	H	OCH_3	H	phenyl
86	3*R*	H	OH	OH	OH	H	CH_3
87	3*S*	H	OH	H	-OCH_2O-		CH_3
88	3*S*	CH_3	OH	H	-OCH_2O-		CH_3
90	3*R*	H	OH	H	OCH_3		CH_3
91	3*S*	H	OH	H	-OCH_2O-		phenyl
92	3*S*	H	OH	OH	OCH_3		phenyl

Fig. (6).
Structures of natural product isoflavans tested for aromatase inhibition.



			R_1	R_9
94	2*R*	3*S*	OH	H
95	2*S*	3*R*	gallate	H
96	2*S*	3*R*	OH	H
97	2*R*	3*R*	gallate	H
98	2*R*	3*R*	OH	OH
99	2*R*	3*S*	gallate	OH
100	2*S*	3*R*	gallate	OH

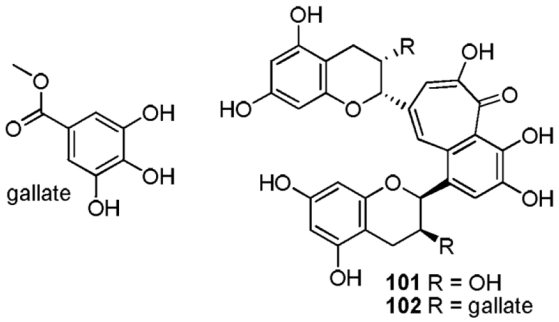


Fig. (7).
Structures of natural product catechins tested for aromatase inhibition.

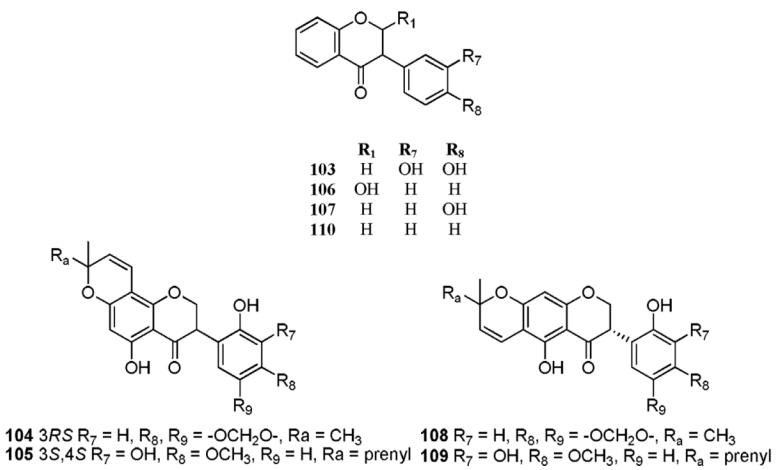
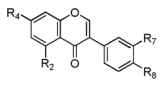


Fig. (8).
Structures of natural product isoflavanones tested for aromatase inhibition.



	R_2	R_4	R_7	R_8
111	OH	OH	H	OCH_3
112	H	OH	H	OH
113	H	OH	H	OCH_3
114	OH	OH	H	OH
115	H	H	H	H
116	H	OH	OH	OH

Fig. (9).
Structures of natural product isoflavones tested for aromatase inhibition.

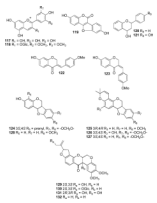


Fig. (10).
Structures of natural product flavonoids (not previously mentioned) tested for aromatase inhibition.

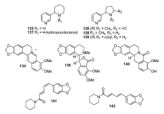


Fig. (11).
Structures of alkaloids tested for aromatase inhibition.

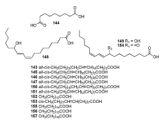


Fig. (12).
Structures of natural product fatty acids tested for aromatase inhibition.

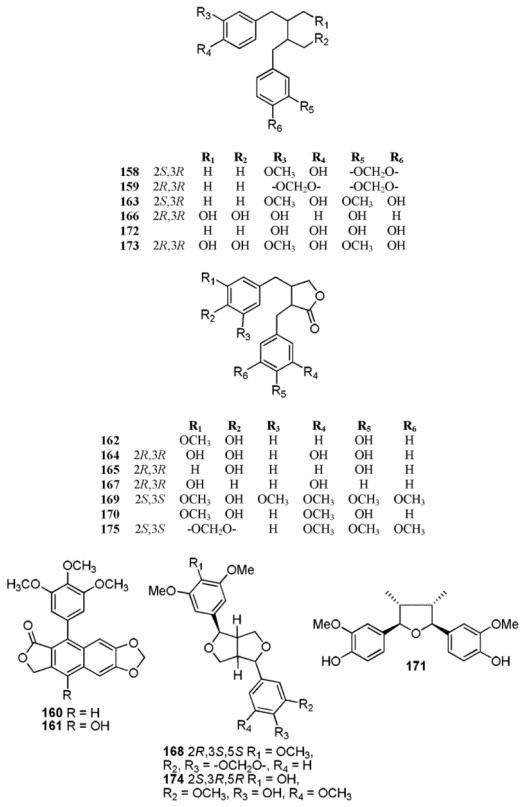
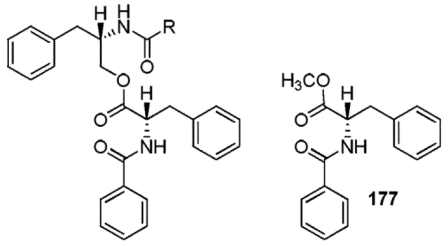
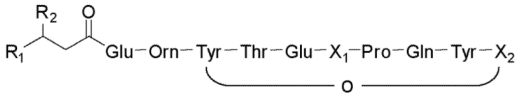


Fig. (13).
Structures of natural product lignans tested for aromatase inhibition.



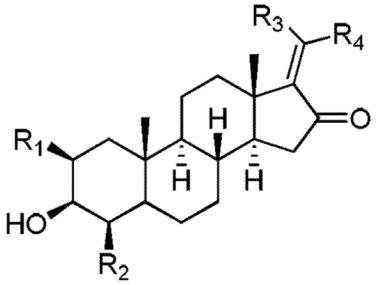
176 R = CH_3
178 R = phenyl

177

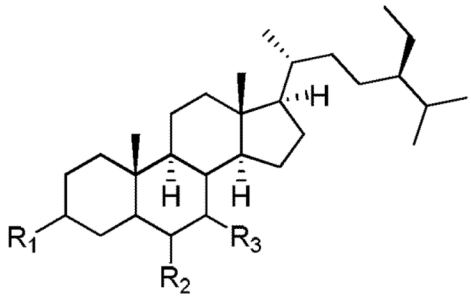


	X_1	X_2	R_1	R_2
179	Ala	Ile	$-CH_2(CH_2)_{10}CH(CH_3)_2$	OH
180	Aba	Ile	$-CH_2(CH_2)_{10}CH(CH_3)_2$	OH
181	Val	Ile	$-CH_2(CH_2)_{10}CH(CH_3)_2$	OH
182	Ala	Ile	$-CH_2(CH_2)_{10}CHCH_2CH_3$ CH_3	OH
183	Val	Val	$-CH_2(CH_2)_{13}CH_3$	OH
184	Val	Val	$-CH_2(CH_2)_{11}CH(CH_3)_2$	OH
185	Aba	Ile	$-CH_2(CH_2)_{10}CHCH_2CH_3$ CH_3	OH
186	Aba	Ile	$-CH_2(CH_2)_{11}CH(CH_3)_2$	OH
187	Val	Ile	$-CH_2(CH_2)_{10}CHCH_2CH_3$ CH_3	OH
188	Val	Ile	$-CH_2(CH_2)_{11}CH(CH_3)_2$	OH
189	Ala	Ile	$-CH_2(CH_2)_{12}CH_3$	H
190	Val	Ile	$-CH_2(CH_2)_{10}CH(CH_3)_2$	H
191	Val	Ile	$-CH_2(CH_2)_{12}CH_3$	H
192	Ala	Ile	$-CH_2(CH_2)_{11}CH(CH_3)_2$	H
193	Aba	Ile	$-CH_2(CH_2)_{10}CHCH_2CH_3$ CH_3	H
194	Val	Ile	$-CH_2(CH_2)_{11}CH(CH_3)_2$	H

Fig. (14).
Structures of natural product peptides tested for aromatase inhibition.



		R_1	R_2	R_3	R_4
212	H-5α	OH	H	CH_3	H
213	H-5α	OH	H	H	CH_3
220	$\Delta^{5(6)}$	H	OH	CH_3	H
221	$\Delta^{5(6)}$	H	OH	H	CH_3



			R_1	R_2	R_3
214	$\Delta^{4(5)}$	H-8β	=O	β-OH	H
215	$\Delta^{4(5)}$	H-8β	=O	H	β-OH
216	$\Delta^{7(8)}$	H-5α	β-OH	H	H
217	$\Delta^{7(8)}$	H-5α	β-OAc	H	H
218	$\Delta^{7(8)}$	H-5α	=O	H	H
219	$\Delta^{5(6)}$	H-8β	β-OH	H	H

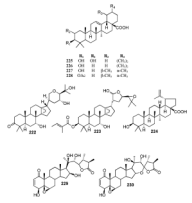
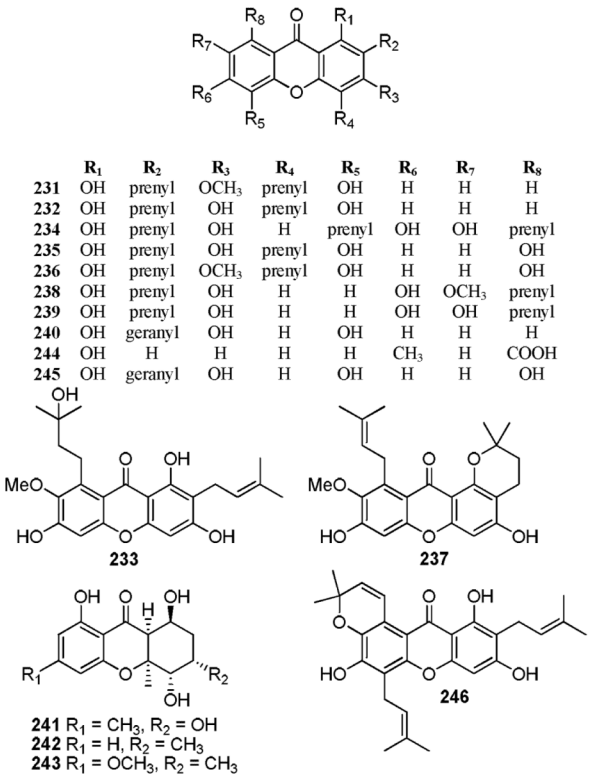


Fig. (15).
Structures of natural product terpenoids tested for aromatase inhibition.



	R1	R2	R3	R4	R5	R6	R7	R8
231	OH	prenyl	OCH_3	prenyl	OH	H	H	H
232	OH	prenyl	OH	prenyl	OH	H	H	H
234	OH	prenyl	OH	H	prenyl	OH	OH	prenyl
235	OH	prenyl	OH	prenyl	OH	H	H	OH
236	OH	prenyl	OCH_3	prenyl	OH	H	H	OH
238	OH	prenyl	OH	H	H	OH	OCH_3	prenyl
239	OH	prenyl	OH	H	H	OH	OH	prenyl
240	OH	geranyl	OH	H	OH	H	H	H
244	OH	H	H	H	H	CH_3	H	COOH
245	OH	geranyl	OH	H	OH	H	H	OH

Fig. (16).
Structures of natural product xanthones tested for aromatase inhibition.

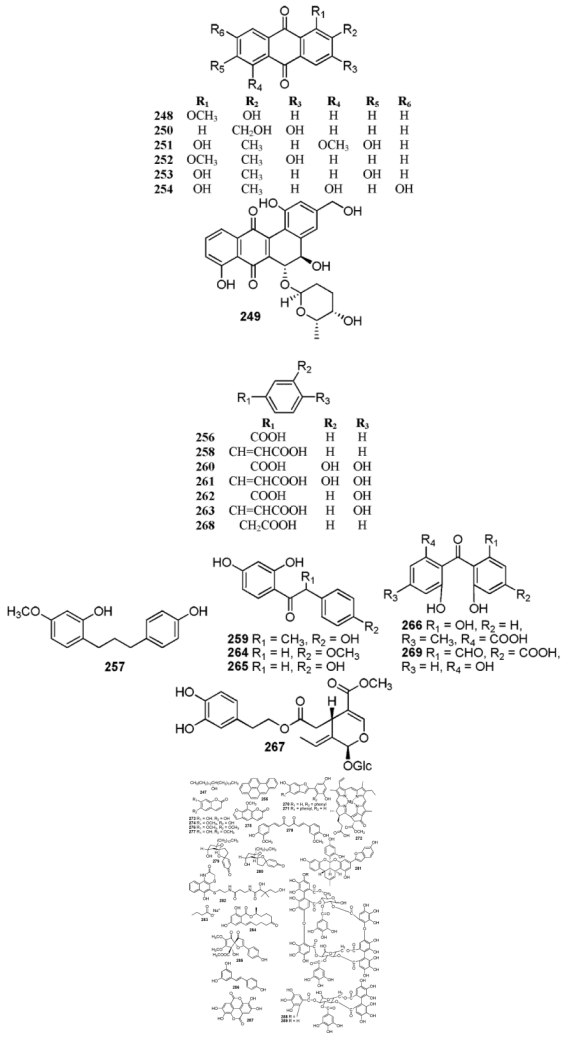


Fig. (17).
Structures of miscellaneous natural products (not previously mentioned) tested for aromatase inhibition.

Table 1

Previous literature reports of natural product extracts tested for aromatase inhibition

Species Name	Common Name	Family	Type	Extraction Solvent	Assay Type	Activity		Ref.(s)
Aesculus glabra	Ohio buckeye	Hippocastanaceae	plant	methanol ($CHCl_3$ partition)	microsomes	42.0	PCA at 20 μg/mL	[143]
Agaricus bisporus	baby button mushroom	Agaricaceae	fungus	water reflux	microsomes	~58	PCA at 100 μL	[115]
Agaricus bisporus	crimini mushroom	Agaricaceae	fungus	water reflux	microsomes	~46	PCA at 100 μL	[115]
Agaricus bisporus	portobello mushroom	Agaricaceae	fungus	water reflux	microsomes	~45	PCA at 100 μL	[115]
Agaricus bisporus	stuffing mushroom	Agaricaceae	fungus	water reflux	microsomes	~20	PCA at 100 μL	[115]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	water reflux	microsomes	~35	PCA at 100 μL	[115]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	water reflux	MCF-7aro cells	14	at 10 μL/mL	[115]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (air dried)	microsomes	83.1	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (air dried, hexane partition)	microsomes	71.1	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (air dried, $CHCl_3$ partition)	microsomes	51.7	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (air dried, water partition)	microsomes	63.1	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (air dried, butanol partition)	microsomes	82.4	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (dehydrated)	microsomes	94.4	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (dehydrated, hexane partition)	microsomes	55.3	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (dehydrated, $CHCl_3$ partition)	microsomes	54.7	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (dehydrated, water partition)	microsomes	73.5	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (dehydrated, butanol partition)	microsomes	55.0	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (fresh)	microsomes	66.4	PCA at 20 μg/mL	[143]

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Species Name	Common Name	Family	Type	Extraction Solvent	Assay Type	Activity		Ref.(s)
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (fresh, hexane partition)	microsomes	72.7	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (fresh, $CHCl_3$ partition)	microsomes	78.8	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (fresh, water partition)	microsomes	89.6	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (fresh, butanol partition)	microsomes	79.4	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	acetone (fresh)	microsomes	59.1	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	acetone (fresh, hexane partition)	microsomes	38.3	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	acetone (fresh, $CHCl_3$ partition)	microsomes	39.2	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	acetone (fresh, water partition)	microsomes	81.5	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	acetone (fresh, butanol partition)	microsomes	85.3	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	water (reflux)	microsomes	96.2	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	water (reflux, hexane partition)	microsomes	80.4	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	water (reflux, $CHCl_3$ partition)	microsomes	56.1	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	water (reflux, water partition)	microsomes	79.4	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	water (reflux, butanol partition)	microsomes	65.3	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (sautéed)	microsomes	85.8	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (sautéed, hexane partition)	microsomes	53.5	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (sautéed, $CHCl_3$ partition)	microsomes	68.2	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (sautéed, water partition)	microsomes	83.8	PCA at 20 μg/mL	[143]
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	methanol (sautéed, butanol partition)	microsomes	57.1	PCA at 20 μg/mL	[143]

Species Name	Common Name	Family	Type	Extraction Solvent	Assay Type	Activity		Ref.(s)
Agaricus bisporus	white button mushroom	Agaricaceae	fungus	Dichloromethane	microsomes	54.4	PCA at 20 μg/mL	[143]
Agaricus bisporus	cremini mushroom	Agaricaceae	fungus	Dichloromethane	microsomes	65.7	PCA at 20 μg/mL	[143]
Agaricus bisporus	portobella mushroom	Agaricaceae	fungus	Dichloromethane	microsomes	59.1	PCA at 20 μg/mL	[143]
Agaricus blazei (1SY16)	almond mushroom	Agaricaceae	fungus	Unknown	microsomes	87.7	PCA at 20 μg/mL	[143]
Agaricus blazei	almond mushroom	Agaricaceae	fungus	Methanol	microsomes	75.2	PCA at 20 μg/mL	[143]
Agaricus blazei	almond mushroom	Agaricaceae	fungus	methanol (hexane partition)	microsomes	72.5	PCA at 20 μg/mL	[143]
Agaricus blazei	almond mushroom	Agaricaceae	fungus	methanol (dichloromethane partition)	microsomes	82.1	PCA at 20 μg/mL	[143]
Agaricus blazei	almond mushroom	Agaricaceae	fungus	methanol (water partition)	microsomes	88.4	PCA at 20 μg/mL	[143]
Agaricus blazei	almond mushroom	Agaricaceae	fungus	Dichloromethane	microsomes	74.5	PCA at 20 μg/mL	[143]
Allium sp.[a]	green onion	Liliaceae	plant	water reflux	microsomes	~75	PCA at 100 μL	[115]
Allium sp.[a]	green onions	Liliaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Allium sp.[a]	spanish onions	Liliaceae	plant	70% ethanol	microsomes	310	units/100 g	[113]
Allium sp.[a]	white onions	Liliaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Alpinia purpurata	red ginger	Zingerberaceae	plant	75% MeOH reflux	microsomes	~78	% inhib.	[105]
Althaea rosea var. *nigra*	hollyhock	Malvaceae	plant	Nd	immunocytochemistry in Leydig cells	weak		[181]
Apium graveolens [a]	celery	Apiaceae	plant	water reflux	microsomes	~80	PCA at 100 μL	[115]
Apium graveolens [a]	celery	Apiaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Asparagus officinalis [a]	asparagus	Liliaceae	plant	70% ethanol	microsomes	1300	units/100 g	[113]
Auricularia sp.	woodear mushroom	Auriculariaceae	fungus	water reflux	microsomes	~86	PCA at 100 μL	[115]
Brassaiopsis glomerulata (leaves)	none	Araliaceae	plant	methanol (hexane partition)	microsomes	6.9	PCA at 20 μg/mL	[143]

Species Name	Common Name	Family	Type	Extraction Solvent	Assay Type	Activity		Ref.(s)
Brassaiopsis glomerulata (leaves)	none	Araliaceae	plant	methanol (ethyl acetate partition)	microsomes	59.3	PCA at 20 μg/mL	[143]
Brassaiopsis glomerulata (leaves)	none	Araliaceae	plant	methanol (water partition)	microsomes	98.2	PCA at 20 μg/mL	[143]
Brassaiopsis glomerulata (leaves)	none	Araliaceae	plant	methanol (hexane partition)	SK-BR-3 cells	7.2	PCA at 20 μg/mL	[143]
Brassaiopsis glomerulata (leaves)	none	Araliaceae	plant	methanol (ethyl acetate partition)	SK-BR-3 cells	37.0	PCA at 20 μg/mL	[143]
Brassaiopsis glomerulata (twigs)	none	Araliaceae	plant	methanol (hexane partition)	microsomes	35.6	PCA at 20 μg/mL	[143]
Brassaiopsis glomerulata (twigs)	none	Araliaceae	plant	methanol (ethyl acetate partition)	microsomes	46.6	PCA at 20 μg/mL	[143]
Brassaiopsis glomerulata (twigs)	none	Araliaceae	plant	methanol (water partition)	microsomes	95.8	PCA at 20 μg/mL	[143]
Brassica juncea [a]	mustard (greens)	Brassicaceae	plant	70% ethanol	microsomes	2700	units/100 g	[113]
Brassica oleracea [a]	broccoli	Brassicaceae	plant	water reflux	microsomes	~85		[115]
Brassica oleracea [a]	broccoli	Brassicaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Brassica oleracea [a]	broccoli (leaves)	Brassicaceae	plant	70% ethanol	microsomes	3600	units/100 g	[113]
Brassica oleracea [a]	cabbage	Brassicaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Brassica oleracea [a]	cauliflower	Brassicaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Brassica oleracea [a]	collards	Brassicaceae	plant	70% ethanol	microsomes	8500	units/100 g	[113]
Brassica oleracea [a]	kale	Brassicaceae	plant	70% ethanol	microsomes	4700	units/100 g	[113]
Brassica rapa var. *rapa*[a]	turnips	Brassicaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Camellia sinensis [a]	black tea	Theaceae	plant	Nd	nd	>50	% inhib.	[182]
Camellia sinensis [a]	green tea	Theaceae	plant	Nd	nd	>50	% inhib.	[182]
Camellia sinensis [a]	green tea (polyphenone-60)	Theaceae	plant	Nd	microsomes	28	μg/mL IC_50	[112]
Camellia sinensis [a]	tea	Theaceae	plant	70% ethanol	microsomes	27000	units/100 g	[113]
Cantharellus sp.	chanterelle mushroom	Cantharellaceae	fungus	water reflux	microsomes	~80	PCA at 100 μL	[115]
Capsicum annuuma [a]	bell pepper	Solanaceae	plant	water reflux	microsomes	~89	PCA at 100 μL	[115]

Species Name	Common Name	Family	Type	Extraction Solvent	Assay Type	Activity		Ref.(s)
Capsicum sp.[a]	pepper (leaves)	Solanaceae	plant	70% ethanol	microsomes	2800	units/100 g	[113]
Capsicum sp.[a]	peppers	Solanaceae	plant	70% ethanol	microsomes	330	units/100 g	[113]
Cestrum sp.	none	Solanaceae	plant	75% MeOH reflux	microsomes	~40	% inhib.	[105]
Chrysanthemum partheniuma [a]	feverfew	Asteraceae	plant	Nd		>50	% inhib.	[182]
Cichorium endivia [a]	endive	Asteraceae	plant	70% ethanol	microsomes	850	units/100 g	[113]
Cichorium endivia [a]	escarole	Asteraceae	plant	70% ethanol	microsomes	830	units/100 g	[113]
Citrus × *limona* [a]	lemons	Rutaceae	plant	70% ethanol	microsomes	660	units/100 g	[113]
Citrus paradisi [a]	grapefruit (juice)	Rutaceae	plant	Nd	microsomes	~68	PCA at 25 μL	[183]
Citrus sinensis [a]	orange	Rutaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Citrus sinensis [a]	orange (juice)	Rutaceae	plant	Nd	microsomes	~90	PCA at 25 μL	[183]
Coccothrinax sp.	none	Arecaceae	plant	75% MeOH reflux	microsomes	~70	% inhib.	[105]
Coffea sp.[a]	coffee	Rubiaceae	plant	70% ethanol	microsomes	13000	units/100 g	[113]
Coix lachrymal-jobi var. *ma-yuen*	adlay or Job's tears	Poaceae	plant	Methanol	rat granulose cells	inhibits	activity at 100 μg/mL	[184]
Cucumis melo [a]	cantaloupe	Cucurbitaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Cucumis sativus [a]	cucumber	Loasaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Curcuma longa [a]	turmeric	Zingiberaceae	plant	Nd	nd	>50	% inhib.	[182]
Cycas cairnsiana	none	Cycadaceae	plant	75% MeOH reflux (ethyl acetate partition)	microsomes	69	% inhib.	[104]
Cycas revoluta	sago palm	Cycadaceae	plant	75% MeOH reflux (methanol partition)	microsomes	79	% inhib.	[104]
Cycas revoluta	sago palm	Cycadaceae	plant	75% MeOH reflux (ethyl acetate partition)	microsomes	86	% inhib.	[104]
Cycas rumphii	none	Cycadaceae	plant	75% MeOH reflux (methanol partition)	microsomes	90	% inhib.	[104]
Cycas rumphii	none	Cycadaceae	plant	75% MeOH reflux (ethyl acetate partition)	microsomes	15	% inhib.	[104]
Daucus carota [a]	carrot	Apiaceae	plant	water reflux	microsomes	~74	PCA at 100 μL	[115]

Species Name	Common Name	Family	Type	Extraction Solvent	Assay Type	Activity		Ref.(s)
Daucus carota [a]	carrot	Apiaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Dioon spinulosum	none	Zamiaceae	plant	75% MeOH reflux (methanol partition)	microsomes	40	% inhib.	[104]
Dioon spinulosum	none	Zamiaceae	plant	75% MeOH reflux (ethyl acetate partition)	microsomes	97	% inhib.	[104]
Encephalartos ferox	bread palm	Zamiaceae	plant	75% MeOH reflux (methanol partition)	microsomes	45	% inhib.	[104]
Encephalartos ferox	bread palm	Zamiaceae	plant	75% MeOH reflux (ethyl acetate partition)	microsomes	97	% inhib.	[104]
Epilobium capense	willowherb	Onagraceae	plant	aqueous methanol	microsomes	60	% inhib. at 200 μg	[130]
Epilobium capense	willowherb	Onagraceae	plant	Methanol	microsomes	54	% inhib. at 200 μg	[130]
Euonymus alatus	“gui-jun woo”	Celastraceae	plant	water reflux	microsomes	11	μg/mL IC_50	[111]
Euonymus alatus	“gui-jun woo”	Celastraceae	plant	water reflux	myometrial cells	0.80	μg/mL IC_50	[111]
Euonymus alatus	“gui-jun woo”	Celastraceae	plant	water reflux	leiomyonal cells	0.07	μg/mL IC_{50}	[111]
Flammulina velutipes	enoki mushroom		fungus	water reflux	microsomes	~78	PCA at 100 μL	[115]
Fragaria sp.[a]	strawberry (juice)	Rosaceae	plant	Nd	microsomes	~52	PCA at 25 μL	[183]
Fragaria sp.	strawberry	Rosaceae	plant	Methanol	microsomes	84.8	PCA at 20 μg/mL	[143]
Fragaria sp.	strawberry	Rosaceae	plant	Acetone	microsomes	65.8	PCA at 20 μg/mL	[143]
Fragaria sp.	strawberry	Rosaceae	plant	methanol/acetone	microsomes	84.3	PCA at 20 μg/mL	[143]
Garcinia mangostana	mangosteen	Clusiaceae	plant	Methanol	microsomes	18.9	PCA at 20 μg/mL	[109]
Garcinia mangostana	mangosteen	Clusiaceae	plant	methanol ($CHCl_3$ partition)	microsomes	29.8	PCA at 20 μg/mL	[109]
Garcinia mangostana	mangosteen	Clusiaceae	plant	Methanol	SK-BR-3 cells	24.1	PCA at 20 μg/mL	[109]
Garcinia mangostana	mangosteen	Clusiaceae	plant	methanol ($CHCl_3$ partition)	SK-BR-3 cells	16.5	PCA at 20 μg/mL	[109]
Glycyrrhiza glabra [a]	licorice	Fabaceae	plant	Nd	nd	>50	% inhib.	[182]

Species Name	Common Name	Family	Type	Extraction Solvent	Assay Type	Activity		Ref.(s)
Glyxine max [a]	soy (infant formulas)	Fabaceae	plant	Nd	*in vivo* brain aromatase	none		[185]
Hericium erinaceus	lion's mane mushroom	Hericiaceae	fungus	Dichloromethane	microsomes	57.9	PCA at 20 μg/mL	[143]
Hordeum vulgare *Humulus lupulus*	alcohol free beer	Poaceae Cannabaceae	plant	Nd	choriocarcinoma-derived JAR cells	65.27	PCA	[114]
Hordeum vulgare [a] *Humulus lupulus* [a]	lager beer	Poaceae Cannabaceae	plant	Nd	choriocarcinoma-derived JAR cells	75.8	PCA	[114]
Hordeum vulgare [a] *Humulus lupulus* [a]	stout	Poaceae Cannabaceae	none	Nd	choriocarcinoma-derived JAR cells	33.9	PCA	[114]
Hordeum vulgare [a] *Humulus lupulus* [a]	xanthohumol-rich stout	Poaceae Cannabaceae	nd	Nd	choriocarcinoma-derived JAR cells	26.4	PCA	[114]
Isodon excisus var. *coreanus*	none	Lamiaceae	plant	methanol (diethyl ether partition)	microsomes	13.7	μg/mL IC_{50}	[110]
Lactuca sp.[a]	iceberg lettuce	Asteraceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Lactuca sp.[a]	romaine lettuce	Asteraceae	plant	70% ethanol	microsomes	560	units/100 g	[113]
Larrea tridentata [a]	chaparral	Zygophyllaceae	plant	Nd	nd	>50	% inhib.	[182]
Lentinula edodes	shiitake mushroom	Marasmiaceae	fungus	water reflux	microsomes	~62	PCA at 100 μL	[115]
Lentinus edodes	shiitake mushroom	Marasmiaceae	fungus	Dichloromethane	microsomes	76.5	PCA at 20 μg/mL	[143]
Lycopersicon esculentum [a]	tomato	Solanaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Lycopersicon esculentum [a]	tomato (leaves)	Solanaceae	plant	70% ethanol	microsomes	6000	units/100 g	[113]
Morinda citrifolia	noni	Rubiaceae	plant	Nd	nd	inhibits		[131]
Murraya paniculata	mock orange	Rutaceae	plant	75% MeOH reflux	microsomes	~68	% inhib.	[105]
Musa sp.[a]	banana	Musaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Nicotiana tabacum [a]	cigarette smoke	Solanaceae	plant	aqueous trap	microsomes	0.25	cigarette equivalents	[113]
Nicotiana tabacum [a]	cigarette smokea	Solanaceae	plant	methylene chloride trap	microsomes	0.07	cigarette equivalents	[113]
Nicotiana tabacum [a]	tobacco (leaves)	Solanaceae	plant	70% ethanol	microsomes	0.025	cigarette equivalents	[113]
Nicotiana tabacum [a]	tobacco (leaves)	Solanaceae	plant	70% ethanol	microsomes	590	units/100 g	[113]

Species Name	Common Name	Family	Type	Extraction Solvent	Assay Type	Activity		Ref.(s)
Opuntia sp.[a]	cactus flower	Cactaceae	plant	water (autoclaved) (dichloromethane-methanol partition)	microsomes	~20	PCA at 100 μL	[186]
Opuntia sp.[a]	cactus flower	Cactaceae	plant	water (autoclaved) (diethyl ether subfraction)	microsomes	~17	PCA at 100 μL	[186]
Opuntia sp.[a]	cactus flower	Cactaceae	plant	water (autoclaved) (petroleum ether-diethyl ether subfraction)	microsomes	~10	PCA at 100 μL	[186]
Persea americana [a]	avocado (meat)	Lauraceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Persea americana [a]	beet (greens)	Amaranthaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Petroselinum crispum [a]	parsley	Apiaceae	plant	70% ethanol	microsomes	1200	units/100 g	[113]
Piper cubeba	none	Piperaceae	plant	96% ethanol	enzyme	<10	μg/mL IC_{50}	[187]
Pleurotus ostreatus	oyster mushroom	Tricholomataceae	fungus	water reflux	microsomes	~94	PCA at 100 μL	[115]
Pleurotus sp.	Italian brown mushroom	Tricholomataceae	fungus	water reflux	microsomes	~36	PCA at 100 μL	[115]
Plumbago capensis	leadwort	Plumbaginaceae	plant	75% MeOH reflux	microsomes	~8	% inhib.	[105]
Prunus persica [a]	peach (juice)	Rosaceae	plant	Nd	microsomes	~89	PCA at 25 μL	[183]
Prunus persica [a]	peach (juice)	Rosaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Prunus sp.[a]	plum (juice)	Rosaceae	plant	Nd	microsomes	~70	PCA at 25 μL	[183]
Prunus sp.[a]	plum	Rosaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Pternandra azurea	none	Melastomataceae	plant	methanol ($CHCl_3$ partition)	microsomes	70.1	PCA at 20 μg/mL	[143]
Punica granatum	pomegranate	Punicaceae	plant	fermented juice	microsomes	51	% inhib.	[188]
Punica granatum	pomegranate	Punicaceae	plant	pericarp polyphenols	microsomes	24	% inhib.	[188]
Pyrus malus [a]	apple (juice)	Rosaceae	plant	Nd	microsomes	~79	PCA at 25 μL	[183]
Pyrus malus [a]	apple	Rosaceae	plant	70% ethanol	microsomes	<80	units/100 g	[113]
Renealmia sp.	none	Bromeliaceae	plant	75% MeOH reflux	microsomes	~18	% inhib.	[105]
Riedelia sp.	none	Ericaceae	plant	75% MeOH reflux	microsomes	~97	% inhib.	[105]
Rubus occidentalis	black raspberry	Rosaceae	plant	none (dried fruit)	microsomes	80.8	PCA at 20 μg/mL	[143]

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Species Name	Common Name	Family	Type	Extraction Solvent	Assay Type	Activity		Ref.(s)
Salix sp.[a]	willow bark	Salicaceae	plant	nd	nd	>50	% inhib.	[182]
Scutellaria barbata	skullcap	Lamiaceae	plant	water reflux	microsomes	23	μg/mL IC_{50}	[111]
Scutellaria barbata	skullcap	Lamiaceae	plant	water reflux	myometrial cells	15.00	μg/mL IC_{50}	[111]
Scutellaria barbata	skullcap	Lamiaceae	plant	water reflux	leiomyonal cells	1.01	μg/mL IC_{50}	[111]
Solanum melongena [a]	eggplant	Solanaceae	plant	70% ethanol	microsomes	190	units/100 g	[113]
Solanum melongena [a]	eggplant (leaves)	Solanaceae	plant	70% ethanol	microsomes	800	units/100 g	[113]
Solanum tuberosum [a]	potato	Solanaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Solanum tuberosum [a]	potato (leaves)	Solanaceae	plant	70% ethanol	microsomes	4500	units/100 g	[113]
Spinacia oleracea [a]	spinach	Amaranthaceae	plant	water reflux	microsomes	~83	PCA at 100 μL	[115]
Spinacia oleracea [a]	spinach	Amaranthaceae	plant	70% ethanol	microsomes	2400	units/100 g	[113]
Taraxacum officinale [a]	dandelion (greens)	Asteraceae	plant	70% ethanol	microsomes	2900	units/100 g	[113]
Theobroma cacao [a]	chocolate	Sterculiaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Theobroma cacao [a]	cocoa	Sterculiaceae	plant	70% ethanol	microsomes	9000	units/100 g	[113]
Trifolium pratense	red clover (flowers)	Fabaceae	plant	Nd	MCF-7 dual assay for AI and estrogenicity	inhibits	aromatase	[116]
Uncaria tomentosa [a]	cat's claw	Rubiaceae	plant	Nd	nd	>50	% inhib.	[182]
Vallaris sp.	none	Apocynaceae	plant	75% MeOH reflux	microsomes	~20	% inhib.	[105]
Viscum album	mistletoe	Viscaceae	plant	75% MeOH reflux	microsomes	~94	% inhib.	[105]
Vitis sp.[a]	black grape (juice)	Vitaceae	plant	Nd	microsomes	~23	PCA at 25 μL	[189]
Vitis sp.[a]	Cabernet Sauvignon, Glen Ellen Proprietor's Reserve (Sonoma, CA)	Vitaceae	plant	Nd	microsomes	7.7	PCA at 50 μL	[86, 106, 107]
Vitis sp.[a]	Cabernet Sauvignon, San Andrés (Lontué Valley, Chile)	Vitaceae	plant	Nd	microsomes	0.36	PCA at 50 μL	[86, 106, 107]
Vitis sp.[a]	Cabernet Sauvignon, Tanglewood (France)	Vitaceae	plant	Nd	microsomes	0.29	PCA at 50 μL	[86, 106, 107]
Vitis sp.[a]	Champagne grape (juice)	Vitaceae	plant	Nd	microsomes	~90	PCA at 25 μL	[189]

Species Name	Common Name	Family	Type	Extraction Solvent	Assay Type	Activity		Ref.(s)
Vitis sp.[a]	Chardonnay, Santa Rita Reserve (Casablanca Valley, Chile)	Vitaceae	plant	Nd	microsomes	80	PCA at 50 μL	[86, 106, 107]
Vitis sp.[a]	Chardonnay, Woodbridge (Woodbridge, CA)	Vitaceae	plant	Nd	microsomes	99.1	PCA at 50 μL	[86, 106, 107]
Vitis sp.[a]	Christmas rose grape (juice)	Vitaceae	plant	Nd	microsomes	~40	PCA at 25 μL	[189]
Vitis sp.[a]	Christmas rose grape (seed)	Vitaceae	plant	Nd	microsomes	~10	PCA at 25 μL	[189]
Vitis sp.[a]	Fumé Blanc, Domaine Napa (Napa Valley, CA)	Vitaceae	plant	Nd	microsomes	112.5	PCA at 50 μL	[86, 106, 107]
Vitis sp.[a]	grape (seed)	Vitaceae	plant	Water	MCF-7aro cells	70.4	% inhib. at 40 μg/mL	[85]
Vitis sp.[a]	grape (seed)	Vitaceae	plant	Water	*in vivo* MCF-7aro xenograft	reduced	tumor weight	[85]
Vitis sp.[a]	grape (seed)	Vitaceae	plant	Water	MCF-7aro cells	80.5	% inhib. at 60 μg/mL	[85]
Vitis sp.[a]	grape (seed)	Vitaceae	plant	Water	*in vivo* MCF-7aro xenograft	reduced	tumor weight	[85]
Vitis sp.[a]	green seedless grape (juice)	Vitaceae	plant	Nd	microsomes	~38	PCA at 25 μL	[189]
Vitis sp.[a]	Merlot, Forest Ville (Sonoma, CA)	Vitaceae	plant	Nd	microsomes	0.46	PCA at 50 μL	[86, 106, 107]
Vitis sp.[a]	Merlot, Hacienda, 1997 (Sonoma, CA)	Vitaceae	plant	Nd	microsomes	3.29	PCA at 50 μL	[86, 106, 107]
Vitis sp.[a]	Merlot, Hacienda, 1998 (Sonoma, CA)	Vitaceae	plant	Nd	microsomes	0.9	PCA at 50 μL	[86, 106, 107]
Vitis sp.[a]	Merlot, JW Morris Winery (Sonoma, CA)	Vitaceae	plant	Nd	microsomes	0.42	PCA at 50 μL	[86, 106, 107]
Vitis sp.[a]	Pinot Noir, Cambiaso (Healdburg, CA)	Vitaceae	plant	Nd	microsomes	0.34	PCA at 50 μL	[86, 106, 107]
Vitis sp.[a]	Pinot Noir, Hacienda (Sonoma, CA)	Vitaceae	plant	Nd	microsomes	2.16	PCA at 50 μL	[86, 106, 107]

Species Name	Common Name	Family	Type	Extraction Solvent	Assay Type	Activity		Ref.(s)
Vitis sp.[a]	Pinot Noir, Hacienda (Sonoma, CA)	Vitaceae	plant	Nd	microsomes	~8	PCA at 25 μL	[86, 106, 107]
Vitis sp.[a]	Pinot Noir, Hacienda (Sonoma, CA)	Vitaceae	plant	Nd	*in vivo* mouse	inhibits		[86, 106, 107]
Vitis sp.[a]	red globe grape (juice)	Vitaceae	plant	Nd	microsomes	~78	PCA at 25 μL	[189]
Vitis sp.[a]	red seedless grape (juice)	Vitaceae	plant	Nd	microsomes	~29	PCA at 25 μL	[183]
Vitis sp.[a]	red seedless grape (juice)	Vitaceae	plant	Nd	MCF-7aro cells	inhibits	aromatase	[183]
Vitis sp.[a]	red seedless grape (juice)	Vitaceae	plant	Nd	*in vivo* MCF-7aro xenograft	70	% reduced tumor size	[183]
Vitis sp.[a]	red seedless grape (juice)	Vitaceae	plant	Nd	microsomes	~30	PCA at 25 μL	[189]
Vitis sp.[a]	Sauvignon Blanc, Turning Leaf (Modesto, CA)	Vitaceae	plant	Nd	microsomes	106.5	PCA at 50 μL	[86, 106, 107]
Vitis sp.[a]	seedless grape	Vitaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
Vitis sp.[a]	Zinfandel, Black Mountain (San Diego, CA)	Vitaceae	plant	Nd	microsomes	0.39	PCA at 50 μL	[86, 106, 107]
Vitis sp.[a]	Zinfandel, Sequoia Ridge (Graton, CA)	Vitaceae	plant	Nd	microsomes	0.39	PCA at 50 μL	[86, 106, 107]
Vitis sp.	grape	Vitaceae	plant	none (dried fruit)	microsomes	75.7	PCA at 20 μg/mL	[143]
Zingiber officinale [a]	ginger (root)	Zingerberaceae	plant	70% ethanol	microsomes	0	units/100 g	[113]
none	propolis	none	misc.	Nd	nd	>50	%inhib.	[182]

nd = no data

[a]Genus and species not provided by author.

Table 2

Previous literature reports of natural product flavones tested for aromatase inhibition

Compound Name	Assay Type	Activity		Ref.(s)
apigenin (**8**)	microsomes	1.2	μM IC_{50}	[122]
apigenin (**8**)	microsomes	2.9	μM IC_{50}	[123]
apigenin (**8**)	microsomes	4.2	μM IC_{50}	[190]
apigenin (**8**)	microsomes	10	μM IC_{50}	[177]
apigenin (**8**)	microsomes	15	μM IC_{50}	[136]
apigenin (**8**)	microsomes	0.9	μg/mL IC_{50}	[121]
apigenin (**8**)	microsomes (modified)	2.9	μM IC_{50}	[124]
apigenin (**8**)	spectrophotometric w/microsomes	0.9	K_s	[120]
apigenin (**8**)	trout ovarian aromatase	84.0	μM IC_{50}	[128]
apigenin (**8**)	JEG-3 cells	0.18	μM IC_{50}	[125]
apigenin (**8**)	Arom+HEK 293 cells	1.4	μM IC_{50}	[125]
apigenin (**8**)	H295R adrenocortical carcinoma cells	20	μM IC_{50}	[127]
apigenin (**8**)	granulose-luteal cells	inhibited	at 10 μmol/L for 24 h	[129]
ayanin (**9**)	microsomes	69.6	PCA at 20 μg/mL	[143]
broussoflavonol F (**10**)	microsomes	7.3	PCA at 20 μg/mL	[143]
broussoflavonol F (**10**)	microsomes	9.7	μM IC_{50}	[135]
broussoflavonol F (**10**)	SK-BR-3 cells	28.4	PCA at 50 μM	[143]
chrysin (**11**)	microsomes	0.5	μM IC_{50}	[122]
chrysin (**11**)	microsomes	0.7	μM IC_{50}	[123]
chrysin (**11**)	microsomes	1.1	μM IC_{50}	[191]
chrysin (**11**)	microsomes	8.9	μM IC_{50}	[136]
chrysin (**11**)	microsomes	1.1	μg/mL IC_{50}	[121]
chrysin (**11**)	microsomes	1	K_i	[118]
chrysin (**11**)	microsomes	2.6	K_i	[119]
chrysin (**11**)	microsomes (modified)	0.7	μM IC_{50}	[124]
chrysin (**11**)	spectrophotometric w/microsomes	0.5	K_s	[120]
chrysin (**11**)	trout ovarian aromatase	>1004	μM IC_{50}	[128]
chrysin (**11**)	JEG-3 cells	0.5	μM IC_{50}	[125]
chrysin (**11**)	Arom+HEK 293 cells	0.6	μM IC_{50}	[125]
chrysin (**11**)	human preadipocyte cells	4.6	μM IC_{50}	[126]
chrysin (**11**)	H295R adrenocortical carcinoma cells	7	μM IC_{50}	[127]
chrysin (**11**)	MCF-7 dual assay for AI and estrogenicity	inhibits		[116]
chrysin (**11**)	endometrial stromal cells	none		[118]
chrysin (**11**)	nd	11	μM IC_{50}	[192]
3',4'-dihydroxyflavone (**12**)	microsomes	90	μM IC_{50}	[132]

Compound Name	Assay Type	Activity		Ref.(s)
3',4'-dihydroxyflavone (**12**)	microsomes	100	μM IC_{50}	[136]
3',4'-dihydroxyflavone (**12**)	microsomes	>200	μM IC_{50}	[132]
5,4'-dihydroxyflavone (**13**)	microsomes	120	μM IC_{50}	[132]
6,4'-dihydroxyflavone (**14**)	microsomes	90	μM IC_{50}	[132]
7,4'-dihydroxyflavone (**15**)	microsomes	2	μM IC_{50}	[132]
7,4'-dihydroxyflavone (**15**)	trout ovarian aromatase	200.0	μM IC_{50}	[128]
7,8-dihydroxyflavone (**16**)	microsomes	8	μM IC_{50}	[123]
7,8-dihydroxyflavone (**16**)	microsomes	2.2	μg/mL IC_{50}	[121]
7,8-dihydroxyflavone (**16**)	microsomes	10	K_i	[119]
7,8-dihydroxyflavone (**16**)	nd	55	μM IC_{50}	[192]
3',4'-dimethoxyflavone (**17**)	microsomes	42	μM IC_{50}	[136]
fisetin (**18**)	microsomes	8.5	μg/mL IC_{50}	[121]
fisetin (**18**)	JEG-3 cells	55	μM IC_{50}	[125]
flavone (**19**)	microsomes	8	μM IC_{50}	[122]
flavone (**19**)	microsomes	10	μM IC_{50}	[132]
flavone (**19**)	microsomes	48	μM IC_{50}	[123]
flavone (**19**)	microsomes	67	μM IC_{50}	[136]
flavone (**19**)	microsomes	375.0	μM IC_{50}	[128]
flavone (**19**)	microsomes (modified)	48.0	μM IC_{50}	[124]
flavone (**19**)	trout ovarian aromatase	731.0	μM IC_{50}	[128]
flavone (**19**)	human preadipocyte cells	68	μM IC_{50}	[126]
flavone (**19**)	JEG-3 cells	>100	μM IC_{50}	[125]
flavone (**19**)	H295R adrenocortical carcinoma cells	none		[127]
galangin (**20**)	microsomes	95	K_i	[119]
galangin (**20**)	JEG-3 cells	12	μM IC_{50}	[125]
3-hydroxyflavone (**21**)	microsomes	140	μM IC_{50}	[132]
3'-hydroxyflavone (**22**)	microsomes	73	μM IC_{50}	[136]
4'-hydroxyflavone (**23**)	microsomes	180	μM IC_{50}	[132]
5-hydroxyflavone (**24**)	microsomes	100	μM IC_{50}	[132]
6-hydroxyflavone (**25**)	microsomes	80	μM IC_{50}	[132]
6-hydroxyflavone (**25**)	JEG-3 cells	5.5	μM IC_{50}	[125]
7-hydroxyflavone (**26**)	microsomes	0.2	μM IC_{50}	[123]
7-hydroxyflavone (**26**)	microsomes	0.5	μM IC_{50}	[132]
7-hydroxyflavone (**26**)	microsomes	8.2	μM IC_{50}	[136]
7-hydroxyflavone (**26**)	microsomes	30.5	μg/mL IC_{50}	[121]
7-hydroxyflavone (**26**)	microsomes (modified)	0.21	μM IC_{50}	[124]
7-hydroxyflavone (**26**)	trout ovarian aromatase	>1001	μM IC_{50}	[128]

Compound Name	Assay Type	Activity		Ref.(s)
7-hydroxyflavone (**26**)	JEG-3 cells	0.35	μM IC_{50}	[125]
7-hydroxyflavone (**26**)	H295R adrenocortical carcinoma cells	4	μM IC_{50}	[127]
isolicoflavonol (**27**)	microsomes	0.1	μM IC_{50}	[135]
kaempferide (**28**)	JEG-3 cells	80	μM IC_{50}	[125]
kaempferol (**29**)	microsomes	32	% inhib. at 50 μM	[130]
kaempferol (**29**)	JEG-3 cells	11	μM IC_{50}	[125]
kaempferol (**29**)	preadipose cells	61	μM IC_{50}	[134]
kaempferol 7,4'-dimethyl ether (**30**)	microsomes	45.6	PCA at 20 μg/mL	[143]
kaempferol 7,4'-dimethyl ether (**30**)	SK-BR-3 cells	99.2	PCA at 50 μM	[143]
luteolin (**31**)	microsomes	8.6	μM IC_{50}	[136]
luteolin (**31**)	microsomes	3.3	μg/mL IC_{50}	[121]
luteolin (**31**)	microsomes (modified)	1.2	μM IC_{50}	[133]
luteolin (**31**)	spectrophotometric w/microsomes	1.0	K_s	[120]
luteolin (**31**)	JEG-3 cells	2	μM IC_{50}	[125]
luteolin (**31**)	preadipose cells	25	μM IC_{50}	[134]
7-methoxyflavone (**32**)	microsomes	3.2	μM IC_{50}	[123]
7-methoxyflavone (**32**)	microsomes (modified)	3.2	μM IC_{50}	[124]
7-methoxyflavone (**32**)	H295R adrenocortical carcinoma cells	none		[127]
morin (**33**)	spectrophotometric w/microsomes	5.0	K_s	[120]
myricetin (**34**)	microsomes	5.6	μg/mL IC_{50}	[121]
myricetin (**34**)	microsomes	41	% inhib. at 50 μM	[130]
myricetin (**34**)	spectrophotometric w/microsomes	5.6	K_s	[120]
oxyayanin B (**35**)	microsomes	83.0	PCA at 20 μg/mL	[143]
prunetin (**36**)	microsomes	none	μM IC_{50}	[123]
prunetin (**36**)	microsomes	7.8	μg/mL IC_{50}	[121]
quercetin (**37**)	microsomes	12	μM IC_{50}	[122]
quercetin (**37**)	microsomes	35	% inhib. at 50 μM	[130]
quercetin (**37**)	spectrophotometric w/microsomes	4.7	K_s	[120]
quercetin (**37**)	trout ovarian aromatase	139.0	μM IC_{50}	[128]
quercetin (**37**)	JEG-3 cells	>100	μM IC_{50}	[125]
quercetin (**37**)	H295R adrenocortical carcinoma cells	none		[127]
quercetin (**37**)	human preadipocyte cells	none		[126]
quercetin (**37**)	granulose-luteal cells	none	at 10 μmol/L for 24h	[129]
quercetin (**37**)	nd	~85	% inhib. at 100 μM	[107]
quercetin (**37**)	nd	nd		[131]
robinetin (**38**)	microsomes	45.7	μg/mL IC_{50}	[121]
rutin (**39**)	human preadipocyte cells	none		[126]
rutin (**39**)	nd	~120	% inhib. at 100 μM	[107]

Compound Name	Assay Type	Activity		Ref.(s)
7,3',4',5'-tetrahydroxyflavone (**40**)	microsomes	45	μM IC_{50}	[136]
5,7,2',4'-tetrahydroxy-3-geranylflavone (**41**)	microsomes	24.0	μM IC_{50}	[135]
7,3',4'-trihydroxyflavone (**42**)	microsomes	38	μM IC_{50}	[136]
5,7,3'-trihydroxy-4'-methoxyflavone (**43**)	microsomes	27	μM IC_{50}	[136]
5,7,4'-trihydroxy-3'-methoxyflavone (**44**)	microsomes	7.2	μM IC_{50}	[136]

nd = no data

Table 3

Previous literature reports of natural product flavanones tested for aromatase inhibition

Compound Name	Assay Type	Activity		Ref.(s)
(2*S*)-abyssinone II (**45**)	microsomes	0.4	μM IC_{50}	[135]
3',4'-dihydroxyflavanone[a] (**46**)	microsomes	160	μM IC_{50}	[132]
5,7-dihydroxyflavanone[a] (**47**)	microsomes	10	μM IC_{50}	[136]
7,8-dihydroxyflavanone[a] (**48**)	microsomes (modified)	8.0	μM IC_{50}	[124]
(2*S*)-2',4'-dihydroxy-2”-(1-hydroxy-1-methylethyl)dihydrofuro[2,3-*h*]flavanone (**49**)	microsomes	0.1	μM IC_{50}	[135]
eriodictyol[a] (**50**)	microsomes	5.3	μM IC_{50}	[136]
eriodictyol[a] (**50**)	microsomes (modified)	0.6	μM IC_{50}	[133]
(2*S*)-euchrenone a7 (**51**)	microsomes	3.4	μM IC_{50}	[135]
flavanone[a] (**52**)	microsomes	8	μM IC_{50}	[122]
flavanone[a] (**52**)	microsomes	8	μM IC_{50}	[132]
flavanone[a] (**52**)	microsomes	28.5	μM IC_{50}	[137]
flavanone[a] (**52**)	microsomes	32	μM IC_{50}	[136]
flavanone[a] (**52**)	microsomes	250.0	μM IC_{50}	[128]
flavanone[a] (**52**)	microsomes	8.7	μg/mL IC_{50}	[121]
flavanone[a] (**52**)	microsomes (modified)	13.8	μM IC_{50}	[133]
flavanone[a] (**52**)	trout ovarian aromatase	>1000	μM IC_{50}	[128]
hesperetin[a] (**53**)	microsomes	1.0	μg/mL IC_{50}	[121]
hesperetin[a] (**53**)	microsomes (modified)	3.3	μM IC_{50}	[133]
hesperidin[a] (**54**)	microsomes	40.9	μg/mL IC_{50}	[121]
4'-hydroxyflavanone[a] (**55**)	microsomes	10	μM IC_{50}	[132]
7-hydroxyflavanone[a] (**56**)	microsomes	3.8	μM IC_{50}	[138]
7-hydroxyflavanone[a] (**56**)	microsomes	10	μM IC_{50}	[136]
7-hydroxyflavanone[a] (**56**)	microsomes (modified)	2.4	μM IC_{50}	[133]
7-hydroxyflavanone[a] (**56**)	H295R adrenocortical carcinoma cells	65	μM IC_{50}	[127]
isoxanthohumol[a] (**57**)	choriocarcinoma-derived JAR cells	139.7	μM IC_{50}	[114]
isoxanthohumol[a] (**57**)	SK-BR-3 cells	25.4	μM IC_{50}	[139]
7-methoxyflavanone[a] (**58**)	microsomes	8.0	μM IC_{50}	[137]
7-methoxyflavanone[a] (**58**)	microsomes (modified)	2.6	μM IC_{50}	[124]
7-methoxyflavanone[a] (**58**)	H295R adrenocortical carcinoma cells	none		[127]
naringenin (**59**[a])	microsomes	2.9	μM IC_{50}	[191]
naringenin (**59**[a])	microsomes	9.2	μM IC_{50}	[123]

Compound Name	Assay Type	Activity		Ref.(s)
(2*S*)-naringenin (**59**)	microsomes	17.0	μM IC_{50}	[135]
naringenin (**59**[a])	microsomes	0.3	K_i	[118]
naringenin (**59**[a])	microsomes	5.1	K_i	[119]
naringenin (**59**[a])	microsomes (modified)	9.2	μM IC_{50}	[124]
naringenin (**59**[a])	JEG-3 cells	1.4	μM IC_{50}	[125]
naringenin (**59**[a])	Arom+HEK 293 cells	3.2	μM IC_{50}	[125]
naringenin (**59**[a])	H295R adrenocortical carcinoma cells	85	μM IC_{50}	[127]
naringenin (**59**[a])	MCF-7 dual assay for AI and estrogenicity	inhibits		[116]
naringenin (**59**[a])	rat granulose cells	inhibits		[184]
naringenin (**59**[a])	endometrial stromal cells	none		[118]
naringin (**60**)	microsomes	1.8	μg/mL IC_{50}	[121]
pinostrobin[a] (**61**)	JEG-3 cells	4	μM IC_{50}	[125]
8-prenylnaringenin[a] (**62**)	microsomes	0.2	μM IC_{50}	[191]
8-prenylnaringenin[a] (**62**)	choriocarcinoma-derived JAR cells	0.065	μM IC_{50}	[114]
8-prenylnaringenin[a] (**62**)	SK-BR-3 cells	0.08	μM IC_{50}	[139]
8-prenylnaringenin[a] (**62**)	breast adipose fibroblast cells	0.3	μM IC_{50}	[191]
(2*S*)-5,7,2',4'-tetrahydroxyflavanone (**63**)	microsomes	2.2	μM IC_{50}	[135]
5,7,4'-trihydroxy-3'-methoxyflavanone (**64**)	microsomes	25	μM IC_{50}	[136]

[a]Optical sign not provided by authors.

Table 4

Previous literature reports of natural product chalcones tested for aromatase inhibition

Compound Name	Assay Type	Activity		Ref.(s)
butein (**65**)	MCF-7aro cells	3.70	μM IC_{50}	[140]
4,2'-dihydroxychalcone (**66**)	microsomes (modified)	>50	μM IC_{50}	[133]
2',4'-dihydroxychalcone (**67**)	microsomes (modified)	>50	μM IC_{50}	[133]
eriodictyol chalcone (**68**)	microsomes (modified)	2.8	μM IC_{50}	[133]
hesperetin chalcone (**69**)	microsomes (modified)	24.2	μM IC_{50}	[133]
2-hydroxychalcone (**70**)	MCF-7aro cells	~45	PCA at 20 μM	[140]
2'-hydroxychalcone (**71**)	microsomes (modified)	>50	μM IC_{50}	[133]
2'-hydroxychalcone (**71**)	MCF-7aro cells	~30	PCA at 20 μM	[140]
4-hydroxychalcone (**72**)	microsomes (modified)	>50	μM IC_{50}	[133]
4-hydroxychalcone (**72**)	MCF-7aro cells	~60	PCA at 20 μM	[140]
4'-hydroxychalcone (**73**)	microsomes (modified)	30.6	μM IC_{50}	[133]
2-hydroxy-4-methoxychalcone (**74**)	microsomes (modified)	>50	μM IC_{50}	[133]
3'-[γ-hydroxymethyl-(*E*)-γ-methylallyl]-2,4,2',4'-tetrahydroxychalcone 11'-*O*-coumarate (**75**)	microsomes	0.5	μM IC_{50}	[135]
isogemichalcone C (**76**)	microsomes	7.1	μM IC_{50}	[135]
isoliquiritigenin (**77**)	microsomes	30.6	PCA at 20 μg/mL	[143]
isoliquiritigenin (**77**)	microsomes (modified)	34.6	μM IC_{50}	[133]
isoliquiritigenin (**77**)	SK-BR-3 cells	9.3	PCA at 50 μM	[143]
isoliquiritigenin (**77**)	MCF-7aro cells	~60	PCA at 20 μM	[140]
naringenin chalcone (**78**)	microsomes (modified)	2.6	μM IC_{50}	[133]
paratocarpin B (**79**)	microsomes	58.1	PCA at 20 μg/mL	[143]
phloretin (**80**)	microsomes (modified)	>50	μM IC_{50}	[133]
pinostrobin chalcone (**81**)	microsomes (modified)	14.3	μM IC_{50}	[133]
2,4,2',4'-tetrahydroxy-3'-prenylchalcone (**82**)	microsomes	3.3	PCA at 20 μg/mL	[143]
2,4,2',4'-tetrahydroxy-3'-prenylchalcone (**82**)	microsomes	4.6	μM IC_{50}	[135]
2,4,2',4'-tetrahydroxy-3'-prenylchalcone (**82**)	SK-BR-3 cells	10.6	PCA at 50 μM	[143]
xanthohumol (**83**)	SK-BR-3 cells	3.2	μM IC_{50}	[139]
xanthohumol (**83**)	choriocarcinoma-derived JAR cells	20.3	μM IC_{50}	[114]

Table 5

Previous literature reports of natural product isoflavans tested for aromatase inhibition

Compound Name	Assay Type	Activity		Ref.(s)
equol (**84**)	microsomes	150	μM IC_{50}	[145]
equol (**84**)	microsomes	850.0	μM IC_{50}	[128]
equol (**84**)	trout ovarian aromatase	793.0	μM IC_{50}	[128]
equol (**84**)	human preadipocyte cells	none		[126]
heminitidulan (**85**)	microsomes	45.1	PCA at 20 μg/mL	[143]
3'-hydroxy-4'-*O*-methylglabridin (**86**)	microsomes	70.0	PCA at 20 μg/mL	[143]
leiocin (**87**)	microsomes	28.6	PCA at 20 μg/mL	[143]
leiocin (**87**)	SK-BR-3 cells	85.5	PCA at 50 μM	[143]
leiocinol (**88**)	microsomes	36.9	PCA at 20 μg/mL	[143]
leiocinol (**88**)	SK-BR-3 cells	101.8	PCA at 50 μM	[143]
methylequol (**89**)	microsomes	20	μM IC_{50}	[145]
4'-*O*-methylglabridin (**90**)	microsomes	25.2	PCA at 20 μg/mL	[143]
4'-*O*-methylglabridin (**90**)	SK-BR-3 cells	71.2	PCA at 50 μM	[143]
nitidulan (**91**)	microsomes	47.1	PCA at 20 μg/mL	[143]
nitidulan (**91**)	SK-BR-3 cells	59.1	PCA at 50 μM	[143]
nitidulin (**92**)	microsomes	71.2	PCA at 20 μg/mL	[143]
sativan (**93**)	microsomes	>50	μM IC_{50}	[123]

Table 6

Previous literature reports of natural product catechins tested for aromatase inhibition

Compound Name	Assay Type	Activity		Ref.(s)
(+)-catechin (**94**)	microsomes	100.0	PCA at 20 μg/mL	[143]
(+)-catechin (**94**)	microsomes	none		[112]
(+)-catechin (**94**)	H295R adrenocortical carcinoma cells	none		[127]
catechin (**94**[a])	human preadipocyte cells	none		[126]
(−)-catechin gallate (**95**)	microsomes	55	μM IC_{50}	[112]
(−)-epicatechin (**96**)	microsomes	94.9	PCA at 20 μg/mL	[143]
(−)-epicatechin (**96**)	microsomes	none		[112]
(−)-epicatechin (**96**)	H295R adrenocortical carcinoma cells	none		[127]
(−)-epicatechin-3-*O*-gallate (**97**)	microsomes	67.1	PCA at 20 μg/mL	[143]
(−)-epicatechin gallate (**97**)	microsomes	20	% inhib. at 100 μM	[112]
epicatechin gallate (**97**[a])	*in vivo* Swiss-Webster mice ovarian aromatase activity	none		[148]
(−)-epigallocatechin (**98**)	microsomes	75.3	PCA at 20 μg/mL	[143]
(−)-epigallocatechin (**98**)	microsomes	100	μM IC_{50}	[112]
(−)-epigallocatechin-3-*O*-gallate (**99**)	microsomes	54.9	PCA at 20 μg/mL	[143]
epigallocatechin gallate (**99**[a])	microsomes	13.79	μM IC_{50}	[146]
(−)-epigallocatechin gallate (**99**)	microsomes	60	μM IC_{50}	[112]
epigallocatechin gallate (**99**[a])	*in vivo* Swiss-Webster mice ovarian aromatase activity	56	% inhib. at 25 μg/kg	[148]
epigallocatechin gallate (**99**[a])	epidemiological E_2 levels	lower	E_2 levels with higher EGCG intake	[147]
(−)-gallocatchin gallate (**100**)	microsomes	15	μM IC_{50}	[112]
theaflavin (**101**)	microsomes	4.17	μM IC_{50}	[146]
theaflavin-3,3'-digallate (**102**)	microsomes	3.45	μM IC_{50}	[146]

[a]Optical sign not provided by authors.

Table 7

Previous literature reports of natural product isoflavanones tested for aromatase inhibition

Compound Name	Assay Type	Activity		Ref.(s)
3',4'-dihydroxyisoflavanone (**103**)	microsomes	>200	μM IC_{50}	[132]
discoloranone A (**104**)	microsomes	85.8	PCA at 20 μg/mL	[143]
discoloranone B (**105**)	microsomes	53.5	PCA at 20 μg/mL	[143]
2-hydroxyisoflavanone (**106**)	microsomes	170	μM IC_{50}	[132]
4'-hydroxyisoflavanone (**107**)	microsomes	160	μM IC_{50}	[132]
isodiscoloranone A (**108**)	microsomes	91.5	PCA at 20 μg/mL	[143]
isodiscoloranone B (**109**)	microsomes	57.2	PCA at 20 μg/mL	[143]
isoflavanone (**110**)	microsomes	120	μM IC_{50}	[132]

Table 8

Previous literature reports of natural product isoflavones tested for aromatase inhibition

Compound Name	Assay Type	Activity		Ref.(s)
biochanin A (**111**)	microsomes	18.9	μg/mL IC_{50}	[121]
biochanin A (**111**)	microsomes	49	μM IC_{50}	[123]
biochanin A (**111**)	microsomes	94.50	μM IC_{50}	[149]
biochanin A (**111**)	microsomes	10.2	μg/mL IC_{50}	[121]
biochanin A (**111**)	microsomes	12	K_i	[119]
biochanin A (**111**)	trout ovarian aromatase	>1000	μM IC_{50}	[128]
biochanin A (**111**)	JEG-3 cells	4	μM IC_{50}	[125]
biochanin A (**111**)	human preadipocyte cells	113	μM IC_{50}	[126]
biochanin A (**111**)	granulosa-luteal cells	none	at 10 μmol/L for 24 h	[129]
biochanin A (**111**)	MCF-7 dual assay for AI and estrogenicity	inhibits		[116]
daidzein (**112**)	microsomes	none	μM IC_{50}	[123]
daidzein (**112**)	microsomes	>50	K_i	[118]
daidzein (**112**)	microsomes	none		[145]
daidzein (**112**)	trout ovarian aromatase	>1002	μM IC_{50}	[128]
daidzein (**112**)	endometrial stromal cells	none		[118]
daidzein (**112**)	human preadipocyte cells	none		[126]
formononetin (**113**)	microsomes	75.7	PCA at 20 μg/mL	[143]
formononetin (**113**)	microsomes	none	μM IC_{50}	[123]
formononetin (**113**)	MCF-7 dual assay for AI and estrogenicity	inhibits		[116]
genistein (**114**)	microsomes	none	μM IC_{50}	[123]
genistein (**114**)	microsomes	>50	K_i	[118]
genistein (**114**)	microsomes	123	K_i	[119]
genistein (**114**)	microsomes	none		[149]
genistein (**114**)	microsomes (modified)	none	μM IC_{50}	[124]
genistein (**114**)	trout ovarian aromatase	>1003	μM IC_{50}	[128]
genistein (**114**)	endometrial stromal cells	none		[118]
genistein (**114**)	MCF-7 dual assay for AI and estrogenicity	none		[116]
genistein (**114**)	H295R adrenocortical carcinoma cells	none		[127]
genistein (**114**)	human preadipocyte cells	none		[126]
isoflavone (**115**)	microsomes	>200	μM IC_{50}	[132]
7,3',4' -trihydroxyisoflavone (**116**)	microsomes	none	μM IC_{50}	[123]

Table 9

Previous literature reports of natural product flavonoids (not previously mentioned) tested for aromatase inhibition (listed alphabetically by compound class)

Compound Name	Compound Class	Assay Type	Activity		Ref.(s)
cyanidin (**117**)	anthocyanin	microsome	72	μM IC_{50}	[136]
malvidin-3-*O*-glucoside (**118**)	anthocyanin	microsome	299	μM IC_{50}	[136]
coumestrol (**119**)	coumestan	microsomes	25	μM IC_{50}	[123]
coumestrol (**119**)	coumestan	microsomes (modified)	50.6	% inhib. at 50 μM	[154]
coumestrol (**119**)	coumestan	microsomes (modified)	35.0	μM IC_{50}	[124]
coumestrol (**119**)	coumestan	trout ovarian aromatase	>1000	μM IC_{50}	[128]
coumestrol (**119**)	coumestan	preadipose cells	17	μM IC_{50}	[134]
flavan-4-ol (**120**)	flavanol	microsomes	120	μM IC_{50}	[132]
4'-hydroxyflavan-4-ol (**121**)	flavanol	microsomes	>200	μM IC_{50}	[132]
bonducellin (**122**)	homoisoflavonoid	microsomes	65.0	PCA at 20 μg/mL	[143]
isobonducellin (**123**)	homoisoflavonoid	microsomes	41.0	PCA at 20 μg/mL	[143]
isobonducellin (**123**)	homoisoflavonoid	SK-BR-3 cells	58.4	PCA at 50 μM	[143]
4'-dehydroxycabenegrin A (**124**)	pterocarpan	microsomes	50.9	PCA at 20 μg/mL	[143]
(−)-hemileiocarpin (**125**)	pterocarpan	microsomes	69.8	PCA at 20 μg/mL	[143]
2-hydroxyleiocarpin (**126**)	pterocarpan	microsomes	73.3	PCA at 20 μg/mL	[143]
leiocarpin (**127**)	pterocarpan	microsomes	83.9	PCA at 20 μg/mL	[143]
medicarpin (**128**)	pterocarpan	microsomes	>50	μM IC_{50}	[123]
amorphigenin (**129**)	rotenoid	microsomes	83.7	PCA at 20 μg/mL	[143]
amorphigenin glucoside (**130**)	rotenoid	microsomes	83.0	PCA at 20 μg/mL	[143]
dalbinol (**131**)	rotenoid	microsomes	86.5	PCA at 20 μg/mL	[143]
rotenone (**132**)	rotenoid	H295R adrenocortical carcinoma cells	0.30	μM IC_{50}	[127]

Table 10

Previous literature reports of alkaloids tested for aromatase inhibition

Compound Name	Assay Type	Activity		Ref.(s)
anabasine (**133**)	microsomes	6600	μM IC_{50}	[113]
berberine (**134**)	microsomes	87.5	PCA at 20 μg/mL	[143]
cotinine (**135**)	microsomes	none		[113]
β-hydrastine (**136**)	microsomes	95.6	PCA at 20 μg/mL	[143]
N-(4-hydroxy-undecanoyl)anabasine (**137**)	microsomes	30	μM IC_{50}	[150]
nicotine (**138**)	microsomes	4	cigarette equiv.	[113]
nicotine (**138**)	microsomes	26000	μM IC_{50}	[113]
N-*n*-octanoylnornicotine (**139**)	microsomes	360	μM IC_{50}	[113]
N-*n*-octanoylnornicotine (**139**)	microsomes	360	μM IC_{50}	[150]
8-oxotetrahydrothalifendine (**140**)	microsomes	96.0	PCA at 20 μg/mL	[143]
1-[1-oxo-5(8,9-methylenedioxyphenyl)-2*E*,4*Z*-pentadienyl]-piperidine (**141**)	microsomes	97.7	PCA at 20 μg/mL	[143]
piperine (**142**)	microsomes	100.6	PCA at 20 μg/mL	[143]

Table 11

Previous literature reports of natural product fatty acids tested for aromatase inhibition

Compound Name	Assay Type	Activity		Ref.(s)
arachidonic acid (**143**)	microsomes	11.5	PCA at 20 μg/mL	[152]
arachidonic acid (**143**)	microsomes	28.2	μM IC_{50}	[152]
arachidonic acid (**143**)	SK-BR-3 cells	147.2	PCA at 100 μM	[152]
azelaic acid (**144**)	microsomes	none		[113]
docosahexaenoic acid (**145**)	microsomes	12.4	PCA at 20 μg/mL	[152]
docosahexaenoic acid (**145**)	microsomes	33.2	μM IC_{50}	[152]
docosahexaenoic acid (**145**)	SK-BR-3 cells	98.2	PCA at 100 μM	[152]
docosapentaenoic acid (**146**)	microsomes	15.7	PCA at 20 μg/mL	[152]
docosapentaenoic acid (**146**)	microsomes	16.8	μM IC_{50}	[152]
docosapentaenoic acid (**146**)	SK-BR-3 cells	94.4	PCA at 100 μM	[152]
eicosapentaenoic acid (**147**)	microsomes	30.2	PCA at 20 μg/mL	[152]
eicosapentaenoic acid (**147**)	microsomes	53.2	μM IC_{50}	[152]
eicosapentaenoic acid (**147**)	SK-BR-3 cells	137.6	PCA at 100 μM	[152]
(9*Z*,11*E*)-12-hydroxy-9,11-octadecadienoic acid (**148**)	microsomes	15.9	%inhib. at 313.0 μM	[155]
(10*E*,12*Z*)-9-hydroxy-10,12-octadecadienoic acid (**149**)	microsomes	84	% inhib.	[151]
linoleic acid (**150**)	microsomes	22.5	PCA at 20 μg/mL	[152]
linoleic acid (**150**)	microsomes	7.4	PCA at 20 μg/mL	[108]
linoleic acid (**150**)	microsomes	48.0	μM IC_{50}	[152]
linoleic acid (**150**)	SK-BR-3 cells	147.6	PCA at 100 μM	[152]
α-linolenic acid (**151**)	microsomes	49.5	PCA at 20 μg/mL	[152]
α-linolenic acid (**151**)	microsomes	44.2	μM IC_{50}	[152]
α-linolenic acid (**151**)	SK-BR-3 cells	92.8	PCA at 100 μM	[152]
myristic acid (**152**)	microsomes	66.7	PCA at 20 μg/mL	[152]
oleic acid (**153**)	microsomes	19.5	PCA at 20 μg/mL	[152]
oleic acid (**153**)	microsomes	32.7	μM IC_{50}	[152]
oleic acid (**153**)	SK-BR-3 cells	99.3	PCA at 100 μM	[152]
(10*E*,12*Z*)-9-oxo-10,12-octadecadienoic acid (**154**)	microsomes	95	% inhib.	[151]
palmitic acid (**155**)	microsomes	83.2	PCA at 20 μg/mL	[152]
pentadecanoic acid (**156**)	microsomes	76.2	PCA at 20 μg/mL	[152]
stearic acid (**157**)	microsomes	89.4	PCA at 20 μg/mL	[152]

Table 12

Previous literature reports of natural product lignans tested for aromatase inhibition

Compound Name	Assay Type	Activity		Ref.(s)
erythro-austrobailignan-6 (**158**)	microsomes (modified)	0	% inhib. at 50 μM	[154]
threo-austrobailignan-5 (**159**)	microsomes (modified)	0	% inhib. at 50 μM	[154]
dehydrodesoxypodophyllotoxin (**160**)	microsomes	96.0	PCA at 20 μg/mL	[143]
dehydropodophyllotoxin (**161**)	microsomes	88.1	PCA at 20 μg/mL	[143]
3'-demethoxymatairesinol[a] (**162**)	microsomes	37	μM IC_{50}	[145]
meso-dihydroguaiaretic acid (**163**)	microsomes (modified)	15.1	% inhib. at 50 μM	[154]
4,4'-dihydroxyenterolactone (**164**)	microsomes	6	μM IC_{50}	[145]
4,4'-enterolactone (**165**)	microsomes	15	μM IC_{50}	[145]
enterodiol (**166**)	microsomes	30	μM IC_{50}	[145]
enterodiol (**166**)	Arom+HEK 293 cells	>10	μM IC_{50}	[153]
enterodiol (**166**)	preadipose cells	>100	μM IC_{50}	[134]
enterolactone (**167**)	Arom+HEK 293 cells	8.90	μM IC_{50}	[153]
enterolactone (**167**)	microsomes	14	μM IC_{50}	[145]
enterolactone (**167**)	preadipose cells	74	μM IC_{50}	[134]
epiaschantin (**168**)	microsomes	76.7	PCA at 20 μg/mL	[143]
(−)-hernolactone (**169**)	microsomes	73.5	PCA at 20 μg/mL	[143]
matairesinol[a] (**170**)	Arom+HEK 293 cells	>10	μM IC_{50}	[153]
nectandrin B (**171**)	microsomes (modified)	30	% inhib. at 50 μM	[154]
nordihydroguaiaretic acid[a] (**172**)	microsomes	11	μM IC_{50}	[145]
nordihydroguaiaretic acid[a] (**172**)	microsomes (modified)	42	% inhib. at 50 μM	[154]
nordihydroguaiaretic acid[a] (**172**)	nd	68.70	μM IC_{50}	[149]
secoisolariciresinol (**173**)	microsomes	10.9	% inhib. at 409.0 μM	[155]
secoisolariciresinol (**173**)	Arom+HEK 293 cells	>10	μM IC_{50}	[153]
(−)-syringaresinol (**174**)	microsomes	60.2	PCA at 20 μg/mL	[143]
(−)-yatein (**175**)	microsomes	74.2	PCA at 20 μg/mL	[143]

nd = no data

[a] Optical information not provided by author.

Table 13

Previous literature reports of natural product peptides tested for aromatase inhibition

Compound Name	Assay Type	Activity		Ref.(s)
N-acetyl-L-phenylalaninyl-*N*-benzoyl-L-phenylalaninate (**176**)	microsomes	83.0	PCA at 20 μg/mL	[108]
N-acetyl-L-phenylalaninyl-*N*-benzoyl-L-phenylalaninate (**176**)	SK-BR-3 cells	114.1	PCA at 50 μM	[108]
N-benzoyl-L-phenylalanine methyl ester (**177**)	microsomes	94.3	PCA at 20 μg/mL	[108]
N-benzoyl-L-phenylalanine methyl ester (**177**)	SK-BR-3 cells	33.3	PCA at 50 μM	[108]
N-benzoyl-L-phenylalaninyl-*N*-benzoyl-L-phenylalaninate (**178**)	microsomes	94.2	PCA at 20 μg/mL	[108]
N-benzoyl-L-phenylalaninyl-*N*-benzoyl-L-phenylalaninate (**178**)	SK-BR-3 cells	121.8	PCA at 50 μM	[108]
SNA-60-367-2 (**179**)	microsomes	60	% inhib. at 100 μg/mL	[156]
SNA-60-367-2 (**179**)	microsomes	63	μM IC_{50}	[156]
SNA-60-367-4 (**180**)	microsomes	65	% inhib. at 100 μg/mL	[156]
SNA-60-367-5 (**181**)	microsomes	63	% inhib. at 100 μg/mL	[156]
SNA-60-367-6 (**182**)	microsomes	74	% inhib. at 100 μg/mL	[156]
SNA-60-367-8 (**183**)	microsomes	61	% inhib. at 100 μg/mL	[156]
SNA-60-367-9 (**184**)	microsomes	55	% inhib. at 100 μg/mL	[156]
SNA-60-367-10 (**185**)	microsomes	68	% inhib. at 100 μg/mL	[156]
SNA-60-367-10 (**185**)	microsomes	42	μM IC_{50}	[156]
SNA-60-367-11 (**186**)	microsomes	72	% inhib. at 100 μg/mL	[156]
SNA-60-367-12 (**187**)	microsomes	60	% inhib. at 100 μg/mL	[156]
SNA-60-367-13 (**188**)	microsomes	50	% inhib. at 100 μg/mL	[156]
SNA-60-367-13 (**188**)	microsomes	66	μM IC_{50}	[156]
SNA-60-367-14 (**189**)	microsomes	31	% inhib. at 100 μg/mL	[156]
SNA-60-367-17 (**190**)	microsomes	48	% inhib. at 100 μg/mL	[156]
SNA-60-367-18 (**191**)	microsomes	49	% inhib. at 100 μg/mL	[156]
SNA-60-367-19 (**192**)	microsomes	49	% inhib. at 100 μg/mL	[156]
SNA-60-367-21 (**193**)	microsomes	36	% inhib. at 100 μg/mL	[156]
SNA-60-367-23 (**194**)	microsomes	32	% inhib. at 100 μg/mL	[156]

Table 14

Previous literature reports of natural product terpenoids tested for aromatase inhibition (listed alphabetically by compound class)

Compound Name	Compound Class	Assay Type	Activity		Ref.(s)
trans-communic acid (**195**)	diterpenoid	recombinant yeast microsomes	0	% inhib. at 1 μM	[157]
12*S*-hydroxylabda-8(17),13(15), 14-trien-19-oic acid (**196**)	diterpenoid	recombinant yeast microsomes	0	% inhib. at 1 μM	[157]
12-hydroxy-6,7-*seco*-abieta-8,11,13-triene-6,7-dial (**197**)	diterpenoid	recombinant yeast microsomes	0	% inhib. at 1 μM	[157]
inflexin (**198**)	diterpenoid	microsomes	9.2	μg/mL IC_{50}	[110]
labda-8(17),13-dien-12*R*,15-olid-19-oic acid (**199**)	diterpenoid	recombinant yeast microsomes	7.2	% inhib. at 1 μM	[157]
12-methoxyabieta-8,11,13-trien-11-ol (**200**)	diterpenoid	recombinant yeast microsomes	0	% inhib. at 1 μM	[157]
13-oxo-15,16-dinorlabda-8(17),11*E*-dien-19-oic acid (**201**)	diterpenoid	recombinant yeast microsomes	0	% inhib. at 1 μM	[157]
14-oxo-15-norlabda-8(17),12*E*-dien-19-oic acid (**202**)	diterpenoid	recombinant yeast microsomes	0	% inhib. at 1 μM	[157]
standishinal (**203**)	diterpenoid	recombinant yeast microsomes	50.2	% inhib. at 1 μM	[157]
totarol (**204**)	diterpenoid	recombinant yeast microsomes	0	% inhib. at 1 μM	[157]
(−)-dehydrololiolide (**205**)	isoprenoid	microsomes	91.5	PCA at 20 μg/mL	[108]
(−)-dehydrololiolide (**205**)	isoprenoid	SK-BR-3 cells	21.8	PCA at 50 μM	[108]
4-[(1*E*)-3-hydroxy-1-butenyl]-3,5,5-trimethyl-(4*R*)-2-cyclohexen-1-one (**206**)	isoprenoid	microsomes	93.5	PCA at 20 μg/mL	[143]
4-(4-hydroxy-2,2,6-trimethyl-7-oxabicyclo[4.1.0]hept-1-yl)-3 *E*-buten-2-one (**207**)	isoprenoid	microsomes	62.3	PCA at 20 μg/mL	[143]
loliolide (**208**)	isoprenoid	microsomes	84.6	PCA at 20 μg/mL	[143]
menthol (**209**)	isoprenoid	microsomes	none		[113]
10-*epi*-8-deoxycumambrin B (**210**)	sesquiterpenoid	microsomes	7.0	μM IC_{50}	[161]
11βH,13-dihydro-10-*epi*-8-deoxycumambrin (**211**)	sesquiterpenoid	microsomes	2.0	μM IC_{50}	[161]
11βH,13-dihydro-10-*epi*-8-deoxycumambrin (**211**)	sesquiterpenoid	JEG-3 choriocarcino ma cells	10	μM IC_{50}	[161]
2β,3β-dihydroxy-5-preg-17(20)-(*E*)-en-16-one (**212**)	steroid	microsomes	81.7	PCA at 20 μg/mL	[143]
2β,3β-dihydroxy-5-preg-17(20)-(*Z*)-en-16-one (**213**)	steroid	microsomes	77.4	PCA at 20 μg/mL	[143]
6β-hydroxystigmasta-4-en-3-one (**214**)	steroid	microsomes	94.2	PCA at 20 μg/mL	[108]
6β-hydroxystigmasta-4-en-3-one (**214**)	steroid	SK-BR-3 cells	46.3	PCA at 50 μM	[108]
7β-hydroxy-4,22-stigmastadien-3-one (**215**)	steroid	microsomes	79.8	PCA at 20 μg/mL	[108]
7β-hydroxy-4,22-stigmastadien-3-one (**215**)	steroid	SK-BR-3 cells	127.6	PCA at 50 μM	[108]
spinasterol (**216**)	steroid	microsomes	96.9	PCA at 20 μg/mL	[108]

Compound Name	Compound Class	Assay Type	Activity		Ref.(s)
spinasterol (**216**)	steroid	SK-BR-3 cells	103.5	PCA at 50 μM	[108]
spinasterol glucoside (**217**)	steroid	microsomes	93.1	PCA at 20 μg/mL	[143]
spinasterone (**218**)	steroid	microsomes	91.9	PCA at 20 μg/mL	[108]
spinasterone (**218**)	steroid	SK-BR-3 cells	98.6	PCA at 50 μM	[108]
stigmasterol (**219**)	steroid	microsomes	99.6	PCA at 20 μg/mL	[108]
stigmasterol (**219**)	steroid	SK-BR-3 cells	114.6	PCA at 50 μM	[108]
(*E*)-volkendousin (**220**)	steroid	microsomes	73.8	PCA at 20 μg/mL	[143]
(*Z*)-volkendousin (**221**)	steroid	microsomes	52.8	PCA at 20 μg/mL	[143]
aglaiaglabretol A (**222**)	triterpenoid	microsomes	97.4	PCA at 20 μg/mL	[143]
aglaiaglabretol B (**223**)	triterpenoid	microsomes	49.4	PCA at 20 μg/mL	[143]
aglaiaglabretol B (**223**)	triterpenoid	SK-BR-3 cells	16.5	PCA at 50 μM	[143]
betulinic acid (**224**)	triterpenoid	microsomes	89.5	PCA at 20 μg/mL	[143]
maslinic acid (**225**)	triterpenoid	microsomes	56.5	PCA at 20 μg/mL	[143]
oleanolic acid (**226**)	triterpenoid	microsomes	83.5	PCA at 20 μg/mL	[108]
oleanolic acid (**226**)	triterpenoid	microsomes	12.4	% inhib. at 40.7 μM	[155]
oleanolic acid (**226**)	triterpenoid	SK-BR-3 cells	93.5	PCA at 50 μM	[108]
ursolic acid (**227**)	triterpenoid	microsomes	103.1	PCA at 20 μg/mL	[143]
ursolic acid (**227**)	triterpenoid	microsomes	30.4	% inhib. at 81.5 μM	[155]
ursolic acid (**227**)	triterpenoid	microsomes	14.0	μg/mL IC_{50}	[110]
ursolic acid (**227**)	triterpenoids	microsomes	32	μM IC_{50}	[193]
ursolic acid 3-*O*-acetate (**228**)	triterpenoid	microsomes	42.7	μg/mL IC_{50}	[110]
ixocarpalactone A (**229**)	withanolide	microsomes	105.6	PCA at 20 μg/mL	[143]
ixocarpalactone B (**230**)	withanolide	microsomes	106.7	PCA at 20 μg/mL	[143]

Table 15

Previous literature reports of natural product xanthones tested for aromatase inhibition

Compound Name	Assay Type	Activity		Ref.(s)
cudraxanthone G (**231**)	microsomes	57.8	PCA at 20 μg/mL	[109]
8-deoxygartanin (**232**)	microsomes	82.6	PCA at 20 μg/mL	[109]
garcinone D (**233**)	microsomes	10.0	PCA at 20 μg/mL	[109]
garcinone D (**233**)	microsomes	5.16	μM IC_{50}	[109]
garcinone D (**233**)	SK-BR-3 cells	50.7	PCA at 50 μM	[109]
garcinone E (**234**)	microsomes	23.9	PCA at 20 μg/mL	[109]
garcinone E (**234**)	microsomes	25.14	μM IC_{50}	[109]
garcinone E (**234**)	SK-BR-3 cells	32.3	PCA at 50 μM	[109]
gartanin (**235**)	microsomes	75.9	PCA at 20 μg/mL	[109]
8-hydroxycudraxanthone G (**236**)	microsomes	55.1	PCA at 20 μg/mL	[109]
1-isomangostin (**237**)	microsomes	52.6	PCA at 20 μg/mL	[109]
α-mangostin (**238**)	microsomes	22.2	PCA at 20 μg/mL	[109]
α-mangostin (**238**)	microsomes	20.66	μM IC_{50}	[109]
α-mangostin (**238**)	SK-BR-3 cells	59.4	PCA at 50 μM	[109]
γ-mangostin (**239**)	microsomes	4.7	PCA at 20 μg/mL	[109]
γ-mangostin (**239**)	microsomes	6.88	μM IC_{50}	[109]
γ-mangostin (**239**)	SK-BR-3 cells	−0.5	PCA at 50 μM	[109]
γ-mangostin (**239**)	SK-BR-3 cells	4.97	μM IC_{50}	[109]
mangostinone (**240**)	microsomes	78.8	PCA at 20 μg/mL	[109]
monodictysin A (**241**)	DBF enzyme[1]	32	% inhib. at 50 μM	[164]
monodictysin B (**242**)	DBF enzyme[1]	9	% inhib. at 50 μM	[164]
monodictysin C (**243**)	DBF enzyme[1]	28.3	μM IC_{50}	[164]
monodictyxanthone (**244**)	DBF enzyme[1]	37	% inhib. at 50 μM	[164]
smeathxanthone A (**245**)	microsomes	80.8	PCA at 20 μg/mL	[109]
tovophylline A (**246**)	microsomes	74.7	PCA at 20 μg/mL	[109]

[1] DBF (*O*-benzylfluorescein benzyl ester) was used as substrate with purified aromatase enzyme

Table 16

Previous literature reports of miscellaneous natural products (not previously mentioned) tested for aromatase (listed alphabetically by compound class)

Compound Name	Compound Class	Assay Type	Activity		Ref.(s)
14-octacosanol (**247**)	alkanol	microsomes	24.3	% inhib. at 29.6 μM	[155]
alizarin-1-methyl ether (**248**)	anthraquinone	microsomes	82.5	PCA at 20 μg/mL	[143]
benzanthraquinone I (**249**)	anthraquinone		94	% inhib. at 25 μM	[168]
3-hydroxy-2-(hydroxymethyl)-anthraquinone (**250**)	anthraquinone	microsomes	82.1	PCA at 20 μg/mL	[143]
morindone-5-methyl ether (**251**)	anthraquinone	microsomes	92.5	PCA at 20 μg/mL	[143]
rubiadin-1-methyl ether (**252**)	anthraquinone	microsomes	99.0	PCA at 20 μg/mL	[143]
soranjidol (**253**)	anthraquinone	microsomes	96.2	PCA at 20 μg/mL	[143]
1,5,7-trihydroxy-2-methyl-anthraquinone (**254**)	anthraquinone	microsomes	50.5	PCA at 20 μg/mL	[143]
benzo[*a*]pyrene (**255**)	aromatic hydrocarbon	microsomes	none		[113]
benzoic acid (**256**)	benzenoid	microsomes	none		[113]
broussonin A (**257**)	benzenoid	microsomes	30.0	μM IC_{50}	[135]
trans-cinnamic acid (**258**)	benzenoid	microsomes	none		[113]
O-desmethylangolensin (**259**)	benzenoid	microsomes	160	μM IC_{50}	[145]
3,4-dihydroxybenzoic acid (**260**)	benzenoid	microsomes	none		[113]
3,4-dihydroxycinnamic acid (**261**)	benzenoid	microsomes	none		[113]
4-hydroxybenzoic acid (**262**)	benzenoid	microsomes	90.8	PCA at 20 μg/mL	[108]
4-hydroxybenzoic acid (**262**)	benzenoid	microsomes	none		[113]
4-hydroxybenzoic acid (**262**)	benzenoid	SK-BR-3 cells	84.3	PCA at 50 μM	[108]
4-hydroxycinnamic acid (**263**)	benzenoid	microsomes	none		[113]
MF-1 (**264**)	benzenoid	microsomes	30	μM IC_{50}	[145]
MF-2 (**265**)	benzenoid	microsomes	100	μM IC_{50}	[145]
monodictyphenone (**266**)	benzenoid	DBF enzyme[1]	25	% inhib. at 50 μM	[164]
oleuropein (**267**)	benzenoid	microsomes	27	μM IC_{50}	[136]
phenylacetic acid (**268**)	benzenoid	microsomes	none		[113]
TAN-931 (**269**)	benzenoid	microsomes	17.2	μM IC_{50}	[165]
TAN-931 (**269**)	benzenoid	*in vivo* Sprague-Dawley rats	reduced	estradiol levels	[165]

Compound Name	Compound Class	Assay Type	Activity		Ref.(s)
demethylmoracin I (**270**)	benzofuran	microsomes	31.1	μM IC_{50}	[135]
moracin N (**271**)	benzofuran	microsomes	31.1	μM IC_{50}	[135]
chlorophyllide *a* (**272**)	chlorophyll	microsomes	80.3	PCA at 20 μg/mL	[143]
esculetin (**273**)	coumarin	microsomes	>640	μM IC_{50}	[136]
isoscopoletin (**274**)	coumarin	microsomes	>640	μM IC_{50}	[136]
8-methoxypsoralen (**275**)	coumarin	*in vivo* female Wistar rats	decreased	aromatase protein	[194]
scoparon (**276**)	coumarin	microsomes	>640	μM IC_{50}	[136]
scopoletin (**277**)	coumarin	microsomes	>640	μM IC_{50}	[136]
curcumin (**278**)	diarylheptanoid	microsomes	none		[149]
aculeatin A (**279**)	dioxadispiroketal	microsomes	66.8	PCA at 20 μg/mL	[143]
aculeatin B (**280**)	dioxadispiroketal	microsomes	77.2	PCA at 20 μg/mL	[143]
albanol A (**281**)	miscellaneous	microsomes	7.5	μM IC_{50}	[135]
FR 901537 (**282**)	miscellaneous	nd	nd		[195]
sodium butyrate (**283**)	miscellaneous	breast adipose fibroblast cells	decreased	promoter specific aromatase mRNA	[196]
zearalenone (**284**)	miscellaneous	granulosa-luteal cells	inhibited	at 10 μmol/L for 24h	[129]
limnophilaspiroketone (**285**)	spiroketone	microsomes	106.2	PCA at 20 μg/mL	[143]
resveratrol (**286**)	stilbenoid	microsomes	51.9	PCA at 20 μg/mL	[143]
resveratrol (**286**)	stilbenoid	microsomes	12.8	μM IC_{50}	[136]
resveratrol (**286**)	stilbenoid	nd	~115	% inhib. at 100 μM	[107]
ellagic acid (**287**)	tannin	microsomes	99.5	PCA at 20 μg/mL	[143]
oenothein A (**288**)	tannin	microsomes	70	% inhib. at 50 μM	[130]
oenothein A (**288**)	tannin	nd	nd		[197]
oenothein B (**289**)	tannin	microsomes	33	% inhib. at 50 μM	[130]
oenothein B (**289**)	tannin	nd	nd		[197]

[1] DBF (*O*-benzylfluorescein benzyl ester) was used as substrate with purified aromatase enzyme nd = no data