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Review

Review: The potential of chalcones as a source of drugs

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Chalcone and dihydrochalcones are intermediates in the biosynthesis of flavonoids and isoflavonoids in plants. These compounds are widely investigated for their anticancer, anti-inflammatory, antimicrobial, antiprotozoal, antifilarial, larvicidal, anticonvulsant, anti-rheumatoid and antioxidant activities and their use as food additives. Chalcones are considered to be an active ingredient in a large number of medicinal herbs. Further chemical investigation of these plants has now resulted in the isolation of chalcone and biologically active derivatives. Chalcone and their derivatives are an attractive molecular scaffold for the search of new biologically active molecules. This review provides a comprehensive analysis of the source plants, chemistry, structure-activity, pharmacological reports of chalcone and derivatives isolated and identified from plants. In recent years a considerable number of investigations conducted on the biological activities of these compounds suggested a wide range of clinical applications.

Key words: Chalcones, dihydrochalcones, derivatives, bioactives, flavonoids, phytochemistry.

INTRODUCTION

Chalcones structure differs considerably from the other members of the flavonoid family. Approximately 201 aglycone structures with varied patterns of hydroxylation, and in some cases, methylation and prenylation, are known. Although many chalcones occur as glycosides, the majority are found as free aglycones. Chalcones are isomerized to flavanones in plants by the enzyme chalcone isomerase, but are readily isomerized *in vitro* in the presence of acid (Seigler, 2002). The biological effect of chalcones was found to be dependent on the presence, the number and position of functional groups such as methoxy, glycosides, hydroxyl, halogens, etc. in both A and B rings (Dhar, 2003).

Chalcones are abundant in edible plants fruits, vegetables, spices, tea and have also been shown to display pharmacologicall varied effects (Chimenti et al.,

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2009). They present a broad spectrum of biological activities such as anticancer, anti-inflammatory, antimalarial, antifungal, antilipidemic, antiprotozoal (antileishmanial and antitrypanosomal), antibacterial, antifilarial, larvicidal, antioxidant, anticonvulsant antimicrobial and antiviral (Rahman, 2011). There has been a tremendous interest in these compounds (Appendix 1) as evidenced by the voluminous work. Therefore, we aimed to compile an up to date and comprehensive review of chalcones that covers their traditional and folk medicine uses, phytochemistry and pharmacology.

BIOLOGICAL ACTIVITY

Scientific investigations of the medicinal properties of chalcones dates back to the 1980s. A summary of the findings of these studies performed is presented below.

Antiinflammatory activity

Recent reports indicate the importance of chalcones as anti-inflammatory agents involved in the inhibition of cell migration and the inhibition of TNF-α production in mouse model. Chalcone derivatives have been extensively reported to inhibit NO synthesis, iNOS and cycloxygenase 2 protein expression in lipopolysaccharide (LPS) stimulated cells. The structure-activity analysis demonstrated that chalcones with substituents that reduce the electronic density in the B ring, such as chlorine atoms or nitro groups, show better biological activity and selectivity in the inhibition of nitrite production, and position 2 in B ring seems to be more important (Wu et al., 2011). Six chalcones were isolated from *Angelica keiskei* 2',4',4-trihydroxy-3'-[2-hydroxy-7-methyl-3-methylene-6-octaenyl]chalcone] (1), 2',4',4-trihydroxy-3'-geranylchalcone (2), 2',4',4-trihydroxy-3'-[6-hydroxy-3,7-dimethyl-2,7-octadienyl]chalcone (3), 2',4-dihydroxy-4'-methoxy-3'-[2-hydroperoxy-3-methyl-3-butenyl] chalcone (4), 2',4-dihydroxy-4'-methoxy-3'-geranylchalcone (5), and 2',4-dihydroxy-4'-methoxy-3'-[3-methyl-3-butenyl]chalcone (6). Among them, compounds 1 to 3 showed potent inhibitory activity of IL-6 production in TNF-α-stimulated MG-63 cell, while compounds 4 to 6 did not. The inhibitory activity of IL-6 production in TNF-α-stimulated MG-63 cell is likely to be affected by the presence of C-4' hydroxyl group in the chalcone moiety (Shin et al., 2011).

The chalcone derivatives isolated from the fruits of *Malotus philippinensis* called mallotophilippens C (7), D (8) and E (9) xanthohumol (10), and dihydroxanthohumol (11) inhibited the production of NO induced by LPS and IFN-y in murine macrophage-like cell line, RAW 264.7. Furthermore, mallotophilippens inhibited inducible iNOS, COX-2, IL-6 and IL-113 mRNA gene expression (Nowakowska, 2007). Daikonya and co-workers hypothesized that the main inhibitory mechanism of these compounds may be the inactivation of the nuclear factor KB (NF-KB) (Daikonya et al., 2004).

Antimicrobial effect

Licochalcone A (12) is a retrochalcone isolated from the roots and rhizomes of *Glycyrrhiza inflata.* It is active against a wide range of Gram positive organisms but not against Gram negative bacteria and eukaryotes. Licochalcone A structure-activity relationship study showed that, of the two phenolic hydroxyl (OH) groups attached to rings A and B of licochalcone A, the OH on ring A was more important for antibacterial activity. The prenyl side chain on ring B contributed to lipophilicity, and could be replaced by groups with comparable lipophilíc character, like n-hexyl, without loss of antibacterial activity. Licochalcone A has been used as a lead compound for the design of more potent antibacterial agents based on the chalcone template (Liu et al., 2008).

Drewes and van Vuuren (2008) isolated from flowers of *Helichrysum gymnocomum* the chalcones 4',6', 8',trihydroxychalcone (14) and 2-hydroxy-4',6'-dibenzyloxychalcone (13) which had minimum inhibitory concentration (MIC) value below 64 µg against of pathogens including *Staphylococcus aureus* and the *S. aureus* methicillin and gentamycin resistant strain. The existence of the benzyloxy group, as well as the presence of the unsubstituted B-ring in chalcone play a role in influencing the antimicrobial activity. Other studies show that *Artocarpus nobilis* (Moraceaes) yielded 2',4',4-trihydroxy-3'-geranylchalcone (15), 2',4',4-trihydroxy-3'-[6-hydroxy-3,7-dimethyl-'2(E),7-oetadienyl] chalcone (16), 2',4',4-trihydroxy-3'-['2-hydroxy-7-methyl-3-methylene-6-oetaenyl]chalcone (17), 2',3,4,4'-tetrahydroxy-3'-geranylchalcone (18) and 2'3,4,4'-tetrahydroxy-3'-[6-hydroxy-3,7-dimethyl-2(E),7-octadienyl] chalcone (19). All the compounds showed fungicidal activity at 5 µg/spot against *Cladosporium cladosporioides*. Furthermore, four chalcones, were isolated from an ethanol extract of the leaves of *Maclura tinctoria* (L.) Gaud. Compounds 2',4',4,2"-tetrahydroxy-3'-[3"-methylbutyl-3"'enyl]chalcone] (20), isovachalcone (21), bakuchalcone (22), and bavachromanol. Isovabachalcone was active against *Candida albicans* (IC_{50} of 3 µg.ml^{-1}) and *Cryptococcus neoformans* (IC_{50} of 7 µg ml^{-1}) (Jayasinghe et al., 2004). Other studies show that the methanolic extract of *Zuccagnia punctata* consisting of 2',4'-dihydroxy-3'-methoxychalcone (23) and 2',4'-dihydroxy chalcone (24) displayed very good activities (MIC = 6.25 and 3.12 µg ml^{-1}) against *Phomopsis*

longicolla Hobbs CE117, and (MIC = 6.25 µg ml^{-1}) against *Colletotrichum truncatum* CE175 (Svetaz et al., 2004). 2',4'-Dihidroxy-3',5'-dimethyl-6' methoxychalcone (25) (Belofsky et al., 2004) isolated from *Dalea versicolor* exhibited individually and in synergy with known antibiotics (berberin, erythromycin and tetracycline) the activity towards the human pathogen *S. aureus* and the opportunistic pathogen *B. cereus*. This compound in the presence of berberine effected a dramatic 30-fold increase in activity against *B. cereus.*

Antiosteoporosis effect

Dimeric dihydrochalcone cycloaltilisin 6 (26) and AC-5-1 (27) were isolated of the bud covers of *Artocarpus altilis*. All the compounds shown to be potent inhibitors of cathepsin K (is a cysteine protease that has been implicated in osteoporosis). Cycloaltilisin 6 was found to be the most potent inhibitor with an IC_{50} of 98 nM followed by AC-5-1 with an IC_{50} of 170 nM and cycloaltilisin 7 (28) with an IC_{50} of 840 nM (Patil et al., 2002).

Antioxidant effect

The methanol extract of *Maclura tinctoria* stem bark led to the isolation of four chalcone glycosides 4'-O-β-D-(2"-p-coumaroyl)glucopyranosyl-4,2',3'-trihydroxychalcone (29), 4'-O-β-D-(2"-*p*-coumaroyl)-6"-acetylglucopyranosyl-4,2',3'-trihydroxychalcone (30), 3'-(3-methyl-2-butenyl)-4'O-β-D-(glucopyranosyl-4,2'-dihydroxy chalcone (31) and 4'-O-β-D-(2"-acetyl-6"-cinnamoyl)glucopyranosyl-4,2',3'-trihydroxychalcone (32). The results showed that 3'-(3-methyl-2-butenyl)-4'O-β-D-(glucopyranosyl-4,2'-dihydroxychalcone was the most active chalcone in antioxidant assays (Cioffi et al., 2003). The fruit and seeds of *Cedrelopis grevei* (Ptaeroxylaceae) yielded uvangoletin (33), flavokawin B (34), 5,7-dimethylpinocembrin (35), 2'-methoxyhelikrausichalcone (36), and the prenylated chalcones, cedrediprenone (37) and cedreprenone (38) (Koorbanally et al., 2003). The antioxidant effect of some dihydrochalcones has been reported in apple fruits (*Malus domestica*). Phloridzin (39), seboldin (40) and trilobatin (41) were isolated from the leaf of *M. domestica*. Phloridzin had a high activity in the oxygen radical antioxidant capacity (ORAC) assay, it have ability to prevent oxidative-dependent formation of AGEs the phenylephrine-induced contraction of isolated rat mesenteric arteries. Sieboldin clearly demonstrated antioxidant activity and prevented vasoeonstrietion and inhibited AGEs formation (De Bernonville et al., 2010).

Eight dihydrochalcones were isolated from the roots of *Anneslea fragrans* var. lanceolata, davidigenin-2'-O-(6"-O-4'"-hydroxybenzoyl)-β-glucoside (42), davidigenin-2'-O-(2"-O-4'"-hydroxybenzoyL)-β-glucoside (43), davidigen-2'-O-(3"-O-4'"-hydroxybenzoyl)-β-glucoside (44), davidigenin-2'-O-(6"-O-syringoyl)-β-glucopyranoside (45), 1-O-3,4-dimethoxy-5-hydroxyphenyl-6-O-(3,5-di-O-methylgalloyl)-β-gluco-pyranoside (46) davidioside (47), 4'-O-methyldavidioside (48) and davidigenin (49). Compounds 46 to 49 showed weak DPPH radical scavenging activity, whereas the other chalcones did not display any DPPH radical scavenging activity. The 2,6-dimethoxy groups of the syringoyl moiety may further stabilize the phenoxyl radicals enhancing the radical scavenging ability of compounds 45 and 46 (Huang et al., 2012).

Syzygium jambos ALston, afforded three compounds phloretin 4'-O-methyl ether (2',6'-dihydroxy-4'-methoxydihydrochalcone) (50), myrigalone G (51) and myrigalone B (52), which showed antioxidant activity higher than that of α-tocopherol by spectrophotometry method (Jayasinghe et al., 2004). Aspalathin (53) and nothofagin (54) were isolated from Rooibos (*Aspalathus linearis*). The most potent radical scavengers were aspalathin (IC_{50} = 3.33 µM) and EGCG (IC_{50} = 3.46 µM), followed by nothofagin (IC_{50} = 4.04 µM), [90].

Antiplasmodial effect

Worldwide, 300-500 million people are infected with malaria each year. Most cases occur in sub-Saharan Africa, with approximately 2 million people dying there each year. Unfortunately, the emergence of malarial parasite strains resistant to chloroquine has eroded this drug´s efficacy. Extensive programs are underway to screen natural products and synthetic derivatives for new agents to treat chloroquine-resistant malaria. The n-hexane extract of leaves of *Piper hostmannianum* var. berbicense (Miq.) (Piperaeeae) exhibited interesting activity against *Plasmodium falciparum* (IC_{50} = 8 µg ml^{-1}) (Portet et al., 2007). An activity bioassay-guided fractionation led to the isolation of dihydrochalcones hostmanin A (55), hostmanin B (56), hostmanin C (57) hostmanin D (58) and 2',6'-dihydroxy-4'-methoxydihydrochalcone (59), as well as linderatone (60), adunctin E (61) and (-)-methyllinderatin (62). All chalcones were actives in vitro against *Plasmodium falciparum*, whereas linderatone and (-)-methyllinderatin were considered to be potentially interesting.

Anticancer activities

Since apoptosis is one of the most potent defenses

against cancer development, efforts have been made to develop a chemoprevention and therapeutic strategies that selectively trigger apoptosis in malignant cancer cells. Particularly interesting are the properties of chalcones in the induction of apoptosis and their ability to change mitochondrial membrane potential (Sabzevari et al., 2004). In cancer, it has been reported that chalcones interfere in several points of the signal transduction pathways related to cellular proliferation, angiogenesis, metastasis, apoptosis and the reversal of multidrug resistance. The largenumber of research articles and patents related to chalcones is already an indication of their importance as a lead class of compounds. Chalcones with fewer hydroxyl groups on rings A and B were more effective in this regards, as compared to chalcones containing more hydroxyl groups. This difference was attributed to the acidity of the phenolic hydroxyl groups. One of the most widely cited mechanisms by which chalcones exert their cytotoxic activity is that of the interference with the mitotic phase of the cell cycle. A large number of methoxylated chalcones with antimitotic activity against HeLa cells was discovered. Other studies show that the capacity of 2'-hydroxychalcones with different methoxy subtitutions on ring B to inhibit cellular proliferation, induce apoptosis and correlate it with the chemical reactive indexes in HepG2 hepatocellular carcinoma cells (Echeverria et al., 2009).

Later, Bertl et al. (2004) studied the potential antiangiogenic effects of xanthohumol (63) and isoxanthohumol (64), chalcones isolated from *Humulus lupulus* (hopse). In *in vitro* conditions they observed a reduction of newly formed capillary growth by xanthohumol at a concentration range of 0.5 to 10 µM (IC_{50} value of 2.2 µM). The inhibitory effect of isoxanthohumol was weaker. Furthermore, xanthohumol effectively blocksed tumour angiogenesis and tumour growth *in vivo* and interferes with several steps in the angiogenic process. Xanthohumol also reduced vascular endothelial growth factor (VEGF) secretion, decreased cell invasion and metalloprotease production in acute and chronic myelogenous leukemia cell lines (DellEva et al., 2007). Moreover, licochalcone E (65), a retrochalcone isolated from the roots of *Glycyrrhiza inflata*, was found to be an inducer of apoptosis in endothelial cells by modulating NFKB and members of the Bcl-2 family (Mojzis et al., 2008).

Similarly, 2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone (66), extracted from the dried flower *Cleistocalyx operculatus*, blocked antiangiogenesis *in vitro* as well as *in vivo*. In *in vitro* conditions it reversibly inhibited VEGF receptor tyrosine kinase phosphorylation. It also inhibited MAPI< and AKT activation of VEGF receptor signal transduction. Systemic administration of this chalcone resulted in the inhibition of subcutaneous tumour growth of human hepatocarcinoma Bel7402 and lung cancer GLC-82 xenografts and a decrease in the tumour vessel density (Zhu et al., 2005).

TRAIL is a naturally occurring anticancer agent appearing in soluble form or expressed in immune cells. TRAIL mediates *in vitro* and *in vivo* apoptosis in cancer cells. Cytotoxic effects of chalcones and dihydrochalcone 2',6'-dihydroxy-4'-methoxychalcone (67), 2',6'-dihydroxy-4'-methoxydihydro chalcone (68) 2' 6' -dihydroxy-4,4' –dimethoxy dihydrochalcone (69) and phloretin (70) markedly augment TRAIL mediated apoptosis in LNCaP cells. Sensitization of prostate cancer cells to TRIAL-mediated apoptosis by chalcones and dihydrochalcones suggest the potential role of these compounds in anticancer immune defense in which endogenous TRAIL takes part. The TRAIL-mediated cytotoxic and apoptotic pathways may be a target of the chemopreventive agents in prostate cancer cells and the overcoming TRAIL-resistance by chalcones and dihydrochalcones may be one of the mechanisms responsible for their cancer preventive effects (Szliszka et al., 2010). The phytochemical study of chloroform extract of *Calythropsis aurea* (Myrtaceae) yielded two chalcones calythropsin (71) and dihydrocalythropsin (72). Calythropsin showed no detectable activity *in vitro* tubulin polymerization assay, however it showed weak cytotoxic activity against L1210 cells with IC_{50} of 7 µM (Beutler et al., 1993).

In another study, the chalcone derricin (73) and lonchocarpin (74) were isolated from hexanic extract from the roots of *Lonchocarpus sericeus* (Fabaceae). Both chalcones possessed cytotoxicity against CEM Leukaemia cell line, inhibiting cell growth with IC_{50} lower than 20 µg/ml. Lonchocarpin was cytotoxic against tumoral cells, but had no effect on sea urchin egg development at tested concentrations. In fact, lonchocarpin was also the least active substance against leukaemia cells presenting a maximal inhibition of 77% in higher tested concentration, while derricin almost completely stopped cell growth (Cunha et al., 2003).

Dihydrochalcones 10',6'-diacetoxy-4,4'-dimethoxydihydrochalcone (75), 4,2',6'-trihydroxy-4'-methoxy dihydrochalcone (76), 2',6'-dihydroxy-4'-methoxydihydrochalcone (77) and chalcone 2',4'-diacetoxy chalcone (78) isolated from the leaves of *Carthamus arborescens* showed cytotoxic activity on cell lines P-388, A-549 and HT-29. Of these chalcones 10',6'-diacetoxy-4,4'-dimethoxy- dihydrochalcone was the most potent against human cell line tested (Barrero et al., 1997). Litseaone A (79) and B (80) were isolated of the stem bark of *Litsea rubescens* and *Litsea pedunculata*. Both compounds exhibited moderate cytotoxic activities with IC_{50} values of 23.0 and 21.5 µg ml^{-1} against liver carcinoma (HepG-2) cell line. Chalcones displayed potent cytotoxic activities with IC_{50} values lower than 14.0 µg ml^{-1} against myeloid leukaemia (HL-60) and epidermoid carcinoma (A431) cell lines were more active than DDP.

Litseaone A exhibited cytotoxic activity against myeloid leukaemia (HL-60) with IC_{50} value 2.1-fold more sensitive to DDP. These chalcones were found to contain the rare epoxy or ethylidenedioxy group. This is the first report on the presence of chalcone in the Litsea plant genus (Li et al., 2011). *Syzygium samarangense* (Bloom) (Myrtaceae), known commonly as wax jambu, is an evergreen tree with origins in Asia. Three C-methylated chalcones, 2',4'-dihydroxy-3',5'-dimethyl-6'-methoxychalcone (81), stercurensin (82), and cardamonin (83) were isolated (Resurrección-Magno et al., 2005).

In another study, the dihydrochalcone 2',4'- dihydroxy-4,6'-dimethoxydihydrochalcone (84) was isolated from the ethyl ether extract of *Iryanthera juruensis* Warb (Myristicaceae) and it was found to be a major cytotoxic metabolite when tested against a panel of cancer cell lines (122). Panduratin A (85) is a cyclohexanyl chalcone found in *Boesenbergia rotunda* induced apoptosis on A375 cancer cells, which was mediated by prolonged ER stress at least in part via the PERK/eIF2α/ATF4/CHOP pathway revealeing that mitochondrion is the primary acting site of Panduratin A on A375 cancer cells (Lai et al., 2015). Flavokawain B (34), a kava chalcone, showed a strong *in vitro* activity against osteosarcoma cell lines. This compound inhibited cell proliferation, induced apoptosis and cell cycle arrest. Furthermore, in contrast to conventional chemotherapeutic drugs, showed less toxicity in normal bone marrow cells (Tao et al., 2013). Cardomonin (83) inhibited prostate cancer cell proliferation and decreased the expression of NFkB1. Moreover, analysis by flow cytometry showed that this compound induced DNA fragmentation, suggesting an effect on apoptosis induction in the PC-3 cell line (Pascoal et al., 2014).

Antiviral effect

Licochalcone G (84), licochalcone A (12), echinantin (86), 5-prenylbutein (87), licochalcone D (88), isoliquiritigenin (89), licoagrochalcone A (90), and kanzonol C (91) were isolated from the acetone extract of the *Glycyrrhiza inflata.* All the isolated compounds shown activity against NAs from influenza viruses. The non-prenylated chalcones echinantin and isoliquiritigenin (IC_{50} 5.80 ± 0.30 and 8.41 ± 0.39 μg ml^{-1}, respectively) exhibited higher activity than the prenylated compounds 5-prenylbutein, the C-5 hydroxy derivative of licoagrochalcone A (IC_{50} 25.87 ± 2.03 μg ml^{-1}) (Go et al., 2005). Xanthohumol (10), chalcone, isolated from *Humulus lupulus* is a selective inhibitor of HIV-1. The EC_{50}'s of xanthohumol on inhibiting HIV-1 p24 antigen and RT production were 1:28 and 1:35 μg ml^{-1}, respectively. Xanthohumol also showed activity against BVDV, HSV-2, and HSV-1, as well as additionally against cytomegalovirus (CMV) (Buckwold et al., 2004).

Licochalcones A (12) and B (92) as well as 3,3',4,4'-tetrahydroxy-2-methoxy chalcone (93) suppressed the TPA-induced HIV promoter, whereas they did not cause any apparent reduction in the Luc activity in pCMVLuc transfected cells. These chalcones had a negative effect on HIV transcription, possibly because they bind to some specific protein factors. Additionally, cardamonin exhibited an appreciable anti-HIV-I PR activity (75.1% inhibition) with an IC_{50} value of 31 μg ml^{-1} (Xu et al., 2000). Glycycoumarin, glycyrin, glycyrol and liquiritigenin isolated from *Glycyrrhiza uralensis*, as well as isoliquiritigenin, licochalcone A and glabridin, develop antivirals activity against hepatitis C virus (HCV) infection (Adianti et al., 2014).

Tyrosinase inhibitor effect

Chalcone (94), 4-hydroxychalcone (95), 4'-hydroxychalcone (96), 2'-hydroxychalcone (97), 2',4'-dihydroxychalcone (98), 2',4-dihydroxychalcone (99), 2',4',4-trihydroxychalcone (100) and 2',4',3,4-tetrahydroxychalcone (101) were tested as inhibitors of tyrosinase mono- and diphenolase activities, showing that the most important factor in their efficacy is the location of the hydroxyl groups on both aromatic rings, with a significant preference to a 4-substituted B ring, rather than a substituted A ring. Neither the number of hydroxyls nor the presence of a catechol moiety on ring B correlated with the increasing tyrosinase inhibition potency. Surprisingly, the addition of a second OH to 4-HC at position 2' (ring A) negated tyrosinase inhibition activity, as observed in 2',4-dihydroxychalcone which was practically inactive (Seo et al., 2003).

CONCLUSION

The pharmacological studies conducted on chalcones indicate the immense potential of these compounds in the treatment of conditions such as osteoporosis, cancer, influenza viruses, as inhibitor of the HIV-1, antimicrobial, tyrosinase inhibitor, plasmodial etc. Not surprisingly, chalcones also exhibits antioxidant and anti-inflammatory effects as oxidative injury underlies many of these diseases. However, the diverse pharmacological activities of the chalcones have only been assayed in *in vitro* tests using laboratory animals, and the results obtained may not necessarily be applicable situation in humans. While there are gaps in the studies conducted so far, which need to be bridged in order to exploit the full medicinal potential of chalcones, it is still very clear that there are compounds which are already widely used and also have an extraordinary potential for the future.

ABBREVIATIONS: AGEs, Advanced glycation end-prcducts; **A-549,** human non-small cell lung cancer; **AKT,** protein kinase B; **COX-2,** cycloxygenase 2; **DPPH,** 1,1-diphenyl-2-picrylhydrazyl; **IFN-y;** interferon gamma; **IL-6,** interleukin 6; **IL-13,** interleukin 13; **iNOS,** NO synthetase; **HepG-2,** liver carcinoma; **HT-29,** human colon cancer; **LPS,** lipopolysaccharide; **MAPI,** multiple activation key; **NF-κB,** nuclear factor kappa-light-chain-enhancer of activated B cells; **NO,** nitrous oxide; **ORAC,** oxygen radical absorbance capacity; **P-388,** murine leukemia; **TNF-α,** tumor necrosis factor-α; **VEGF,** vascular endothelial growth factor.

Conflict of interest

Authors declare that there are no conflicts of interest.

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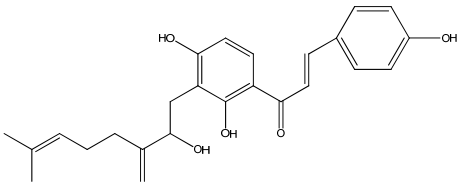
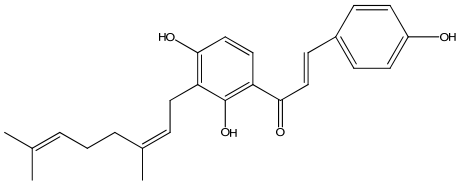
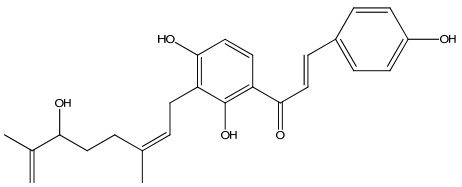
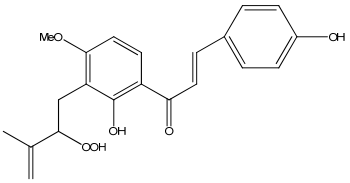
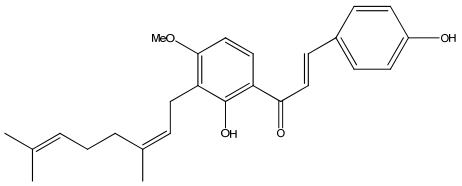
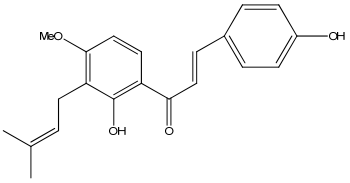
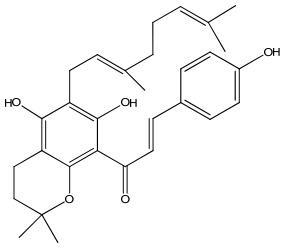
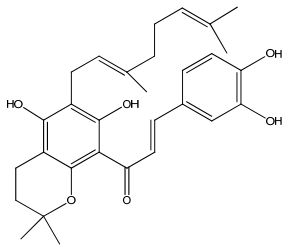
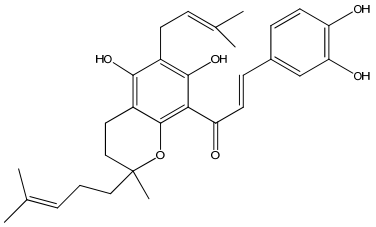
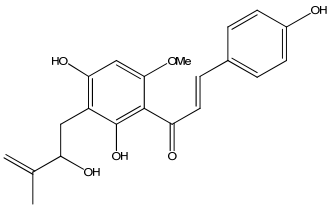
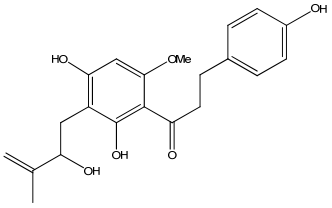
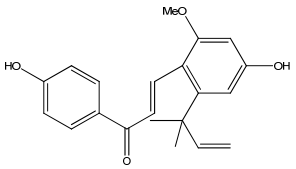
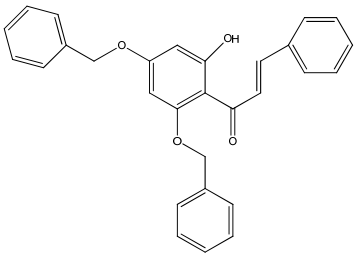
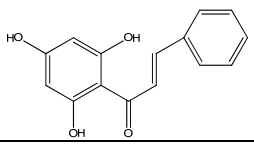
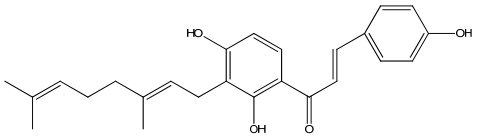
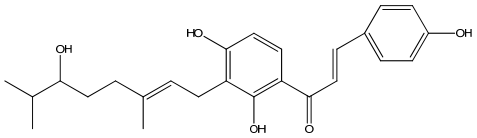
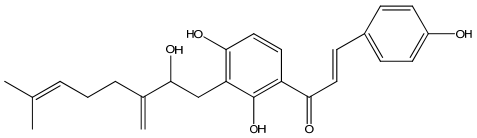
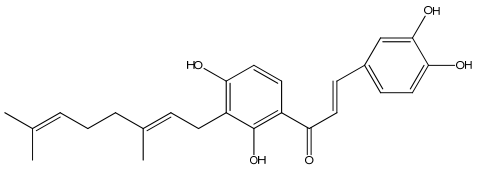
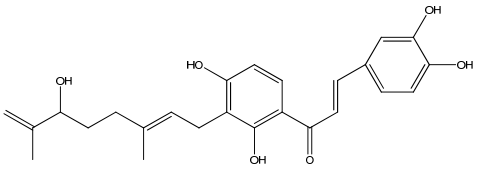
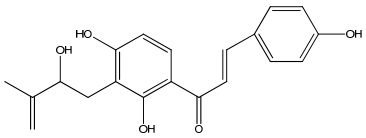
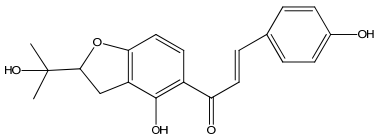
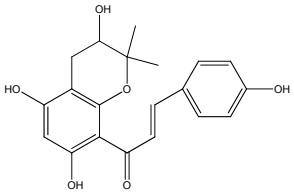
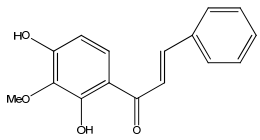
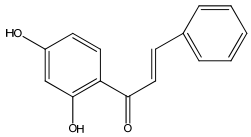
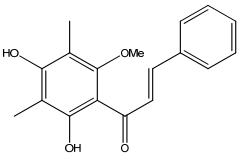
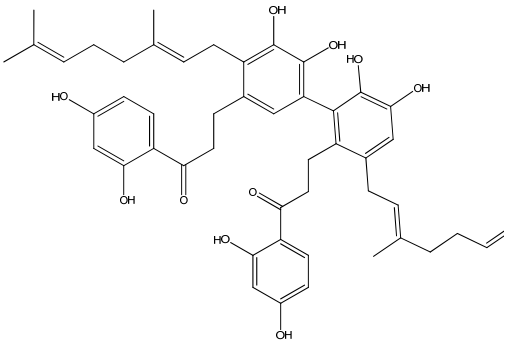
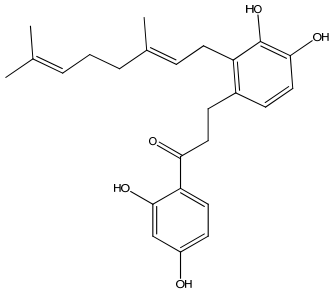
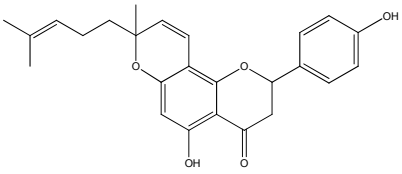
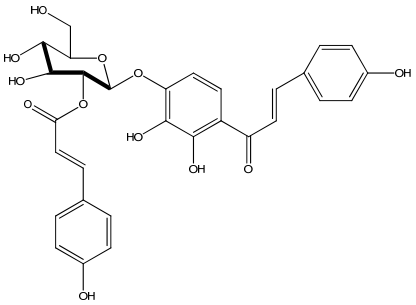
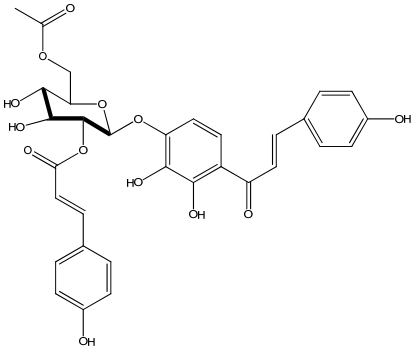
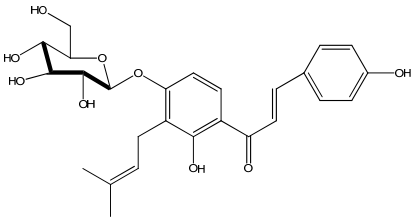
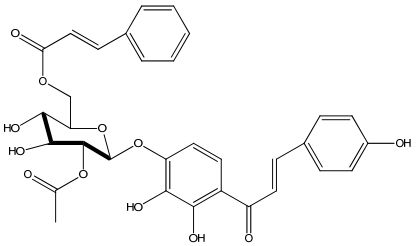
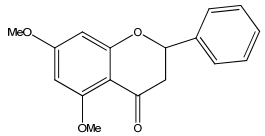
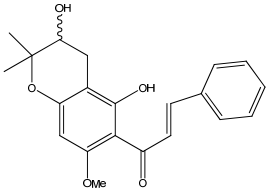
Appendix 1. Compound names and their structures.

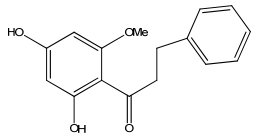
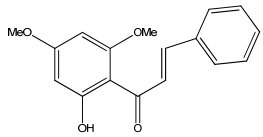
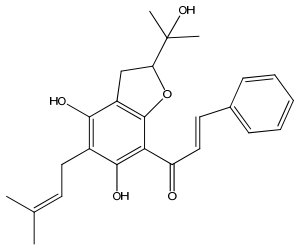
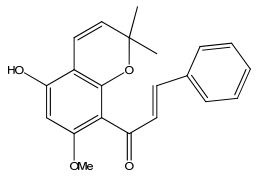
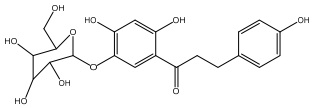
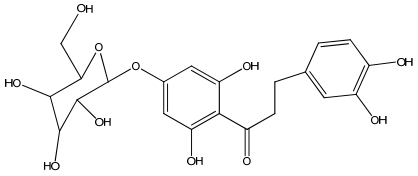
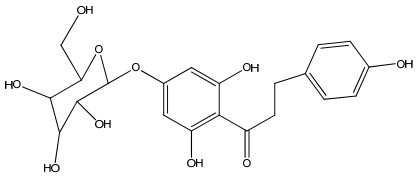
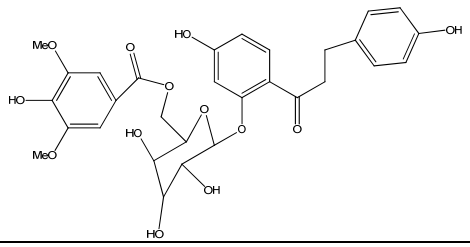
S/NO	Name of compound	Molecular structure
1	2',4',4-trihydroxy-3'-[2-hydroxy-7-methyl-3-methylene-6-octaenyl]chalcone]	
2	2',4',4-trihydroxy-3'-geranylchalcone	
3	2',4',4-trihydroxy-3'-[6-hydroxy-3,7-dimethyl-2,7-octadienyl]chalcone	
4	2',4-dihydroxy-4'-methoxy-3'-[2-hydroperoxy-3-methyl-3-butenyl] chalcone	
5	2',4-dihydroxy-4'-methoxy-3'-geranylchalcone	
6	2',4-dihydroxy-4'-methoxy-3'-[3-methyl-3-butenyl]chalcone	
7	Mallotophilippens C	

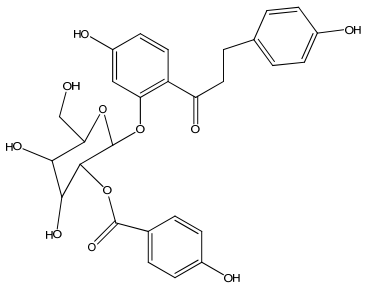
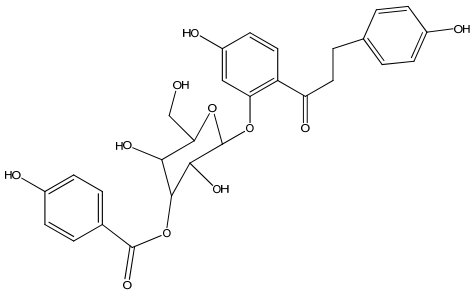
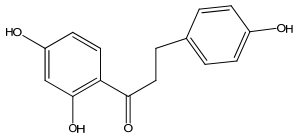
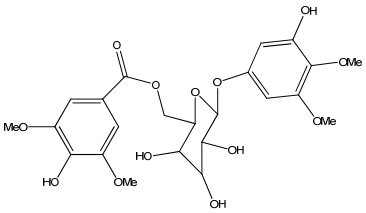
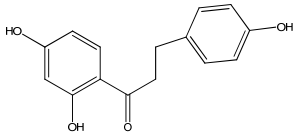
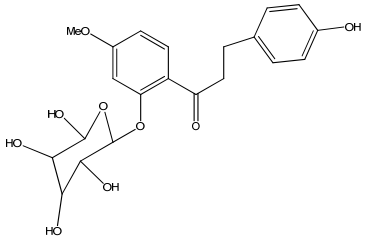
8	Mallotophilippens D	
9	Mallotophilippens E	
10	Xanthohumol	
11	Dihydroxanthohumol	
12	Licochalcone A	
13	2-Hydroxy-4',6'-dibenzyloxychalcone	
14	benzyloxy group	

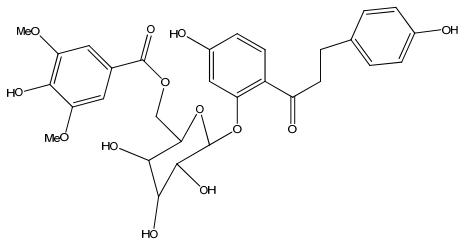
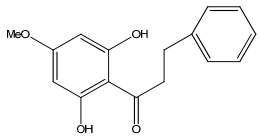
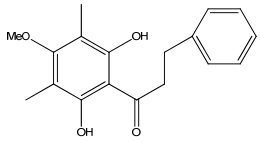
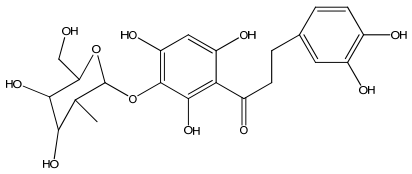
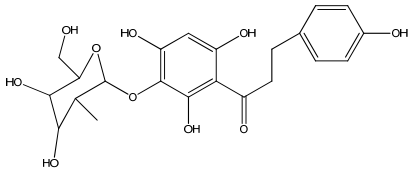
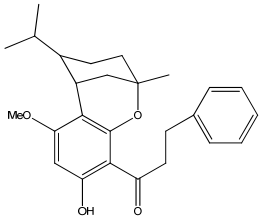
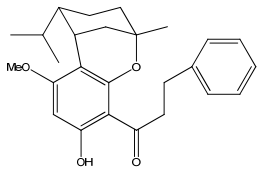
15	2',4',4-trihydroxy-3'-geranylchalcone	
16	2',4',4-trihydroxy-3'-[6-hydroxy-3,7-dimethyl-'2(E),7-oetadienyl] chalcone	
17	2',4',4-trihydroxy-3'-['2-hydroxy-7-methyl-3-methylene-6-oetaenyl)chalcone	
18	2',3,4,4'-tetrahi-droxy-3'-geranylchalcone	
19	2'3,4,4'-tetrahydroxy-3'-[6-hydroxy-3,7-dimethyl-2(E),7-octadienyl) chalcone	
20	2',4',4,2"-tetrahydroxy-3'-[3"-ethyl]chalcone	
21	Isovachalcone	
22	Bakuchalcone	

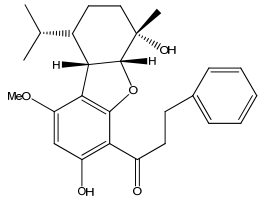
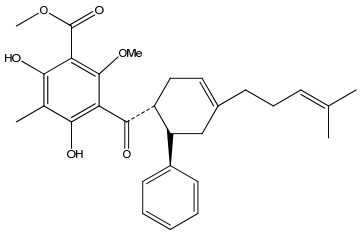
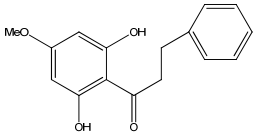
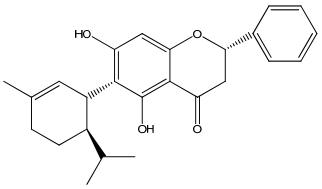
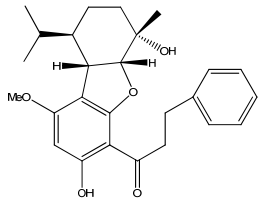
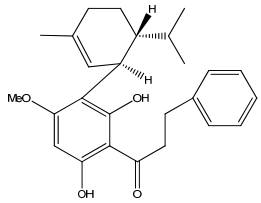
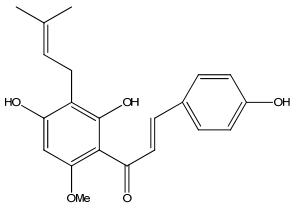
23	2',4'-dihydroxy-3'-methoxychalcone	
24	2',4'-dihydroxy chalcone	
25	2',4'-Dihidroxy-3',5'-dimethyl-6' methoxychalcone	
26	Dimeric dihydrochalcone cycloaltilisin 6	
27	AC-5-1	
28	Cycloaltilisin 7	

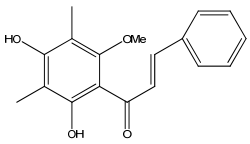
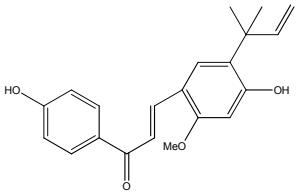
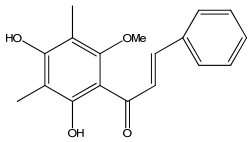
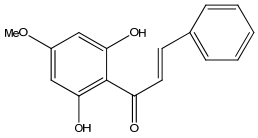
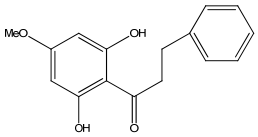
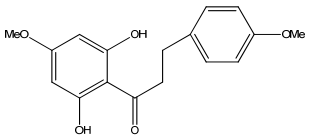
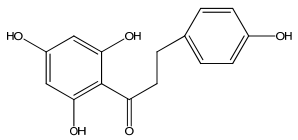
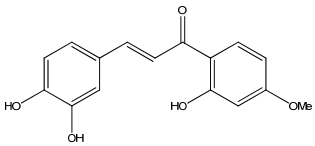
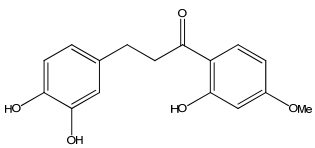
29	4'-O-β-D-(2''-p-coumaroyl)glucopyranosyl-4,2',3'-trihydroxychalcone	
30	4'-O-β-D-(2''-p-coumaroyl)-6''-acetylglucopyranosyl-4,2',3'-trihydroxychalcone	
31	3'-(3-methyl-2-butenyl)-4'O-β-D-(glucopyranosyl-4,2'-dihydroxy chalcone	
32	4'-O-β-D-(2''-acetyl-6''-cinnamoyl)glucopyranosyl-4,2',3'-trihydroxychalcone	
33	Uvangoletin	
34	Flavokawin B	

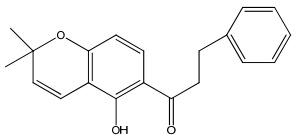
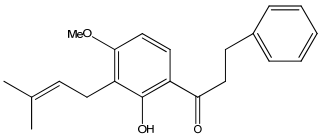
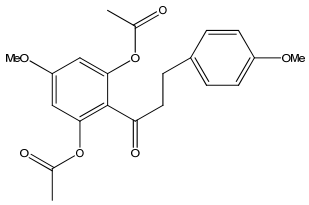
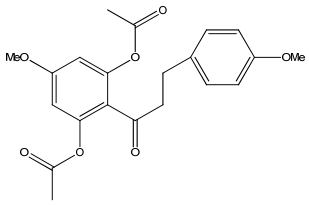
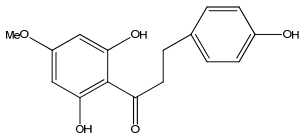
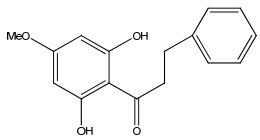
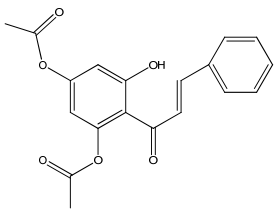
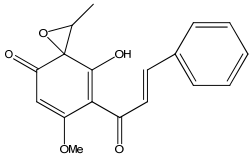
35	5,7-dimethylpinocembrin	
36	2'-methoxyhelikrausichalcone	
37	Cedrediprenone	
38	cedreprenone	
39	Phloridzin	
40	Seboldin	
41	Trilobatin	
42	Davidigenin-2'-O-(6"-O-4"'-Hydroxybenzoyl)-¡l-glucoside	

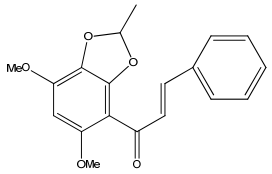
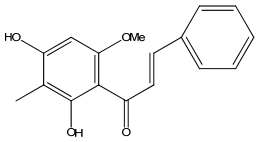
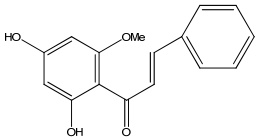
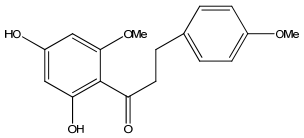
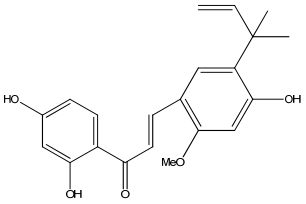
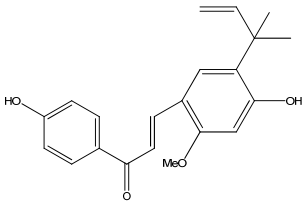
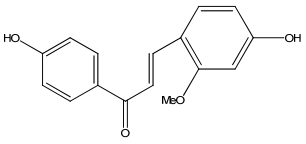
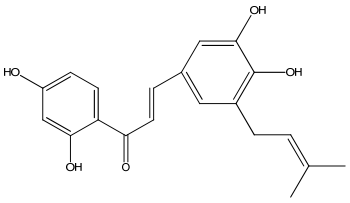
43	Davidigenin-2'-O-(2"-O-4'"-hydroxybenzoyL)-β-glucoside	
44	Davidigen-2'-O-(3"-O-4'"-hydroxybenzoyl)-β-glucoside	
45	Davidigenin-2'-O-(6"-O-syringoyl)-β-glucopyranoside	
46	1-O-3,4-dimethoxy-5-hydroxyphenyl-6-O-(3,5-di-O-methylgalloyl)-β-glucopy ranoside	
47	Davidioside	
48	4'-O-methyldavidioside	

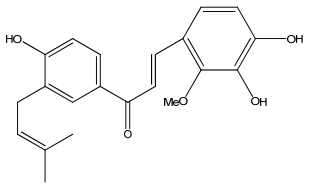
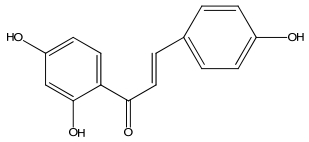
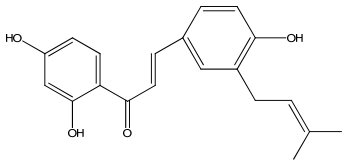
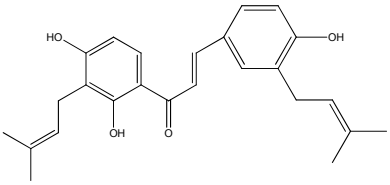
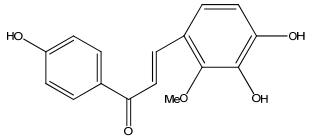
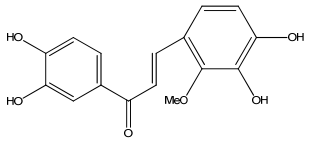
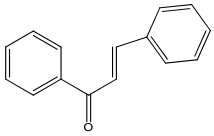
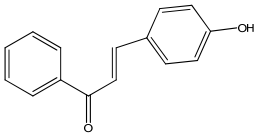
49	Davidigenin	
50	Phloretin 4'-O-methyl ether (2',6'-dihydroxy-4'-methoxydihydrochalcone)	
51	Myrigalone G	
52	Aspalathin	
53	Nothofagin	
54	Dihydrochalcones hostmanin A	
55	Hostmanin B	

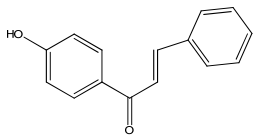
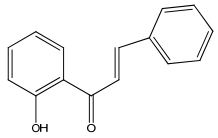
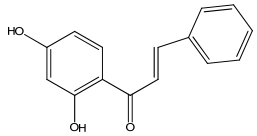
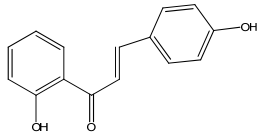
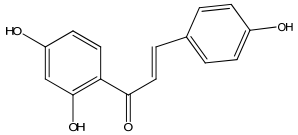
56	Hostmanin C	
57	Hostmanin D	
58	2',6'-dihydroxy-4'-methoxydihydrochalcone	
59	linderatone	
60	Adunctin E	
61	(-)-methyllinderatin	
62	Xanthohumol	

63	Isoxanthohumol	
64	licochalcone E	
65	2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone	
66	2',6'-dihydroxy-4'-methoxychalcone	
67	2',6'-dihydroxy-4'-methoxydihydro chalcone	
68	2' 6' -dihydroxy-4,4' –dimethoxy dihydrochalcone	
69	Phloretin	
70	Calythropsin	
71	Dihydrocalythropsin	

72	Chalcone derricin	
73	lonchocarpin	
74	4,10',6'-diacetoxy-4,4'-dimethoxydihydrochalcone	
75	Dihydrochalcones 10',6'-diacetoxy-4,4'-dimethoxydihydrochalcone	
76	4,2',6'-trihydroxy-4'-methoxy dihydrochalcone	
77	2',6'-dihydroxy-4'-methoxydihydrochalcone	
78	2',4'-diacetoxy chalcone	
79	Litseaone A	

80	Litseaone B	
81	Stercurensin	
82	cardamonin	
83	2',4'- dihydroxy-4,6'-dimethoxydihydrochalcone	
84	Licochalcone G	
85	licochalcone A	
86	Echinantin	
87	5-prenylbutein	

88	licochalcone D	
89	Isoliquiritigenin	
90	licoagrochalcone A	
91	kanzonol C	
92	Licochalcones A	
93	Licochalcones B	
94	Chalcone	
95	4-Hydroxychalcone	

96	4'-Hydroxychalcone	
97	2'-Hydroxychalcone	
98	2',4'-Dihydroxychalcone	
99	2',4-Dihydroxychalcone	
100	2',4',4-Trihydroxychalcone	
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