frontiers | Frontiers in Chemistry

TYPE Review
PUBLISHED 15 August 2022
DOI 10.3389/fchem.2022.964089

OPEN ACCESS

EDITED BY
Raghu Raj,
DAV College Amritsar, India

REVIEWED BY
Vera L. M. Silva,
University of Aveiro, Portugal
Sumit Kumar,
University of Cape Town, South Africa

*CORRESPONDENCE
Feng Sang,
fengsang@sdut.edu.cn

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Medicinal and Pharmaceutical Chemistry, a section of the journal Frontiers in Chemistry

RECEIVED 08 June 2022
ACCEPTED 20 July 2022
PUBLISHED 15 August 2022

CITATION
Zhai J, Sun B and Sang F (2022), Progress of isolation, chemical synthesis and biological activities of natural chalcones bearing 2-hydroxy-3-methyl-3-butenyl group. *Front. Chem.* 10:964089. doi: 10.3389/fchem.2022.964089

Progress of isolation, chemical synthesis and biological activities of natural chalcones bearing 2-hydroxy-3-methyl-3-butenyl group

Jiadai Zhai[1,2†], Bingxia Sun[1†] and Feng Sang[1*]

[1]Research Center of Chemical Biology and Pharmaceutical Chemistry, School of Life Sciences and Medicine, Shandong University of Technology, Zibo, China, [2]School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, China

Chalcones have a three-carbon α,β-unsaturated carbonyl system composed of two phenolic rings. Many chalcones have shown broad spectrum of biological activities with clinical potentials against various diseases. They are usually abundant in seeds, fruit skin, bark and flowers of most edible plants. Among them, chalcones bearing 2-hydroxy-3-methyl-3-butenyl (HMB) group have been reported several times in the past few decades due to their novel scaffolds and numerous interesting biological activities. In this paper, we reviewed the isolation of twelve natural chalcones and a natural chalcone-type compound bearing 2-hydroxy-3-methyl-3-butenyl group discovered so far, and reviewed their synthesis methods and biological activities reported in the literature. We anticipate that this review will inspire further research of natural chalcones.

KEYWORDS

chalcone, 2-hydroxy-3-methyl-3-butenyl, isolation, synthesis, biological activity

1 Introduction

The existing chalcones mainly include natural products and synthetic compounds (Rudrapal et al., 2021; Zhang et al., 2021; Yuan et al., 2022), and have been shown to exhibit a variety of biological activities, such as anticancer (Konieczny et al., 2007), anti-inflammatory (Nowakowska, 2007), antibacterial (Nielsen et al., 2005), antiviral (Duran et al., 2021), antimalaria (Smit and N'Da, 2014), and so on. It is an important approach for preclinical drug development to find new scaffolds from natural products and screen out lead compounds with high activity and low toxicity through chemical synthesis and structure-activity relationship study (SAR) (Gomes et al., 2017; Duvauchelle et al., 2021; Jasim et al., 2021; Knockleby et al., 2021). Chalcones have been extensively studied, and many reviews have been published in a wide variety of journals (Zhuang et al., 2017; Qin et al., 2020; Salehi et al., 2021). However, to our knowledge, there is no review of natural chalones bearing HMB group so far. Since the 1990s, twelve natural chalcones (1–7, 9–13) and a natural chalcone-type compound (8, Angusticornin A) with HMB group on A-ring or B-ring have been isolated and reported successively (Baba et al., 1990; Hano et al., 1995; Pistelli et al., 1996; Stevens et al., 2000; ElSohly et al., 2001; Ngameni et al., 2004; Ngadjui et al., 2005; RenQi and Shi, 2008; Shaffer et al., 2016; Yang and Jiang, 2021)

(Figure 1). And the HMB group in their structures have also been proved to be an essential functional group for some biological activities (Sugii et al., 2005; Park et al., 2015). This review provides a research progress of the isolation, chemical synthesis and biological activities of natural chalcones bearing HMB group, and the plant species and biological activities of these chalcones are illustrated in Table 1.

2 Natural chalcones and a natural chalcone-type compound bearing HMB group

2.1 Xanthoangelol D (1)

2.1.1 Isolation and biological activities

Xanthoangelol D and five other chalcones were extracted from fresh roots of *Angelica keiskei* collected in Hachijyo Island (Japan) by using ethyl acetate (Baba et al., 1990). Subsequently, the results of Sugii et al. showed that Xanthoangelol D suppresses basal and tumor necrosis factor-α-induced endothelin-1 (ET-1) production, by inhibiting the activation of nuclear factor-kappa B (NF-κB), therefore, may be useful for the treatment of diseases involved NF-κB activation (Sugii et al., 2005). Kil et al. also isolated Xanthoangelol D from the aerial parts of *Angelica keiskei* Koidzumi together with twelve other chalcones, and Xanthoangelol D did not exhibit significant activity in the assay of promoter activity on heat shock protein 25 (*hsp25*, murine form of human *hsp27*) (Kil et al., 2015). Xanthoangelol D showed strong potein tyrosine phosphatase 1B (PTP1B) inhibitory effect with IC_{50} value of 3.97 ± 0.37 μg/ml (Li et al., 2015). Interestingly, the inhibitory effects of Xanthoangelol D (substitution of A-ring with the HMB group) on severe acute respiratory syndrome coronavirus (SARS-CoV) chymotrypsin-like protease activity produced 4-

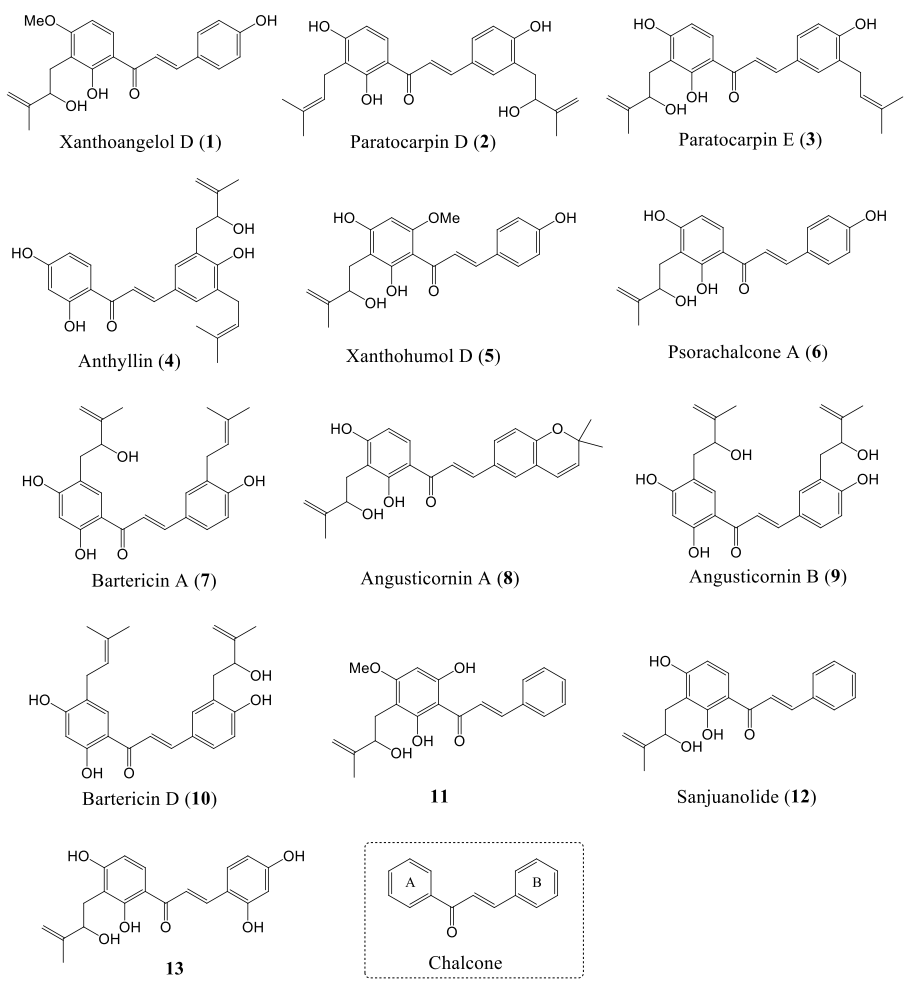


FIGURE 1
Structures of natural chalcones and a chalcone-type compound bearing HMB group (**1**-**13**) and chalcone.

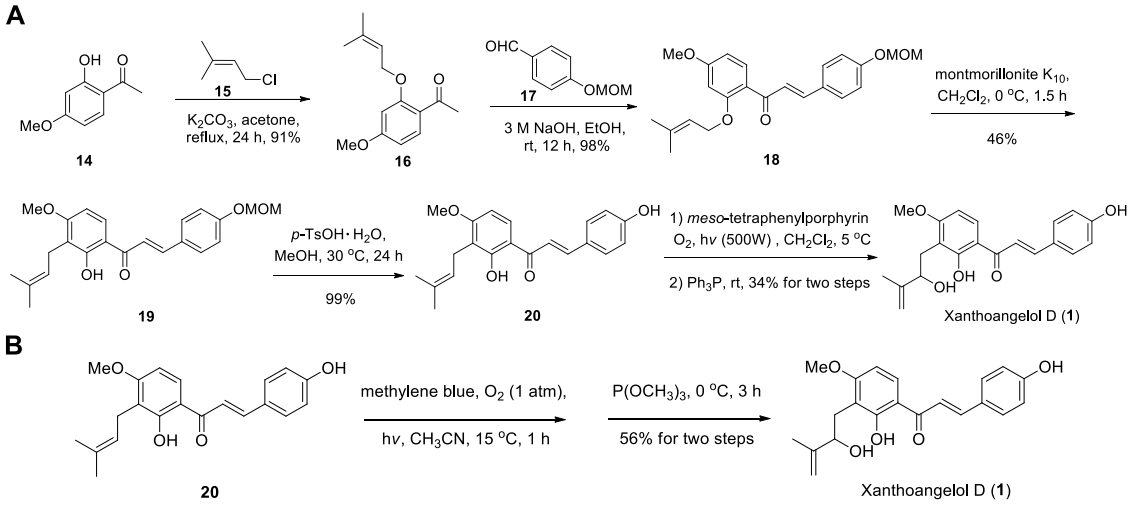
TABLE 1 Plant species and biological activities of natural chalcones bearing HMB group.

Chalcones	Plant Species	Biological Activities	References
Xanthoangelol D (**1**)	*Angelica keiskei*	NF-κB inhibitory activity	Baba et al. (1990)
		Enzyme inhibitory activity	Sugii et al. (2005)
		Antiviral activity	Li et al. (2015)
			Park et al. (2015)
Paratocarpin D (**2**)	*Paratocarpus venenosa*	No cytotoxic or anti-inflammatory activity	Hano et al. (1995)
	Adansonia digitata L.		Liu et al. (2018)
			Ibraheem et al. (2021)
Paratocarpin E (**3**)	*Paratocarpus venenosa*	Cytotoxic activity	Hano et al. (1995)
	Hedysarum gmelinii	Anti-inflammatory activity	Liu et al. (2005)
	Euphorbia humifusa	Antibacterial activity	Gao et al. (2016)
			Liu et al. (2018)
			Li et al. (2019)
Anthyllin (**4**)	*Anthyllis hermanniae*	Unreported	Pistelli et al. (1996)
	Humulus lupulus cv.	Anti-inflammatory activity	Stevens et al. (2000)
	Humulus lupulus L.	Enzyme inhibitory activity	Zhao et al. (2003)
	Humulus lupulus L.	Enzyme inhibitory activity	Liu et al. (2005)
	Humulus lupulus L.	Antioxidant and cytotoxic activity	Choi et al. (2011)
Xanthohumol D (**5**)	*Humulus lupulus*	Enzyme inhibitory activity	Tronina et al. (2013)
		Anti-inflammatory activity	Yu et al. (2014)
	Humulus lupulus L.	Antibacterial activity	Sangiovanni et al. (2019)
			Fu et al. (2020)
Psorachalcone A (**6**)	*Maclura tinctoria* L.	Antifungal activity	ElSohly et al. (2001)
	Psoralea corylifolia	Enzyme inhibitory activity	Li et al. (2002)
	Dorstenia angusticornis and *Dorstenia barteri* var. *subtriangularis*	No antibacterial activity	Yin et al. (2004)
	Morus nigra	No cytotoxic activity	Ngadjui et al. (2005)
		Antibacterial activity	Zhai et al. (2019)
		No enzyme inhibitory activity	Li et al. (2019)
			Wang et al. (2021)
Bartericin A (**7**)	*Dorstenia barteri* var. *subtriangularis*	Antibacterial activity	Ngameni et al. (2004)
			Fu et al. (2020)
Bartericin D (**10**)	*Dorstenia barteri* var. *subtriangularis*	Unreported	Ngameni et al. (2004)
Angusticornin A (**8**)	*Dorstenia angusticornis* and *Dorstenia barteri* var. *subtriangularis*	Antibacterial activity	Ngadjui et al. (2005)
			Fu et al. (2020)
Angusticornin B (**9**)	*Dorstenia angusticornis* and *Dorstenia barteri* var. *subtriangularis*	Synergistic antibacterial activity	Ngadjui et al. (2005)
			Kuete et al. (2011)
chalcone **11**	*Anaphalis lactea*	No antibacterial activity	RenQi and Shi. (2008)
			Fu et al. (2020)
Sanjuanolide (**12**)	*Dalea frutescens*	Cytotoxic activity	Shaffer et al. (2016)
	Artocarpus integer	Cytotoxic activity	Zhai et al. (2019)
		Anti-inflammatory activity	Fang et al. (2019)
			Duong et al. (2021)
chalcone **13**	*Morus alba*	Antioxidant activity	Yang and Jiang. (2021)

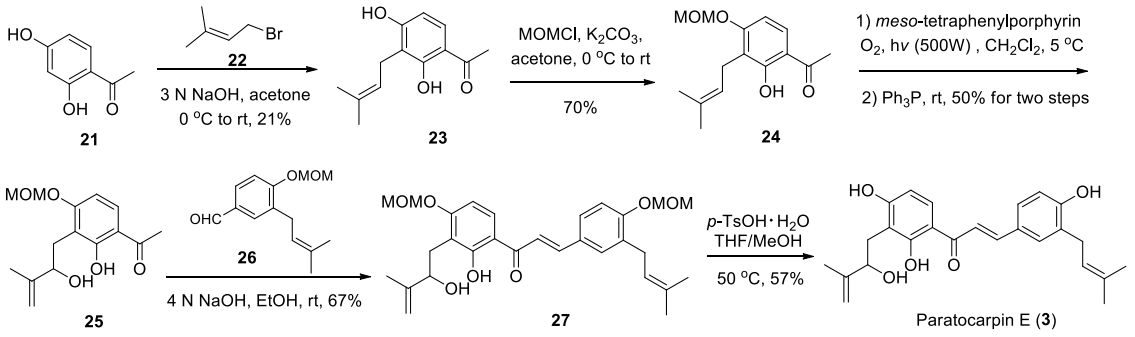
fold (IC_{50} = 26.6 ± 5.2 μM) higher potency than analogue that substitution of A-ring with the 3-methyl-2-butenyl group (Park et al., 2015). Furthermore, Xanthoangelol D did not exhibit anti-platelet-activities *in vivo* according to Ohkura et al. (Ohkura et al., 2016).

2.1.2 Chemical synthesis

Li et al. reported the first synthesis of Xanthoangelol D with Schenck ene reaction using tetraphenylporphin (TPP) as the photosensitizer followed by reduction with triphenylphosphine (Li et al., 2019), and the key intermediate **20** can be obtained through



SCHEME 1
(A) Synthesis of Xanthoangelol D by Li et al.; **(B)** Synthesis of Xanthoangelol D by Sugamoto et al.



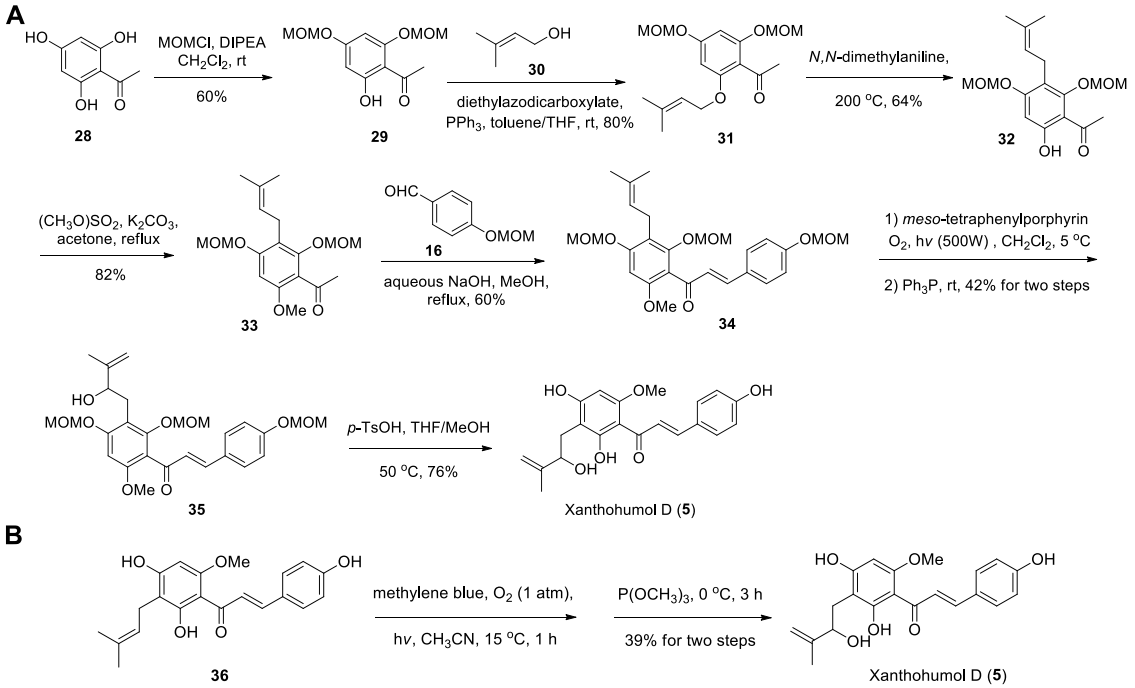
SCHEME 2
Synthesis of Paratocarpin E.

Claisen-Schmidt condensation, [1,3]-sigmatropic rearrangement and deprotection by using the method of Sugamoto et al. (Sugamoto et al., 2008; Sugamoto et al., 2011) (Scheme 1A). One year later, Sugamoto et al. synthesized Xanthoangelol D in 56% yield by using the photooxygenation of prenylated chalcone **(20)** in the presence of methylene blue in acetonitrile followed by reduction with trimethylphosphite (Sugamoto et al., 2020) (Scheme 1B). These two methods described above provide important reference for the construction of HMB group in chalcone derivatives.

2.2 Paratocarpin D and E (2, 3)

2.2.1 Isolation and biological activities

In 1995, Paratocarpin D and E were isolated from the Indonesian moraceous plant (Bark of *Paratocarpus venenosa* Zoll) by Hano et al. (1995) for the first time. Liu et al. (2005) also reported the isolation of Paratocarpin E along with two other new chalcones from the roots of *Hedysarum gmelinii* (collected from Inner Mongolia, China), and it was the first time that Paratocarpin E has been isolated from *Hedysarum* genus (Liu et al., 2005). Gao et al. isolated Paratocarpin E from *Euphorbia humifusa* Wild., and Paratocarpin E showed significant cytotoxicity against five cancer cell lines (MCF-7, 786-O, 769-P, U-937 and HL-60) with IC_{50} values ranging from 19.6 to 28.6 μM. According to the report, Paratocarpin E typical apoptosis of MCF-7 cells by activating p38 and JNK and inhibiting Erk pathway, and affect apoptosis and autophagy by promotes the activation and nuclear translocation of NF-κB (Gao et al., 2016; Al-Emam et al., 2019). Paratocarpin D and E were evaluated for antiproliferative activity against five human cancer cell lines (HepG2, A549, Du145, BGC823, and HCT116) and *in vitro* anti-inflammatory activity by

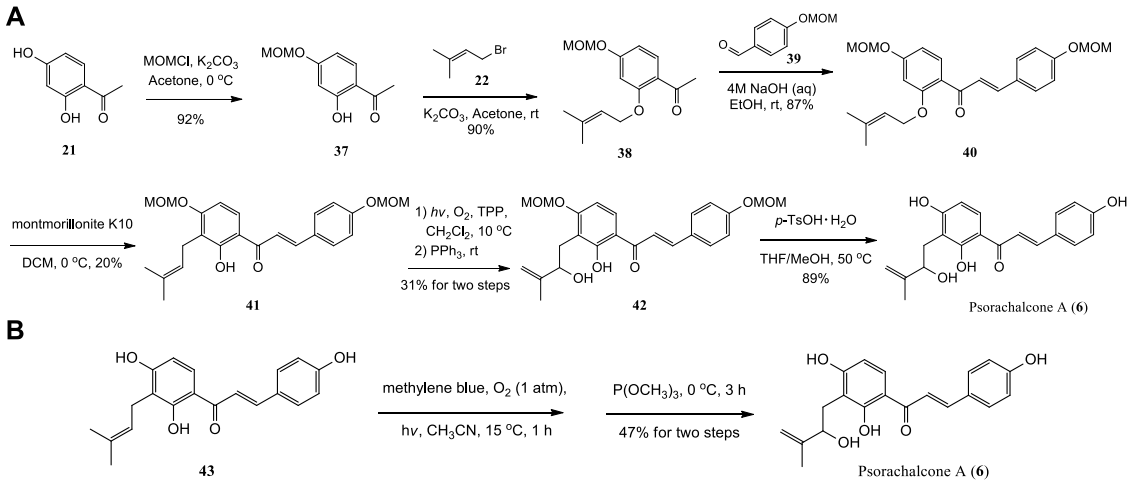


SCHEME 3
(A) Synthesis of Xanthohumol D by Fu et al.; **(B)** Synthesis of Xanthohumol D by Sugamoto et al.

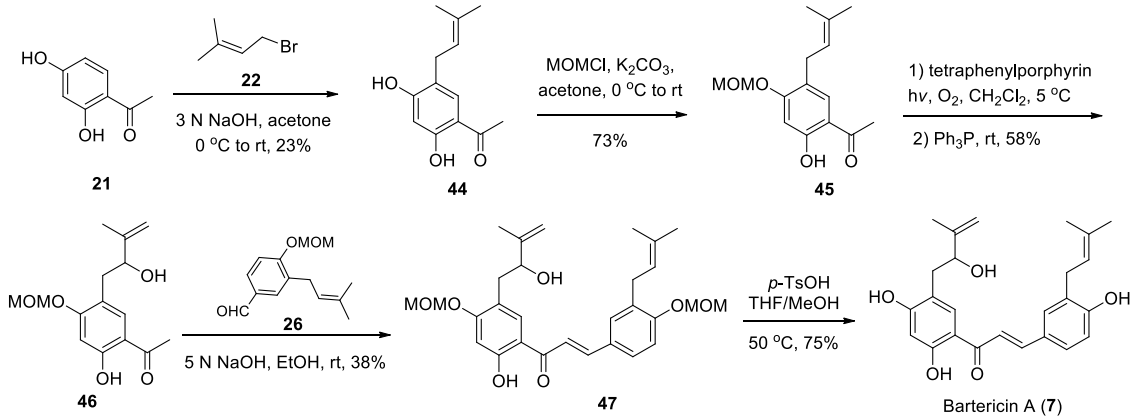
Liu et al. (2005) but only Paratocarpin E exhibited weak inhibitory effects (IC_{50} values in the range of 10.33–18.18 μM) on lipopolysaccharide-induced nitric oxide production in murine microglial BV-2 cells (Liu et al., 2018). Furthermore, the racemate Paratocarpin E obtained by chemical synthesis exhibited significant antibacterial activity (MIC = 6.25 μg/ml) against *Bacillus subtilis* strain (Li et al., 2019). In 2021, Ibraheem et al. isolated Paratocarpin D from baobab (*Adansonia digitata* L.) fruit pulp methanolic extract, however, no activity data of individual compounds were reported (Ibraheem et al., 2021).

2.2.2 Chemical synthesis

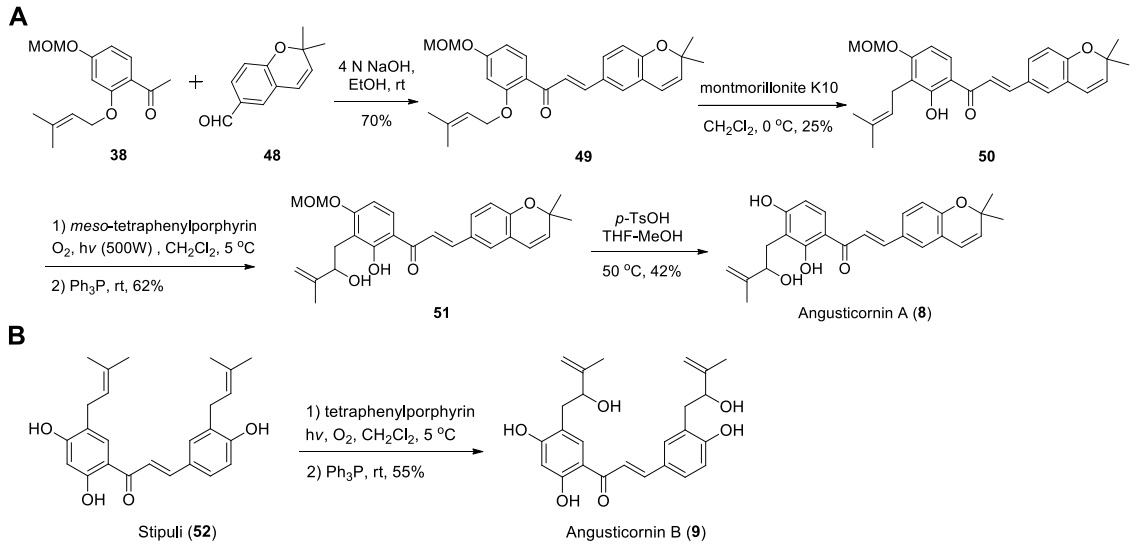
Li et al. reported the synthesis of Paratocarpin E using key intermediate **24** as the starting material, employing Schenck ene reaction, Claisen-Schmidt condensation and



SCHEME 4
(A) Synthesis of Psorachalcone A by Zhai et al.; **(B)** Synthesis of Psorachalcone A by Sugamoto et al.



SCHEME 5
Synthesis of Bartericin A.



SCHEME 6
(A) Synthesis of Angusticornin A; **(B)** Synthesis of Angusticornin B.

deprotection, respectively (Li et al., 2019) (Scheme 2). And the intermediate **24** can be prepared from 2,4-dihydroxyacetophenone **(21)** in two steps (Dong et al., 2007). However, the chemical synthesis of Paratocarpin D has not been reported yet.

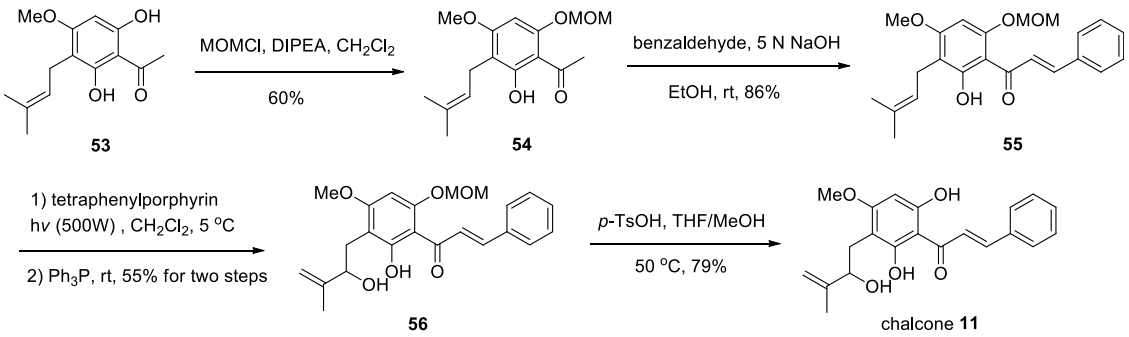
2.3 Anthyllin (4)

In 1996, Anthyllin has been isolated from the aerial parts of *Anthyllis hermanniae*, along with six chalcone and isoflavonoid derivatives (Pistelli et al., 1996). Up to now, there have been no previous reports on biological activity or chemical synthesis of Anthyllin.

2.4 Xanthohumol D (5)

2.4.1 Isolation and biological activities

In 2000, Xanthohumol D was isolated from *Humulus lupulus* cv. "Galena" by Stevens et al. for the first time (Stevens et al., 2000; Bocquet et al., 2018; Zhou et al., 2021). Zhao et al. isolated Xanthohumol D from the ethyl acetate fraction of *Humulus lupulus* L., and Xanthohumol D significantly inhibited NO



SCHEME 7
Synthesis of chalcone **11**.

production at 5 μg/ml (completely suppressed the expression of inducible NO synthase induced by lipopolysaccharide/IFN-γ) (Zhao et al., 2003; Zhao et al., 2005). In 2004, Chadwick et al. isolated Xanthohumol D from spent Nugget hop pellets (*Humulus lupulus* L. cv. Nugget) by supercritical CO_2 extraction Chadwick et al. (2004). Subsequently, Xanthohumol D was tested for induction of quinone reductase in Heap 1c1c7 murine hepatoma cells by Liu et al. (2005) and the CD value was 7.4 ± 0.7 μM. Chesnokova et al. also isolated Xanthohumol D from hops (*Humulus lupulus*) by using Soxhlet apparatus Chesnokova et al. (2009). Choi et al. isolated Xanthohumol D from ethanolic extract of hops (*Humulus lupulus* L.), and Xanthohumol D was used to determine the inhibition of quinone reductase-2 (IC_{50} = 110 ± 27 μM) (Choi et al., 2011; Cieśla and Moaddel, 2016; Wei et al., 2016; Chen et al., 2018). Tronina et al. (2013) assessed the ability of Xanthohumol D to scavenge 2,2′-diphenyl-1-picrylhydrazyl (DPPH) radicals (IC_{50} = 2.37 ± 0.40 μM). In addition, the antiproliferative activity of Xanthohumol D against MCF-7 (IC_{50} = 20.60 ± 0.22 μM), PC-3 (IC_{50} = 37.88 ± 13.90 μM) and HT-29 (IC_{50} = 78.33 ± 8.83 μM) human cancer cell lines were also determined. Yu et al. (2014) isolated Xanthohumol D and seven other chalcones from *Humulus lupulus*, and the quinone reductase induction activity results showed that Xanthohumol D has moderate activity (IR = 2.22 ± 0.05, viability = 0.45%) in using human Heap 1c1c7 cells at the concentration of 20 μM. Sangiovanni et al. (2019) isolated Xanthohumol D from hop extracts (*Humulus lupulus* L. cultivar Cascade), and reported the anti-inflammatory activity of the hop extracts (Xanthoangelol D and Xanthoangelol A as the main active components) in human gastric epithelial cells. Fu et al. (2020) evaluated the antibacterial activities of synthetic Xanthohumol D against two Gram positive bacteria (*Staphylococcus aureus* CMCC 26003, *Bacillus subtilis* CMCC(B) 63,501) and two Gram negative bacteria (*Escherichia coli* CMCC 44102, *Pseudomonas aeruginosa* CMCC (B) 10,104), and Xanthohumol D showed significant activity towards *Bacillus subtilis* (MIC = 12.5 μg/ml) but no obvious inhibitory activity to the other three strains (MIC > 200 μg/ml).

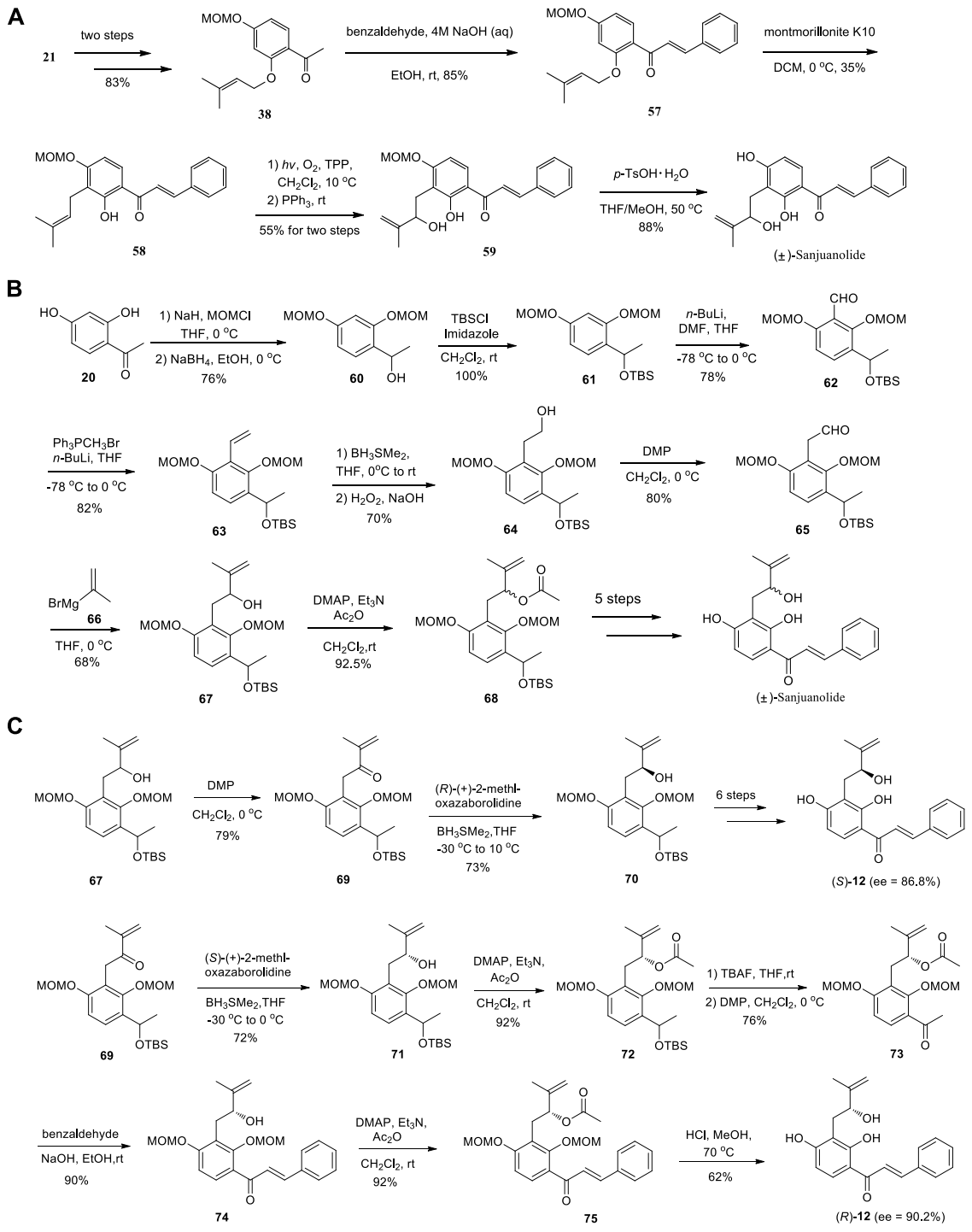
2.4.2 Chemical synthesis

Fu et al. reported the first synthesis of Xanthohumol D commenced from the Schenck ene reaction of intermediate **34**, which introduced the HMB groups. Then **35** was carried out in using catalytic amounts of *p*-TsOH leading to the target product Xanthohumol D (Fu et al., 2020) (Scheme 3A). The key intermediate **34** was prepared from **28** by using the method of Khupse et al. (Khupse and Erhardt, 2007). Sugamoto et al. (2020) also synthesized Xanthohumol D by using the same procedure employed for the synthesis of Xanthoangelol D from prenylated chalcone **(36)** (Scheme 3B).

2.5 Psorachalcone A (6)

2.5.1 Isolation and biological activities

In 2001, ElSohly et al. isolated 2′,4′,4,2″-tetrahydroxy-3′-[3″-methylbut-3″-enyl]-chalcone **(6)** from an ethanol extract of the leaves of *Maclura tinctoria* (L.) Gaud, but did not give it a Latin name. Chalcone **6** showed inhibitory activity against *Candida albicans* (IC_{50} = 15 μg/ml) and *Cryptococcus neoformans* (IC_{50} = 7 μg/ml) (ElSohly et al., 2001; Nowakowska, 2007). Li et al. (2002) evaluated the fatty acid synthase inhibitory activity of chalcone **6**, and chalcone **6** exhibited marginal activity with IC_{50} of 46 μg/ml. Compound **6** was also isolated from the seeds of *Psoralea corylifolia*, and did not showed significant antibacterial activities against two pathogenic bacteria *Staphylococcus aureus* and *S. epidermidis* (MIC > 0.147 mM) (Yin et al., 2004). Ngadjui et al. (2005) isolated chalcone **6** from the twigs of *Dorstenia angusticornis* and *Dorstenia barteri* var. *subtriangularis*.



SCHEME 8
(A) Synthesis of (±)-Sanjuanolide by Zhai et al.; **(B)** Synthesis of (±)-Sanjuanolide by Fang et al.; **(C)** Synthesis of (*S*)-Sanjuanolide and (*R*)-Sanjuanolide by Fang et al.

Until 2005, Yu et al. isolated chalcone **6** and named it as Psorachalcone A (Yu et al., 2005; Xu et al., 2012). Zhai et al. evaluated the antiproliferative effects of synthetic Psorachalcone A against five cancer cells (PC-3, A375, PANC-1, A549 and MDA-MB-231), but no obvious inhibitory activity was observed (IC_{50} > 25 μM) (Zhai et al., 2019). Li et al. (2019) evaluated the antibacterial activities

of synthetic Psorachalcone A against two Gram positive bacteria and two Gram negative bacteria, and Psorachalcone A showed slight activity towards Gram-positive bacteria (*Staphylococcus aureus*, MIC = 50 μg/ml; *Bacillus subtilis*, MIC = 25 μg/ml) but no obvious activity to Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*, MIC > 200 μg/ml). In 2021, Psorachalcone A was isolated from the fruits of *Morus nigra* Linn., and did not exhibit obvious effect of inhibiting 3-phosphoglycerate dehydrogenase (Wang et al., 2021).

2.5.2 Chemical synthesis

The first synthesis of Psorachalcone A and its new analogues were achieved from 2,4-dihydroxyacetophenone **(21)** through six steps by Zhai et al. (2019). Methoxymethyl (MOM) was used to protect the C4′-hydroxy group of 21 selectively. And MOM-protected **37** was prenylated with bromide **22** to afford **38**, which was further reacted with 39 to afford **40** by Claisen-Schmidt condensation. Then **40** was subjected to [1,3]-sigmatropic rearrangement, Schenck ene reaction and deprotection to obtain Psorachalcone A (Scheme 4A). Sugamoto et al. (2020) synthesized Psorachalcone A by using the same procedure employed for the synthesis of Xanthoangelol D from prenylated chalcone **(43)** (Scheme 4B).

2.6 Bartericin A and D (7, 10)

2.6.1 Isolation and biological activities

Bartericin A and Bartericin D were isolated from the twigs of *Dorstenia barteri* var. *subtriangularis* successively, along with several other diprenylated chalcones (Ngameni et al., 2004; Ngadjui et al., 2005). (±)-Bartericin A obtained by the synthetic method was used to evaluate its antibacterial activity, and it showed moderate inhibitory activity against two Gram positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*, MIC = 25 μg/ml) (Fu et al., 2020).

2.6.2 Chemical synthesis

Fu et al. completed the first chemical synthesis of Bartericin A from the key intermediate **45** (Fu et al., 2020), and the preparation of **45** referred to the report of Dong et al. (Tan et al., 1999; Dong et al., 2007), which is similar to the synthetic steps of Paratocarpin E (Scheme 5). In addition, the chemical synthesis of Bartericin D has not been reported until now.

2.7 Angusticornin A and B (8, 9)

2.7.1 Isolation and biological activities

Angusticornin A and B were first isolated from the twigs of *Dorstenia angusticornis* and *Dorstenia barteri* var. *subtriangularis* (Ngadjui et al., 2005; Simo et al., 2005). According to the report by Kuete et al., Angusticornin B didn′t exhibit obvious antimicrobial activity against a serials of Gram-negative multidrug-resistant bacteria, but increased significantly against *Escherichia coli* AG100A (MIC values, 64 vs. 16 mg/L) in the presence of the efflux pump inhibitor phenylalanine arginine β-naphthylamide (20 mg/L) (Kuete et al., 2011). Angusticornin A and B obtained by the synthetic method were used to evaluate their antibacterial activities, and only Angusticornin A showed moderate inhibitory activity against *Bacillus subtilis* (MIC = 25 μg/ml) (Li et al., 2019; Fu et al., 2020).

2.7.2 Chemical synthesis

Angusticornin A was synthesized from methyl ketone **38** and aldehyde **48** (Damodar et al., 2017) through Claisen-Schmidt condensation, [1,3]-sigmatropic rearrangement, Schenck ene reaction and deprotection (Li et al., 2019) (Scheme 6A). Angusticornin B was prepared from natural product Stipulin **(52)** by Schenck ene reaction (Scheme 6B) Fu et al. (2020).

2.8 2′,6′-dihydroxy-3′-(2-hydroxy-3-methyl-3-butenyl)-4′-methoxychalcone (11)

2.8.1 Isolation and biological activities

Ren et al. isolated chalcone **11** from the whole plant of *Anaphalis lactea* (RenQi and Shi, 2008). The synthetic chalcone **11** was evaluated the antibacterial activities against two Gram positive bacteria (*Staphylococcus aureus* CMCC 26003, *Bacillus subtilis* CMCC(B) 63,501) and two Gram negative bacteria (*Escherichia coli* CMCC 44102, *Pseudomonas aeruginosa* CMCC(B) 10,104), but no obvious activity was observed in the four test strains (MIC > 200 μg/ml) (Fu et al., 2020).

2.8.2 Chemical synthesis

According to Fu et al., methoxymethylation of compound **53** (Grayfer et al., 2016), and then subjected to Claisen-Schmidt condensation, Schenck ene reaction, and demethoxymethylation of **56** to obtain chalcone **11** (Fu et al., 2020) (Scheme 7).

2.9 Sanjuanolide (12)

2.9.1 Isolation and biological activities

In 2016, Sanjuanolide was isolated from *Dalea frutescens* by Shaffer et al., and it exhibited slightly greater cytotoxic activities against PC-3 (IC_{50} = 11 ± 4 μM) and DU 145 (IC_{50} = 7 ± 3 μM) prostate cancer cell lines (Shaffer et al., 2016). Sanjuanolide was also isolated from the leaves and stem bark of *Artocarpus integer* in 2021 (Duong et al., 2021). Zhai et al. (2019) reported the anti-cancer activities of the synthetic Sanjuanolide against PC-3, A375, PANC-1, A549 and MDA-MB-231 cell lines, and Sanjuanolide showed moderate inhibitory activity against PC-3 (IC_{50} = 17.5 μM) and A375 (IC_{50} = 13.1 μM) cells. According to the report of Fang et al., (*R*)-Sanjuanolide efficiently inhibited the lipopolysaccharides-

induced expression of tumor necrosis factor alpha and interleukin-6 (IC_{50} = 1.1 μM), but (*S*)-Sanjuanolide didn′t showed significant anti-inflammatory effect. Furthermore, (*R*)-Sanjuanolide effectively inhibited the mRNA expression of several inflammatory cytokines after the lipopolysaccharides challenge *in vitro* (Fang et al., 2019).

2.9.2 Chemical synthesis

Zhai et al. (2019) completed the total synthesis of (±)-Sanjuanolide from commercially available materials in seven steps (12% overall yield) (Scheme 8A), along with its seven new analogues. At the same time, Fang et al. completed the total synthesis of (±)-Sanjuanolide (Scheme 8B) in 15 steps with overall yield of 3.8%. In addition, (*S*)-Sanjuanolide and (*R*)-Sanjuanolide were also prepared in 17 steps with overall yields of 7.3% and 4.2%, respectively (Fang et al., 2019) (Scheme 8C).

2.10 2,2′,4,4′-tetrahydroxy-3-(2″-hydroxy-3″-methylbutyl-3″-alkenyl) chalcone (13)

Chalcone **13** was isolated from a *Morus alba* leaf by Yang et al., and it has a high free radical scavenging capacity while exhibits an IC_{50} of 21.6 μM against DPPH radicals (Yang and Jiang, 2021). In addition, no chemical synthesis of chalcone **13** has been reported so far.

3 Conclusion and outlook

Chalcone scaffolds, which is considered as the key bioactive precursors of plant flavonoids, have attracted more and more attention in medicinal chemistry and pharmacology. Herein, the isolation, chemical synthesis and biological activities of twelve natural chalcones and a chalcone-type compound bearing HMB group are reviewed. Although only a few dozen isolated or synthesized chalcones with HMB group have been reported, their various biological activities have aroused extensive interest of academic researchers, and it is believed that more and more natural or synthetic chalcones with HMB group will be presented in the further study. Furthermore, natural flavonoids with HMB group, which showed exciting biological activities, have also been reported by researchers in the past several decades, such as Ephedroidin and Dinklagin C (Lee et al., 1998; Pistelli et al., 1998; Xu et al., 2015; Owor et al., 2020). Moreover, further research on chalcones with HMB group might have much potential for drug discovery, especially as an adjuvant for a combination strategy between antibiotics and chalcones. And further studies on SAR, pharmacokinetics and toxicology are still needed, since the chemistry and biological importance of these biologically active compounds have not been systematically explored. Therefore, rational chemical derivatization of the natural chalcones and flavonoids bearing HMB group is necessary for further investigation of SAR, which play a key role in the screening of novel lead compounds.

Author contributions

JZ and BS: wrote the original draft. FS: conceived the topic and approved the final draft. All authors read and gave approval to the final draft.

Funding

This work was supported by the Natural Science Foundation of Shandong Province (No. ZR2021MB093), (No. ZR2021QH177) and (No. ZR2016HQ04).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Al-Emam, A., Al-Shraim, M., Eid, R. A., Jamil, A.-M., Moustafa, M. F., and Radad, K. (2019). Cytotoxicity of *Euphorbia peplus* extract on MCF7 breast cancer cells. *Folia Biol. (Praha).* 67 (3), 127–139. doi:10.3409/fb_67-3.13

Baba, K., Nakata, K., Taniguchi, M., Kido, T., and Kozawa, M. (1990). Chalcones from *Angelica keiskei*. *Phytochemistry* 29 (12), 3907–3910. doi:10.1016/0031-9422(90)85357-L

Bocquet, L., Sahpaz, S., Hilbert, J. L., Rambaud, C., and Rivière, C. (2018). *Humulus lupulus* L., a very popular beer ingredient and medicinal plant: Overview of its phytochemistry, its bioactivity, and its biotechnology. *Phytochem. Rev.* 17, 1047–1090. doi:10.1007/s11101-018-9584-y

Chadwick, L. R., Nikolic, D., Burdette, J. E., Overk, C. R., Bolton, J. L., Breemen, R. B., et al. (2004). Estrogens and congeners from spent hops (*Humulus lupulus*). *J. Nat. Prod.* 67 (12), 2024–2032. doi:10.1021/np049783i

Chen, G., Huang, B. X., and Guo, M. (2018). Current advances in screening for bioactive components from medicinal plants by affinity ultrafiltration mass spectrometry. *Phytochem. Anal.* 29 (4), 375–386. doi:10.1002/pca.2769

Chesnokova, A. N., Lutskii, V. I., and Gorshkov, A. G. (2009). Prenylated chalcones from *Humulus lupulus*. *Chem. Nat. Compd.* 45 (5), 712–714. doi:10.1007/s10600-009-9424-9

Choi, Y., Jermihov, K., Nam, S.-J., Sturdy, M., Maloney, K., Qiu, X., et al. (2011). Screening natural products for inhibitors of quinone reductase-2 using ultrafiltration LC-MS. *Anal. Chem.* 83 (3), 1048–1052. doi:10.1021/ac1028424

Cieśla, Ł., and Moaddel, R. (2016). Comparison of analytical techniques for the identification of bioactive compounds from natural products. *Nat. Prod. Rep.* 33, 1131–1145. doi:10.1039/c6np00016a

Damodar, K., Kim, J.-K., and Jun, J.-G. (2017). Efficient, collective synthesis and nitric oxide inhibitory activity of rubrolides E, F, R, S and their derivatives. *Tetrahedron Lett.* 58 (1), 50–53. doi:10.1016/j.tetlet.2016.11.096

Dong, X., Fan, Y., Yu, L., and Hu, Y. (2007). Synthesis of four natural prenylflavonoids and their estrogen-like activities. *Arch. Pharm. Weinh.* 340 (7), 372–376. doi:10.1002/ardp.200700057

Duong, T.-H., Nguyen, H. T., Nguyen, C. H., Tran, N.-M.-A., Danova, A., Tran, T.-M.-D., et al. (2021). Identification of highly potent α-glucosidase inhibitors from *Artocarpus integer* and molecular docking studies. *Chem. Biodivers.* 18 (12), e2100499. doi:10.1002/cbdv.202100499

Duran, N., Polat, M. F., Aktas, D. A., Alagoz, M. A., Ay, E., Cimen, F., et al. (2021). New chalcone derivatives as effective against SARS-CoV-2 agent. *Int. J. Clin. Pract.* 75 (12), e14846. doi:10.1111/ijcp.14846

Duvauchelle, V., Majdi, C., Bénimélis, D., Dunyach-Remy, C., Meffre, P., and Benfodda, Z. (2021). Synthesis, structure elucidation, antibacterial activities, and synergistic effects of novel juglone and naphthazarin derivatives against clinical methicillin-resistant *Staphylococcus aureus* strains. *Front. Chem.* 9, 773981. doi:10.3389/fchem.2021.773981

ElSohly, H. N., Joshi, A. S., Nimrod, A. C., Walker, L. A., and Clark, A. M. (2001). Antifungal chalcones from *Maclura tinctoria*. *Planta Med.* 67 (1), 87–89. doi:10.1055/s-2001-10621

Fang, B., Xiao, Z., Qiu, Y., Shu, S., Chen, X., Chen, X., et al. (2019). Synthesis and anti-inflammatory evaluation of (*R*)-(*S*)-and (±)-Sanjuanolide isolated from *Dalea frutescens*. *J. Nat. Prod.* 82 (4), 748–755. doi:10.1021/acs.jnatprod.8b00596

Fu, L., Sun, B., Zhai, J., Li, Y., Liu, X., Song, R., et al. (2020). Synthesis and antibacterial activity study of natural 5'-hydroxyisoprenyl chalcones. *Chin. J. Org. Chem.* 40 (1), 201–208. doi:10.6023/cjoc201907027

Gao, S., Sun, D., Wang, G., Zhang, J., Jiang, Y., Li, G., et al. (2016). Growth inhibitory effect of Paratocarpin E, a prenylated chalcone isolated from *Euphorbia humifusa* Wild., by induction of autophagy and apoptosis in human breast cancer cells. *Bioorg. Chem.* 69, 121–128. doi:10.1016/j.bioorg.2016.10.005

Gomes, M. N., Muratov, E. N., Pereira, M., Peixoto, J. C., Rosseto, L. P., Cravo, P. V. L., et al. (2017). Chalcone derivatives: Promising starting points for drug design. *Molecules* 22 (8), 1210. doi:10.3390/molecules22081210

Grayfer, T. D., Grellier, P., Mouray, E., Dodd, R. H., Dubois, J., and Cariou, K. (2016). Mallotojaponins B and C: Total synthesis, antiparasitic evaluation, and preliminary SAR studies. *Org. Lett.* 18 (4), 708–711. doi:10.1021/acs.orglett.5b03676

Hano, Y., Itoh, N., Hanaoka, A., Itoh, Y., and Nomura, T. (1995). Paratocarpins A-E, five new isoprenoid-substituted chalcones from *Paratocarpus venenose* Zoll. *Heterocycles* 41 (1), 191–198. doi:10.3987/COM-94-6938

Ibraheem, S., Idris, Y. M. A., Mustafa, S., Kabeir, B., Abas, F., Maulidiani, M., et al. (2021). Phytochemical profile and biological activities of Sudanese baobab (*Adansonia digitata* L.) fruit pulp extract. *Int. Food Res. J.* 28 (1), 31–43. doi:10.47836/ifrj.28.1.03

Jasim, H. A., Nahar, L., Jasim, M. A., Moore, S. A., Ritchie, K. J., and Sarker, S. D. (2021). Chalcones: Synthetic chemistry follows where nature leads. *Biomolecules* 11 (8), 1203. doi:10.3390/biom11081203

Khupse, R. S., and Erhardt, P. W. (2007). Total synthesis of Xanthohumol. *J. Nat. Prod.* 70 (9), 1507–1509. doi:10.1021/np070158y

Kil, Y.-S., Choi, S.-K., Lee, Y.-S., Jafari, M., and Seo, E.-K. (2015). Chalcones from *Angelica keiskei*: Evaluation of their heat shock protein inducing activities. *J. Nat. Prod.* 78 (10), 2481–2487. doi:10.1021/acs.jnatprod.5b00633

Knockleby, J., Djigo, A. D., Lindamulage, I. K., Karthikeyan, C., Trivedi, P., and Lee, H. (2021). Lead optimization of novel quinolone chalcone compounds by a structure–activity relationship (SAR) study to increase efficacy and metabolic stability. *Sci. Rep.* 11, 21576. doi:10.1038/s41598-021-01058-z

Konieczny, M. T., Konieczny, W., Sabisz, M., Skladanowski, A., Wakieć, R., Augustynowicz-Kopeć, E., et al. (2007). Synthesis of isomeric, oxathiolone fused chalcones, and comparison of their activity toward various microorganisms and human cancer cells line. *Chem. Pharm. Bull.* 55 (5), 817–820. doi:10.1248/cpb.55.817

Kuete, V., Alibert-Franco, S., Eyong, K. O., Ngameni, B., Folefoc, G. N., Nguemeving, J. R., et al. (2011). Antibacterial activity of some natural products against bacteria expressing amultidrug-resistant phenotype. *Int. J. Antimicrob. Agents* 37 (2), 156–161. doi:10.1016/j.ijantimicag.2010.10.020

Lee, S.-J., Wood, A. R., Maier, C. G.-A., Dixon, R. A., and Mabry, T. J. (1998). Prenylated flavonoids from *Maclura pomifera*. *Phytochemistry* 49 (8), 2573–2577. doi:10.1016/S0031-9422(98)00380-X

Li, J.-L., Gao, L.-X., Meng, F.-W., Tang, C.-L., Zhang, R.-J., Li, J.-Y., et al. (2015). PTP1B inhibitors from stems of *Angelica keiskei* (ashitaba). *Bioorg. Med. Chem. Lett.* 25 (10), 2028–2032. doi:10.1016/j.bmcl.2015.04.003

Li, X.-C., Joshi, A. S., ElSohly, H. N., Khan, S. I., Jacob, M. R., Zhang, Z., et al. (2002). Fatty acid synthase inhibitors from plants: Isolation, structure elucidation, and SAR studies. *J. Nat. Prod.* 65 (12), 1909–1914. doi:10.1021/np020289t

Li, Y., Sun, B., Zhai, J., Fu, L., Zhang, S., Zhang, J., et al. (2019). Synthesis and antibacterial activity of four natural chalcones and their derivatives. *Tetrahedron Lett.* 60 (43), 151165. doi:10.1016/j.tetlet.2019.151165

Liu, G., Eggler, A. L., Dietz, B. M., Mesecar, A. D., Bolton, J. L., Pezzuto, J. M., et al. (2005). Screening method for the discovery of potential cancer chemoprevention agents based on mass spectrometric detection of alkylated Keap1. *Anal. Chem.* 77 (19), 6407–6414. doi:10.1021/ac050892r

Liu, Y., Chen, H.-B., Qiao, L., and Zhao, Y.-Y. (2005). Two new isoprenyl chalcones from *Hedysarum gmelinii*. *J. Asian Nat. Prod. Res.* 7 (5), 723–727. doi:10.1080/1028602042000324925

Liu, Y., Zhang, J., Wen, R., Tu, G.-Z., Chen, H.-B., Liang, H., et al. (2018). Anti-inflammatory and antiproliferative prenylated chalcones from *Hedysarum gmelinii*. *J. Asian Nat. Prod. Res.* 20 (11), 1009–1018. doi:10.1080/10286020.2018.1450390

Ngadjui, B. T., Watchueng, J., Keumedjio, F., Ngameni, B., Simo, I. K., and Abegaz, B. M. (2005). Prenylated chalcones, flavone and other constituents of the twigs of *Dorstenia angusticornis* and *Dorstenia barteri* var. *Phytochemistry* 66 (6), 687–692. doi:10.1016/j.phytochem.2004.10.016

Ngameni, B., Ngadjui, B. T., Folefoc, G. N., Watchueng, J., and Abegaz, B. M. (2004). Diprenylated chalcones and other constituents from theTwigs of *Dorstenia barteri* var. *Phytochemistry* 65 (4), 427–432. doi:10.1016/j.phytochem.2003.10.021

Nielsen, S. F., Larsen, M., Boesen, T., Schønning, K., and Kromann, H. (2005). Cationic chalcone antibiotics. Design, synthesis, and mechanism of action. *J. Med. Chem.* 48 (7), 2667–2677. doi:10.1021/jm049424k

Nowakowska, Z. (2007). A review of anti-infective and anti-inflammatory chalcones. *Eur. J. Med. Chem.* 42 (2), 125–137. doi:10.1016/j.ejmech.2006.09.019

Ohkura, N., Ohnishi, K., Taniguchi, M., Nakayama, A., Usuba, Y., Fujita, M., et al. (2016). Anti-platelet effects of chalcones from *Angelica keiskei* Koidzumi (ashitaba) *in vivo*. *Pharmazie* 71 (11), 651–654. doi:10.1691/ph.2016.6678

Owor, R. O., Bedane, K. G., Zühlke, S., Derese, S., Ong'amo, G. O., Ndakala, A., et al. (2020). Anti-inflammatory flavanones and flavones from *Tephrosia linearis*. *J. Nat. Prod.* 83 (4), 996–1004. doi:10.1021/acs.jnatprod.9b00922

Park, J.-Y., Ko, J.-A., Kim, D. W., Kim, Y. M., Kwon, H.-J., Jeong, H. J., et al. (2015). Chalcones isolated from *Angelica keiskei* inhibit cysteine proteases of SARS-CoV. *J. Enzyme Inhib. Med. Chem.* 31 (1), 23–30. doi:10.3109/14756366.2014.1003215

Pistelli, L., Bertoli, A., Giachi, I., and Manunta, A. (1998). Flavonoids from *Genista ephedroides*. *J. Nat. Prod.* 61 (11), 1404–1406. doi:10.1021/np980112s

Pistelli, L., Spera, K., Flamini, G., Mele, S., and Morelli, I. (1996). Isoflavonoids and chalcones from *Anthyllis hermanniae*. *Phytochemistry* 42 (5), 1455–1458. doi:10.1016/0031-9422(96)00128-8

Qin, H.-L., Zhang, Z.-W., Lekkala, R., Alsulami, H., and Rakesh, K. P. (2020). Chalcone hybrids as privileged scaffolds in antimalarial drug discovery: A key review. *Eur. J. Med. Chem.* 193, 112215. doi:10.1016/j.ejmech.2020.112215

Ren, Z.-Y., Qi, H.-Y., and Shi, Y.-P. (2008). Phytochemical investigation of *Anaphalis lactea*. *Planta Med.* 74 (8), 859–863. doi:10.1055/s-2008-1074547

Rudrapal, M., Khan, J., Dukhyil, A. A. B., Alarousy, R. M. I. I., Attah, E, I., Sharma, T., et al. (2021). Chalcone scaffolds, bioprecursors of flavonoids: Chemistry, bioactivities, and pharmacokinetics. *Molecules* 26 (23), 7177. doi:10.3390/molecules26237177

Salehi, B., Quispe, C., Chamkhi, I., Omari, N. E., Balahbib, A., Sharifi-Rad, J., et al. (2021). Pharmacological properties of chalcones: A review of preclinical including molecular mechanisms and clinical evidence. *Front. Pharmacol.* 11, 592654. doi:10.3389/fphar.2020.592654

Sangiovanni, E., Fumagalli, M., Santagostini, L., Forino, M., Piazza, S., Colombo, E., et al. (2019). A bio-guided assessment of the anti-inflammatory activity of hop extracts (*Humulus lupulus* L. Cv. Cascade) in human gastric epithelial cells. *J. Funct. Foods* 57, 95–102. doi:10.1016/j.jff.2019.03.041

Shaffer, C. V., Cai, S., Peng, J., Robles, A. J., Hartley, R. M., Powell, D. R., et al. (2016). Texas native plants yield compounds with cytotoxic activities against prostate cancer cells. *J. Nat. Prod.* 79 (3), 531–540. doi:10.1021/acs.jnatprod.5b00908

Simo, I. K., Ngadjui, B. T., and Abegaz, B. M. (2005). Prenylated flavonoids and other constituents from the twigs of *Dorstenia angusticornis*. *Biochem. Syst. Ecol.* 33 (12), 1283–1287. doi:10.1016/j.bse.2005.07.015

Smit, F. J., and N′Da, D. D. (2014). Synthesis, *in vitro* antimalarial activity and cytotoxicity of novel 4-Aminoquinolinyl-chalcone amides. *Bioorg. Med. Chem.* 22 (3), 1128–1138. doi:10.1016/j.bmc.2013.12.032

Stevens, J. F., Taylor, A. W., Nickerson, G. B., Ivancic, M., Henning, J., Haunold, A., et al. (2000). Prenylflavonoid variation in *Humulus lupulus*: Distribution and taxonomic significance of xanthogalenol and 4'-*O*-methylxanthohumol. *Phytochemistry* 53 (7), 759–775. doi:10.1016/S0031-9422(00)00005-4

Sugamoto, K., Kurogi, C., Matsusita, Y.-I., and Matsui, T. (2008). Synthesis of 4-hydroxyderricin and related derivatives. *Tetrahedron Lett.* 49 (47), 6639–6641. doi:10.1016/j.tetlet.2008.09.015

Sugamoto, K., Matsusita, Y.-I., Matsui, K., Kurogi, C., and Matsui, T. (2011). Synthesis and antibacterial activity of chalcones bearing prenyl or geranyl groups from *Angelica keiskei*. *Tetrahedron* 67 (29), 5346–5359. doi:10.1016/j.tet.2011.04.104

Sugamoto, K., Yoshifuji, T., Soejima, S., and Honda, Y. (2020). Synthesis of chalcones bearing 2-Hydroperoxy-3-methyl-3-butenyl or 2-Hydroxy-3-methyl-3-butenyl group from prenylated chalcones. *Synth. Commun.* 50 (10), 1523–1527. doi:10.1080/00397911.2020.1745242

Sugii, M., Ohkita, M., Taniguchi, M., Baba, K., Kawai, Y., Tahara, C., et al. (2005). Xanthoangelol D isolated from the roots of *Angelica keiskei* inhibits endothelin-1 production through the suppression of nuclear factor-κb. *Biol. Pharm. Bull.* 28 (4), 607–610. doi:10.1248/bpb.28.607

Tan, W., Li, W., Huang, C., Li, Y., and Xing, Y. (1999). Facile syntheses of 3′, 4′-methylenedioxy- 2″, 2″-dimethylpyrano-[5″, 6″:7, 8]-flavoneand (±)-Ponganone III, two pyranoflavanoids. *Synth. Commun.* 29 (19), 3369–3377. doi:10.1080/00397919908085964

Tronina, T., Bartmańska, A., Filip-Psurska, B., Wietrzyk, J., Popłoński, J., and Huszcza, E. (2013). Fungal metabolites of Xanthohumol with potent antiproliferative activity on human cancer cell lines *in vitro*. *Bioorg. Med. Chem.* 21 (7), 2001–2006. doi:10.1016/j.bmc.2013.01.026

Wang, Y., Zheng, M., Jiang, Q., Xu, Y., Zhou, X., Zhang, N., et al. (2021). Chemical components of the fruits of Morus nigra Linn. Methyl caffeate as a potential anticancer agent by targeting 3-phosphoglycerate dehydrogenase. *J. Agric. Food Chem.* 69 (42), 12433–12444. doi:10.1021/acs.jafc.1c03215

Wei, H., Zhang, X., Tian, X., and Wu, G. (2016). Pharmaceutical applications of affinity-ultrafiltration mass spectrometry: Recent advances and future prospects. *J. Pharm. Biomed. Anal.* 131, 444–453. doi:10.1016/j.jpba.2016.09.021

Xu, M.-J., Wu, B., Ding, T., Chu, J.-H., Li, C.-Y., Zhang, J., et al. (2012). Simultaneous characterization of prenylated flavonoids and isoflavonoids in *Psoralea corylifolia* L. By liquid chromatography with diode-array detection and quadrupole time-of-flight mass spectrometry. *Rapid Commun. Mass Spectrom.* 26 (19), 2343–2358. doi:10.1002/rcm.6361

Xu, W.-H., Al-Rehaily, A. J., Yousaf, M., Ahmad, M. S., Khan, S., and Khan, I. A. (2015). Two new flavonoids from *Retama raetam*. *Helv. Chim. Acta* 98 (4), 561–568. doi:10.1002/hlca.201400315

Yang, B., and Jiang, Y. (2021). *Chalcone compound and preparation method thereof*. Pub. No.US 2021/0331995 A1. Date: Oct. 28, 2021.

Yin, S., Fan, C.-Q., Wang, Y., Dong, L., and Yue, J.-M. (2004). Antibacterial prenylflavone derivatives from *Psoralea corylifolia*, and their structure-activity relationship study. *Bioorg. Med. Chem.* 12 (16), 4387–4392. doi:10.1016/j.bmc.2004.06.014

Yu, L., Chen, Y., Liu, J., Lu, Y., and Gui, S. (2005). Chalcones from the seeds of *Psoralea corylifolia*. *ChemInform* 79 (7), 1173–1177. doi:10.1002/chin.200548207

Yu, L., Zhang, F., Hu, Z., Ding, H., Tang, H., Ma, Z., et al. (2014). Novel prenylated bichalcone and chalcone from *Humulus lupulus* and their quinone reductase induction activities. *Fitoterapia* 93, 115–120. doi:10.1016/j.fitote.2013.12.019

Yuan, L., Cai, Y., Zhang, L., Liu, S., Li, P., and Li, X. (2022). Promoting apoptosis, a promising way to treat breast cancer with natural products: A comprehensive review. *Front. Pharmacol.* 12, 801662. doi:10.3389/fphar.2021.801662

Zhai, J., Fu, L., Li, Y., Zhao, R., Wang, R., Deng, H., et al. (2019). Synthesis and biological activities evaluation of Sanjuanolide and its analogues. *Bioorg. Med. Chem. Lett.* 29 (2), 326–328. doi:10.1016/j.bmcl.2018.11.020

Zhang, C., Yue, H., Sun, P., Hua, L., Liang, S., Ou, Y., et al. (2021). Discovery of chalcone analogues as novel NLRP3 inflammasome inhibitors with potent anti-inflammation activities. *Eur. J. Med. Chem.* 219, 113417. doi:10.1016/j.ejmech.2021.113417

Zhao, F., Nozawa, H., Daikonnya, A., Kondo, K., and Kitanaka, S. (2003). Inhibitors of nitric oxide production from hops (*Humulus lupulus* L.). *Biol. Pharm. Bull.* 26 (1), 61–65. doi:10.1248/bpb.26.61

Zhao, F., Watanabe, Y., Nozawa, H., Daikonnya, A., Kondo, K., and Kitanaka, S. (2005). Prenylflavonoids and phloroglucinol derivatives from hops (*Humulus lupulus*). *J. Nat. Prod.* 68 (1), 43–49. doi:10.1021/np0499113

Zhou, K., Yang, S., and Li, S.-M. (2021). Naturally occurring prenylated chalcones from plants: Structural diversity, distribution, activities and biosynthesis. *Nat. Prod. Rep.* 38 (12), 2236–2260. doi:10.1039/d0np00083c

Zhuang, C., Zhang, W., Sheng, C., Zhang, W., Xing, C., and Miao, Z. (2017). Chalcone: A privileged structure in medicinal chemistry. *Chem. Rev.* 117 (12), 7762–7810. doi:10.1021/acs.chemrev.7b00020