Academia Journal of Medicinal Plants 7(10): 000-000, October 2019
DOI: 10.15413/ajmp.2019.0159
ISSN: 2315-7720

Academia Publishing

CrossMark click for updates

Research Paper

Isolation, synthesis and pharmacological applications of cirsimaritin – A short review

Adeem Mahmood* and Hamad Z. Alkhathlan

Department of Chemistry, College of Science, King Saud University, P. O. Box 2455, Riyadh - 11451, Saudi Arabia.

E-mail: madeem@ksu.edu.sa. Tel: +966-11-4675910. Fax: +966-11-4675992.

Accepted 25th October, 2019

ABSTRACT

The present study was conducted to explore the pharmacological applications of a bioactive flavonoid; Circimaritin. Isolation, synthesis and pharmacological activities of a flavanol, Cirsimaritin (4',5-Dihydroxy-6,7-dimethoxyflavone) or Skofulein, are discussed in this review. It is an active flavone that possessed a number of potent pharmacological activities such as anti-oxidant, anti-microbial, anti-oxidant, anti-microbial, anti-cancer, anti-inflammatory, anti-diabetic and many more. This review article shows that the circimaritin contains important pharmacological properties including antioxidant, antiinflammatory, antimicrobial, antidiabetic, anticancer, antagonistic properties, neurological effects, cardiovascular, and hepatoprotective properties.

Key words: Circimaritin, isolation, synthesis, anti-oxidant anti-microbial, anti-cancer, anti-inflammatory, anti-diabetic, antagonistic properties.

INTRODUCTION

Flavonoids in Medicinal chemistry are well known biologically active drug molecules responsible for many vital pharmacological activities (Wang et al., 2017). The compound (Cirsimaritin or Skrofulein (Figure 1), also known as 4',5-Dihydroxy-6,7-dimethoxyflavone) belongs to the class of organic compounds known as 7-O-methylated flavonoids. These are flavonoids with methoxy groups attached to the C7 atom of the flavonoid backbone. This compound has been isolated from naturally occurring various medicinal plants and is synthesized in the laboratory. It is an active flavone associated with several potent pharmacological activities and unveiled strong*anti*-H pylori activity, having selectivity for many other microorganisms tested (Suleimenov et al., 2008; Kawase and Motohashi, 2004; Kim et al., 2015), and *anti*-oxidant (Ben et al., 2011; Nyiligira et al., 2008), *anti*-bacterial (Isobe et al., 2006), bacterial drug resistance (Markham, 1983), *anti*-spasmodic (Weimann et al., 2002) and cyclooxygenase-1 inhibitory activities (Kelm et al., 2000). Additionally, cirsimaritin has been found to exhibit: i) the *anti*-cancer effects in the cell line of the human gallbladder carcinoma GBC-SD and ii) a kidney renal protection in tubular epithelial LLC-PK1 cells (Quan et al., 2010; Yokozawa et al., 1999). So far, many studies on biological functions of cirsimaritin have been conducted; however, some investigations are still under way such as its role in the melanin production.

For this review, a number of scientific databases such as ISI web of Knowledge, Pubmed, Science direct and Google Scholar were employed to access information, and covers the literature from 1963 to 2017. This article includes only original and highly cited research articles that were published in English language; articles in other languages are excluded.

Isolation of cirsimaritin

Circimaritin was initially isolated in 1963 (from *Cirsium martimum* MAKINO (Compositae) by Morita and Shimizu (1963). Subsequently, this compound was isolated from various medicinal plants, such as *Cantuarea pseudosinaica* (Al-Wahaibi et al., 2018), *Microtea debilis* (Hasrat et al., 1997), *Salvia paleastina* (Miski et al., 1983), *Centaurea*

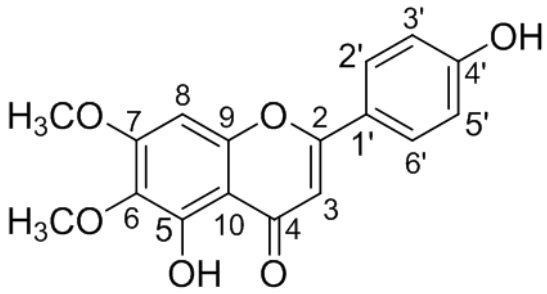
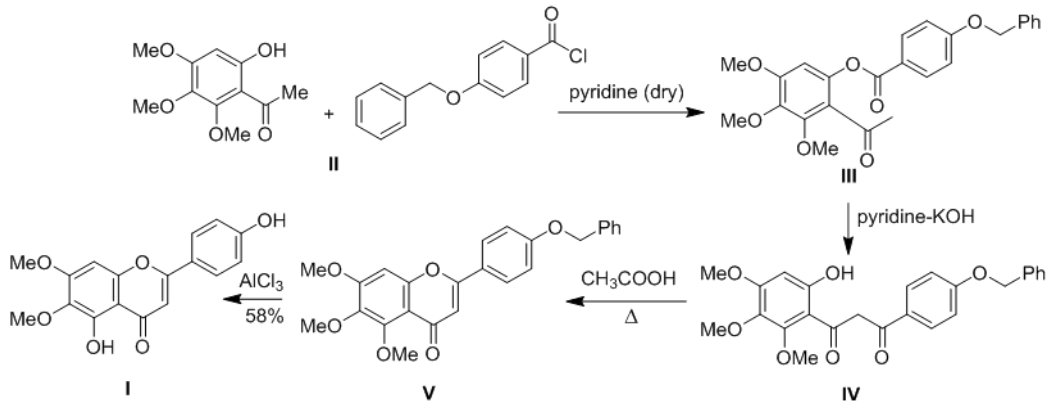


Figure 1: Circimaritin.



Scheme 1: Synthesis of circimaritin.

scoparia (Youssef and Frahm, 1995), *Artemisia judaica* (Abdalla and Abu Zarga, 1987), *Salvia apiana* (Srivedavyasasri et al., 2016), *Centuarea kilaea* (Sen et al., 2017), *Salvia fruticosa* (Kanetis et al., 2017), *Stevia satureiifolia* (Beer et al., 2016), *Eremophila lucida* (Tahtah et al., 2016), *Asphodeline anatolica* (Marino et al., 2016), *Rosmarinus officinalis* (Abdelhalim et al., 2015), *Buddleja polystachya* (Al Ati et al., 2015), *Perovskia atriplicifolia* (Zhong et al., 2015), *Satureja khuzistanica* (Malmir et al., 2015), *Ocimum basilicum* L. (Berim et al., 2014), *Tanacetum chiliophyllum* (Polatoğlu et al., 2013), *Dracocephalum kotschyi* (Fattahi et al., 2013), *Seriphidium stenocephalum* (Shafiq et al., 2013), *Tecurium ramosissimum* (Ben Sghaier et al., 2011), *Praxelis clematidea* (Maia et al., 2011), *Teucrium polium* (Stefkov et al., 2011), *Aeollanthus rydingianus* (Rijo et al., 2009), *Lippia javanica* (Mujovo et al., 2008), *Artemisia vestita* (Yin et al., 2008), *Artemisia ordosica II* (Zhang et al., 2006), *Perovskia abrotanoies* (Khaliq et al., 2007), *Hyptis faciculala* (Isobe et al., 2006), *Incarvillea arguta* (Yu et al., 2005), *Lippia dulcis* and Mexican oregano (*Lippia graveolens*) (Ono et al., 2014), [6*Herba artemisiae Scopariae* (Lin et al., 2005), *Santolina insularis* (Cottiglia et al., 2005), *Trollius chinensis* (Wang et al., 2004), *Artemisia scoparia* (Zhang et al., 2002), *Salvia officinalis* (Kavvadias et al., 2003), *Baccharis conferta* (Weimann et al., 2002), *Origanum intercedens* (Bosabalidis et al., 1998), *Ocimum gratissimum* (Vieira et al., 2001), *Osimum sanctum* (Kelm et al., 2000), *Becium grandiflorum* (Grayer and Veitch, 1998), *Clerodendrum mandarinorum* (Zhu et al., 1996), *Eriodictyon californicum* (Liu et al., 1992), *Plectranthus amboinicus* (Peter et al., 2015) and from genus *Artemisia e.g. Artemisia monosperma* (Saleh et al., 1987), *Artemisia hispanica* (Sans et al., 1989), *Artemisia annua* (Shilin et al., 1989), *Artemisia xerophytica* (Belenovskaya et al., 1982), *Artemisia xanthochroa* (Chemesova et al., 1984), *Artemisia scoparia* (Chandraskharan et al., 1981), *Artemisia meatlanticae* (Bouzid et al., 1982) and *Artemisia capilaris* (Namba et al., 1983).

Synthesis of cirsimaritin

The cirsimaritin was subsequently synthesized by Fukui et al. (1964) right after its isolation *C. martimum*. Protocol was started from the esterification of 6-hydroxy-2, 3, 4-trimethoxyacetophenone (**II**) with *p*-benzyloxybenzoyl chloride in the presence of dry pyridine. The benzoate **III** formed was then subjected to the Baker-Venkataraman rearrangement with pyridine-potassium hydroxide (Scheme **1**) (Fukui et al., 1964).

The resulting re-arranged diketone**IV** was then converted into 4'-benzyloxy- 5, 6, 7-trimethoxyflavone (**V**) through heating with acetic acid and sodium acetate. Finally the flavone (**I**) was obtained in 58% yield through the

Table 1: Pharmacological activities of cirsimaritin.

Activities	References
Anti-oxidant	Malmir et al., 2015; Fattahi et al., 2013; Ben Sghaier et al., 2011; Ibañez et al., 2003; Tundis et al., 2013; Kelm et al., 2000
Anti-inflammatory	Al Ati et al., 2015; Malmir et al., 2015; Cottiglia et al., 2005; Kelm et al., 2000; Kuo et al., 2011; Bai et al., 2011
Anti-microbial	Isobe et al., 2006; Miski et al., 1983; Kanetis et al., 2017; Marino et al., 2016; Polatoğlu et al., 2013; Rijo et al., 2009; Nyiligira et al., 2008; El-Gendy et al., 2008; Kavvadias et al., 2003; Miski et al., 1983; Exarchou et al., 2015; Maia et al., 2011; Isobe et al., 2006
Anti-diabetic	Tahtah et al., 2016; Malmir et al., 2015; Stefkov et al., 2011; Ono et al., 2014
Anti-cancer	[Sen et al., 2017; Bai et al., 2011; Quan et al., 2010; Mujovo et al., 2008; Moghaddam et al., 2012; Ben Sghaier et al., 2011; Bai et al., 2011
Antagonistic properties	Youssef and Frahm, 1995; Hasrat et al., 1997a, b; Shen et al., 1994;Zhu et al., 1996; Liu et al., 1992
Anti-spasmodic	Abdalla and Abu Zarga, 1987; Weimann et al., 2002
Typanocidal and Leishmanicidal	Beer et al., 2016
Anti-depressant, Anxiolytic and *Anti*-nociceptive	Shen et al., 1994; Abdelhalim et al., 2015
Repiratory stimulating	Wang et al., 2002; Wang et al., 2002
AhR activation	Amakura et al., 2014
Tyrosinase activity	Kim et al., 2015
Enzyme inhibitory activities	Shafiq et al., 2013; Tundis et al., 2013

debenzylation of **V** with hydrogen and subsequent demthylation at position 5 with aluminium chloride (Scheme **1**).

PHARAMACOLOGICAL APPLICATIONS OF CIRSIMARITIN

The pharamacological applications of cirsimaritin are shown in Table 1.

Anti-oxidant activity

Circimaritin has shown a significant anti-oxidant activity at the concentration of 1 µg (Malmir et al., 2015). Furthermore, its high antioxidant activities have been evaluated by showing its importance to pursue the radical ABTS(+) (Fattahi et al., 2013) *via* chemical assays such as CUPRAC (cupric reducing antioxidant capacity), RP (reducing power) and FRAP (ferric reducing *anti*-oxidant power) (Ben Sghaier et al., 2011) and DPPH (free radical method) using subcritical water extraction at temperature ranging from 25 to 200°C with values around 11.3 μg/mL (Ibañez et al., 2003). In another study, cirsimaritin obtained through the bioassay-directed extraction of *Ocimum sanctum* has demonstrated good *anti*-oxidant activity at 10-μM concentrations (Kelm et al., 2000).

Anti-inflammatory activity

Cirsimaritin isolated from traditionally used medicinal plants showed the most significant *anti*-inflammatory activity (Al Ati et al., 2015; Zhong et al., 2015). The results could be correlated with the *in vitro* and *in vivo anti*-inflammatory properties reported from these medicinal plants. Similarly, the topical *anti*-inflammatory activity of

circimaritin was also depited by employing the croton oil-induced dermatitis in mouse ear (Cottiglia et al., 2005). *Anti*-inflammatory activity or cyclooxygenase inhibitory activity of this compound at slightly higher levels was assayed at 1000-μM concentrations. This was comparable to others antiinfalammatory drugs *e.g.*naproxen, ibuprofen and aspirin at 10, 10, and 1000-μM concentrations, respectively (Kelm et al., 2000). The Rosemary (*Rosmarinus officinalis*) extract containing circimaritin prevents the inflammatory mediators expression along with the dose-dependent responses. However, the simultaneous connection of the anti-inflammatory activity between rosemary extract (from SC-CO(2) at 5,000 psi and 80°C) and its purecarnosic acid (CA) *via* lipopolysaccharide (LPS)-treated murine RAW 264.7 macrophage cells had been determined. Results showed a high inhibitory effect on lipid peroxidation (IC_{50} 33.4 µg/mL) in an extract obtained from the most effective extraction conditions. Moreover, the SC-CO(2) and CA distinctly inhibited the LPS-induced nitric oxide (NO) production, tumor necrosis factor-α (TNF-α), phosphorylated inhibitor-kappaB (P-IκB), dose based nuclear factor-kappaB (NF-κB)/p65 as well as the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). Infact the cirsimaritin with an *anti*-inflammatory effect presented to the best inhibitory activity on NO (IC_{50} of 22.5 μM or 7.47 μg/mL) over SC-CO(2) extract (IC_{50} of 14.50 µg/mL). However, the SC-CO(2) extract elicits the effective inhibition of LPS-induced NF-κB signaling in RAW 264.7 cells hence extends efficacy in the nutraceutical formulation to prevent inflammatory diseases (Kuo et al., 2011).

Anti-microbial activity

Cirsimaritin is well regarded for its amtimicrobial activity against the bacterial strains such as *Staphylococcus aureus*, *S. epidermidis*, *Klebsiella pneumoniae, Escherichia coli*, *Pseudomonas aeruginosa* and *Proteus vulgaris* (Miski et al., 1983).

The plant extracts containing cirsimaritin were evaluated for their antimicrobial activity against *S. aureus* including methicillin-resistant strains-MRSA strains (Marino et al., 2016) and found to be effective in reducing spore germination as well as the *in vitro* mycelial growth of *Botrytis cinerea* at 10 and 25°C (Kanetis et al., 2017). Moreover, its insecticidal contact toxicity against *Sitophilus granaries* and *B. cereus* showed the same inhibition concentration (125 microL/mg) with the positive control chloramphenicol (Polatoğlu et al., 2013). Additionally, the isolated circimaritin showed minimum inhibitory concentration (MIC) values of 3.90-15.62 µg/ml for *S. aureus* and of 7.81 µg/ml for *Enterococcus hirae* (Rijo et al., 2009). The fraction of *V. rehmannii* was also found to be responsible for antimicrobial activity where cirsimaritin was detected and exhibited scavenging activity (IC_{50}: 22.14±1.74 to 33.06±1.68 µg/ml) in the anti-oxidant assay (Nyiligira et al., 2008). Similarly, circimaritin obtained from marine protoplast fusion between Streptomyces strains, Merv 1996 and Merv 7409 was reported anti-micribuial product for the first time (El-Gendy et al., 2008). Furthermore, circimaritin from the benzodiazepine receptor binding assay-guided fractionation of the methanol extract of *Salvia officinalis* L .competitively showed 3H-flumazenil binding to the benzodiazepine receptor with IC_{50} 350 µM (Kavvadias et al., 2003). Similarly, from the leaves of *Salvia palaestina Bentham* (Labiatae), the isolated flavones cirsimaritin proved to have good microbial activity against all the bacterial strains (Miski et al., 1983).

In another study, the methoxylated flavone Cirsimaritin isolated from *Salvia fruticosa* has been estimated for its anti-fungal activity against the fungal species *Aspergillus tubingensis*, *Penicillium digitatum* and *Botrytis cinerea* (Exarchou et al., 2015). In fact, the compound (circimaritin) with estimated MIC and MFC values extends its potential use in food and agricultural systems through its effective antifungal activity against *P. digitatum* and *B. cinerea*.

Circimaritin isolated from the chemical studies of *P. clematidea* R.M. King & Robinson was investigated for its toxicity against *S. aureus* SA-1199B (the NorA efflux pump retaining strain). Efflux pumps (an integral bacterial membrane protein) out antibiotics from the cell that influence the bacterial drug resistance. This kind of property of the flavone showed the degree of lipophilicity due to the presence of the methoxyl groups (Maia et al., 2011) that further exhibited potent antibacterial activity against *Helicobacter pylori* (Isobe et al., 2006).

Anti-diabetic activity

To accelerate the enzyme protein-tyrosine phosphatase 1B (PTP1B) for the treatment of T2D and its adverse complications, cirsimaritin acts as potential PTP1B inhibitor (Tahtah et al., 2016). In addition, Cirsimaritin exhibited a considerable β-glucosidase inhibitory activity at 10 µg (Malmir et al., 2015). Another study was carried out to examine extract from commercial herbs containing circimaritin for its potential to inhibit insulin secreting enzyme (dipeptidyl peptidase IV (DPP-IV)) and insulin signaling enzyme (protein tyrosine phosphatase 1B (PTP1B)) (Ono et al., 2014). The respective cirsimaritin present in green house-grown Mexican oregano and rosemary significantly inhibits DPP-IV with IC_{50} value of 0.43±0.07 µM.

The biochemical mechanism of insulinotropic and antihyperglycemic effects of antidiabetic activities from *T. polium* plant extracts containing circimaritin was studied (Stefkov et al., 2011). A distinct insulinotropic effect on INS-1E cells at 500 µg/ml has been shown by the extract and mixture of commercial flavonoids. The identical doses of

intragastric (*i.g.*) administration of the extract (125 mg/kg) in both normo- and hyperglycemic rats were found to be more efficient in lowering the blood glucose as compared with the intraperitoneal injection (35% vs. 24% reduction) with highest effect (50% reduction) 8 h after administration. After 1.5 weeks of treatment, the effect level was compared with i.g. administration of 2.5 mg/kg of glibenclamide (38% reduction) and found to be ineffective on blood lipid profiles. In OGTT (oral glucose tolerance test) the extract dropped blood glucose levels by ~35%. Hence the treatment lowered hepatic glycogen and tended to normalize the activity of gluconeogenic enzymes.

Anti-cancer activity

Circimaritin was tested against *Mycobacterium tuberculosis* and HIV-1 reverse transcriptase and found to inhibit the HIV-1 reverse transcriptase enzyme by 91, at 100 µg/mL (Mujovo et al., 2008). In another study (Moghaddam et al., 2012), on the evaluation of the compound, *in-vitro* anti-proliferative activity was carried out in contrast to the established normal and malignant cell lines using the MTT assay. The methoxylated hydroxyflavones (cirsimaritin) showed preferential activities against tumor cells treat tumors. In addition, circimaritin inhibit the excellent action in human leukemia cells apoptosis induction and cell proliferation, the ABTS assay with TEAC value 2.04 µM (Ben Sghaier et al., 2011).

Studies have shown that the cirsimaritin has significant *anti*-cancer activity against breast cancer, and the value (0.5-50 µg/mL) was taken against one normal cell line (L-929, mouse fibroblast) and some human cancer cell lines (MCF-7; cervix carcinoma; PC-3; prostate carcinoma and breast carcinoma) using MTT assay with IC_{50} value 4.3 µg/mL (Sen et al., 2017). In addition, cirsimaritin showed cytotoxicity in human cancer cell lines against COLO-205 cells with IC_{50} value of 6.1 µM (Bai et al., 2011). Furthermore, cirsimaritin was found to provoke the generation of reactive oxygen species in GBC-SD cells in a human gallbladder that triggers ER stress mitochondrial apoptotic pathways (Quan et al., 2010).

Antagonistic properties (Adenosine active)

Studies have shown that circimaritin exhibits adenosine antagonistic properties at the adenosine-A1 receptor in-rates with acute renal failure (Hasrat et al., 1997). The *in-vivo* study in rats has been investigated through the cirsimaritin absorption and the inhibition of [3H]-DPCPX binding to the adenosine-A1 receptor by urine samples. In addition, the lower heart rate and blood pressure induced by adenosine was significantly inhibited by cirsimaritin. From *Microtea debilis* (Hasrat et al., 1997), the cirsimaritin was detected in both the urine and plasma where its concentrations in the plasma were 0.126 +/- 0.04, 0.138 +/- 0.015, and 0.120 +/- 0.022 μM, whereas at the same time in the urine were 2.05 +/- 1.86, 5.05 +/- 2.6 and 2.06 +/- 0.09 μM, respectively. This indicates that in both kidney and urinary tract, the interaction of adenosine along with [3H]5'-N-ethylcarboxamidoadenosine ([3H]NECA) binding to adenosine-A2 receptors can elicit the inhibition based on the concentrations of cirsimaritin .In another ligand-binding study (Hasrat et al., 1997), the bioassay-guided fractionation led to the isolation of cirsimaritin 4'-O-glucoside; an active antagonist ligand (adenosine A1 receptor). Similalrly, ethanolic extract of *Clerodendrum mandarinorum* was assessed for CNS activity against 18 radioligand receptor binding assays. And found that the cirsimaritin-4'-glucoside was active in the adenosine-1 binding assay with only IC_{50} = 3.0 µM (Zhu et al., 1996).

In *Artemisia Herba-alba*, the isolated circimaritin or 4',5-dihydroxy-6, 7-dimethoxy flavone (skrofulein), was found to inhibit the [methyl-3H]diazepam binding to rat brain membranes *in vitro* with IC_{50} value of 23 μM. The GABA-ratios (the IC_{50}values in the absence/presence of GABA in the binding assay) was 1.2 for skrofulein, suggesting that this flavone is antagonist or partial agonist of benzodiazepine receptors (Shen et al., 1994). To investigate the circimaritin as an active chemopreventive agent, a small concentration of only 10 µg/ml from *E. californicum* indicates the high benzo[a]pyrene metabolism inhibition and its ultimate carcinogenic DNA-binding metabolites activation (Liu et al., 1992).

Respiratory stimulant

The circimarition inhibitory effect has been shown through the blockade of phospholipase D signaling pathway against the formyl-methionyl-leucyl-phenylalanine (fMLP)-induced respiratory burst in rat neutrophils (Wang et al., 2002). Rather reducing, cirsimaritin was used as an inhibitor in the superoxide [anion O^{*-2} generation (IC_{50} 11.5+/-2.2 µM) and O^2consumption (IC_{50} 17.0+/-3.9 µM)] in PMA-activated (phorbol 12-myristate-13-acetate) or NADPH oxidase preparation as well as during the dihydroxyfumaric acid auto-oxidation. In addition, it also partially inhibited the fMLP-induced [Ca(2+)] changes instead of elevating cellular cAMP levels. Moreover, cirsimaritin induced a concentration-dependent reduction in the phosphatidic acid and phosphatidylethanol formation, (with IC_{50} 15.1±6.5 µM and 15.6±3.4 µM, respectively) from fMLP-stimulated neutrophils in contrast to the phosphatidylethanol formation when PMA was used. Similarly cirsimaritin reduced the membrane translocation of ARF and Rho A, while the GTPgammaS-stimulated membrane-associated ARF and Rho in cell lysate were resistant to cirsimaritin (Wang et al., 2002) that clearly indicates that cirsimaritin involves in the inhibition of fMLP-induced respiratory burst through the blockade of

phospholipase D signaling pathway.

Anti-depressant, anxiolytic and anti-nociceptive

The flavone (cirsimaritin) from *A. herba-alba* inhibited the binding of [methyl-3H]diazepam with IC_{50} of 1.3 and 23 mmol/l to rat brain membranes *in vitro* (Shen et al., 1994) and found itself a antagonist of benzodiazepine receptors. The circimaritin GABA-ratios were found to be 1.2, that is, a slight increase in [35S] TBPS binding. Moreover, the presence of cirsimaritin elicits an antinociceptive, antidepressant and anxiolytic activity (Abdelhalim et al., 2015) which demonstrated CNS activity of antinociception, antidepressant and anxiolysis in mouse models. This activity was enhanced by pentylenetetrazol, suggesting a mode of action via GABA- receptors at a site other than the high affinity benzodiazepine binding site.

Anti-spasmodic activity

The cirsimaritin from *A. judaica* and its bio-assays on the guinea-pig ileum were described (Abdalla and Abu Zarga, 1987). It was also found during the *in-vivo* study of guinea-pig ileum that the cirsimaritin was involved in the concentration-effect curves of histamine, acetylcholine, and $BaCl_2$. The maximum contractions induced by the above agents are inhibited by 35.5, 47.6, and 79.5%, respectively. These investigations support the *A. judaica* L. to be used as a folk medicine for certain gastrointestinal disorders. In another study, the cirsimaritin isolated from the flavonoid-rich fractions of *B. conferta*, affect as a dose-dependent antispasmodic (Weimann et al., 2002).

Trypanocidal and leishmanicidal activities

The cytotoxicity of cirsimaritin as a potential antiprotozoal compound on mammalian cells along with the antileishmanial activity was evaluated on *T. cruzi* epimastigotes and *Leishmania braziliensis* promastigotes using concentrations of 0-100 µg/mL for 3 days, whereas on trypomastigotes and amastigotes of *T. cruzi* for a day and 5 days, respectively (Beer et al., 2016). The MTT assay was used to assess the circimaritin's cytotoxicity (12.5-500 µg/mL) on Vero cells.

Tyrosinase activity

The melanin-inducing properties of cirsimaritin from *Lithocarpus d*ealbatus were investigated in murine B16F10 melanoma cells (Kim et al., 2015). Based on this, cirsimaritin was used to enhance tyrosinase (tyrosinase-related protein TRP1, TRP2 protein) levels. Additionally, the element-binding protein (CREB) gets quick response by the cirsimaritin induced phosphorylation of cyclic adenosine monophosphate (cAMP) in a dose-dependent manner. It was observed that the cirsimaritin-mediated enhancement of tyrosinase activity was significantly reduced by H89 inhibitor (acAMP-dependent protein kinase). These findings clearly indicate that cirsimaritin involves in the stimulation of melanogenesis in B16F10 cells that were increased by the activation of CREB along with the upregulation of MITF and cAMP signiling activated tyrosinase expression. Moreover, the cirsimaritin's melanogenic effect was established through *in-vivo* study in human epidermal melanocytes. The above findings support the putative use of cirsimaritin in UV-photoprotection as well as hair coloration treatments.

AhRactivity

According to some literature survey, lower immune responses through the activation of aryl hydrocarbon receptor (AhR), suppressed allergies and autoimmune diseases (Amakura et al., 2014). This study was carried out on the natural AhR agonists in foods, where 37 health food materials have influence on the AhR using a reporter gene assay with the high AhR activity in aqueous ethanol extracts of cassia seed. In addition, for the characterization of the AhR-activating substances in these samples, the chemical constituents of the respective extracts must be identified. The potentAhR activity ($10\text{-}10^2$ µM) of the circimaritin was also evaluated from an active ethyl acetate fraction of the rosemary extract (Amakura et al., 2014).

Enzyme inhibitory activities

Cirsimaritin isolated from *S. stenocephalum* were tested for *in vitro* enzyme inhibitory activities against acetylcholinesterase, butyrylcholinesterase, and lipoxygenase and found to exhibit significant activity against all the tested enzymes (Shafiq et al., 2013). In another study, ethyl acetate extract of *Nepeta crassifolia* containing cirsimaritin was examined for its angiotensin-converting enzyme (ACE) inhibitory activity and antioxidant properties through three *in vitro* replicas [2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) and ferric reducing antioxidant power (FRAP) assay]. The ethyl acetate and n-butanol fractions of *N. crassifolia* showed significantly high DPPH radical scavenging activity with IC_{50} values of 9.6 and 12.1 µg/mL, respectively. Similarly the highest ACE inhibitory activity was found in both *N. binaludensis* and *N. crassifolia*, with IC_{50} values of 59.3 and 81.7 µg/mL, respectively for n-butanol fraction (Tundis et al., 2013).

CONCLUSION

Cirsimaritin has been studied for its synthesis, isolation and

pharmacological properties in the last two decades. We have briefly discoursed some of the important pharmacological properties including antioxidant, antiinflammatory, antimicrobial, antidiabetic, anticancer, antagonistic properties, neurological effects, cardiovascular, and hepatoprotective. However, research on Leishmanicidal activity, AhR activation, tyrosinase activity and neurological aspect of circimaritin showed that it is not adequate for its application in humans. Cirsimaritin is a versatile molecule and should be investigated further for its wider applications in human health, including their therapeutic activities.

ACKNOWLEDGEMENT

The authors cordially acknowledge the Department of Chemistry, King Saud University for their support.

REFERENCES

Abdalla SS, Abu Zarga MH (1987). Effects of Cirsimaritin, a Flavone Isolated from Artemisia judaica. Planta Med. 53(4): 322-324.

Abdelhalim A, Karim N, Chebib M, Aburjai T, Khan I, Johnston GA, Hanrahan J (2015). Antidepressant, Anxiolytic and Antinociceptive Activities of Constituents from Rosmarinus Officinalis. J. Pharm. Pharm. Sci. 18(4): 448-59.

Al Ati HY, Fawzy GA, El Gamal AA, Khalil AT, El Din El Tahir K, Abdel-Kader MS6, Gilani AH (2015). Phytochemical and biological evaluation of Buddleja polystachya growing in Saudi Arabia Pak. J. Pharm. Sci. 28(4 Suppl): 1533-40

Al-Wahaibi LHN, Mahmood A, Khan M, Alkhathlan HZ (2018). Comparative Study on the Essential Oils of Artemisia judaica and A. herba alba from Saudi Arabia. Arabian J. Chem. https://doi.org/10.1016/j.arabjc.03.004

Amakura Y, Yoshimura M, Takaoka M, Toda H, Tsutsumi T, Matsuda R, Teshima R, Nakamura M, Handa H, Yoshida T (2014). Characterization of natural aryl hydrocarbon receptor agonists from cassia seed and rosemary. Molecules.19(4): 4956-4966.

Bai N, He K, Roller M, Lai CS, Shao X, Pan MH, Bily A, Ho CT (2011). Flavonoid glycosides from Microtea debilis and their cytotoxic and anti-inflammatory effects. Fitoterapia. 82(2): 168-172.

Beer MF, Frank FM, Germán Elso O, Ernesto Bivona A, Cerny N, Giberti G, *et al* (2016). Trypanocidal and leishmanicidal activities of flavonoids isolated from Stevia satureiifolia var. satureiifolia. Pharm. Biol. 54(10): 188-95.

Belenovskaya LM, Markova LP, Kapranova GI (1982). Artemisia xerophytica phenolic compounds Khim, Prir. Soedin. 1: 121-122.

Ben Sghaier M, Skandrani I, Nasr N, Franca MG, Chekir-Ghedira L, Ghedira K (2011). Flavonoids and sesquiterpenes from Tecurium ramosissimum promote antiproliferation of human cancer cells and enhance antioxidant activity: a structure-activity relationship study. Environ Toxicol. Pharmacol. 32(3): 336-348.

Ben SM, Skandrani I, Nasr N, Franca MG, Chekir-Ghedira L, Ghedira K (2011). Flavonoids and sesquiterpenes from Tecurium ramosissimum promote antiproliferation of human cancer cells and enhance antioxidant activity: a structure-activity relationship study. Environ. Toxicol. Pharmacol. 32(3): 336–348.

Berim A, Park JJ, Gang DR (2014). Unexpected roles for ancient proteins: flavone 8-hydroxylase in sweet basil trichomes is a Rieske-type, PAO-family oxygenase. Plant J. 80(3): 385-395.

Bilto YY, Abdalla SS (1998). Effects of selected flavonoids on deformability, osmotic fragility and aggregation of human erythrocytes. ClinHemorheol Microcirc.18(2-3):165-173.

Bosabalidis A, Gabrieli C, Niopas I (1998). Flavone aglycones in glandular hairs of Origanum x intercedens.Phytochemistry. 49(6): 1549-1553.

Bouzid N, Fouraste I, Voirin B, Favare-Bornrin J, Lebreton PH (1982). A methylated flavone from Artemisia mesatlantica. Phytochemistry. 21: 803-804.

Bower AM, Real Hernandez LM, Berhow MA, de Mejia EG (2014). Bioactive compounds from culinary herbs inhibit a molecular target for type 2 diabetes management, dipeptidyl peptidase IV. J. Agric. Food Chem. 62(26): 6147-6158.

Chandraskharan I, Kahan HA, Ghanim A (1981). Flavonoids from Artemisia scoparia. Planta Med. 43(11): 1515-1516.

Cottiglia F, Casu L, Bonsignore L, Casu M, Floris C, Sosa S, Altinier G, Della Loggia R (2005). Topical anti-inflammatory activity of flavonoids and a new xanthone from Santolinainsularis. Z. Naturforsch. C. J. Biosci. 60(1-2): 63-66.

El-Gendy MM, Shaaban M, El-Bondkly AM, Shaaban KA (2008). Bioactive benzopyrone derivatives from new recombinant fusant of marine Streptomyces. Appl. Biochem. Biotechnol. 150(1): 85-96.

Exarchou V, Kanetis L, Charalambous Z, Apers S, Pieters L, Gekas V, Goulas V (2015). HPLC-SPE-NMR characterization of major metabolites in Salvia fruticosa Mill. extract with antifungal potential: relevance of carnosic acid, carnosol, and hispidulin. J. Agric. Food Chem. 63(2): 457-463.

Fattahi M, Nazeri V, Torras-Claveria L, Sefidkon F, Cusido RM, Zamani Z, Palazon J (2013). Identification and quantification of leaf surface flavonoids in wild-growing populations of Dracocephalumkotschyi by LC-DAD-ESI-MS. Food Chem. 141(1):139-146.

Fukui K, Matsumoto T, Matsuzaki S (1964). Synthetic Studies of the Flavone Derivatives. IV. The Synthesis of Cirsimaritin. Bull. Chem. Soc. Japan. 37: 265.

Grayer RJ, Veitch NC (1998). An 8-hydroxylated external flavone and its 8-O-glucoside from Becium grandiflorum .Phytochemistry. 47(5): 779-782.

Hasrat JA, De Bruyne T, De Backer JP, Vauquelin G, Vlietinck AJ (1997). Cirsimarin and cirsimaritin, flavonoids of Microtea debilis (Phytolaccaceae) with adenosine antagonistic properties in rats: leads for new therapeutics in acute renal failure. J. Pharm. Pharmacol. 49(11): 1150-1156.

Hasrat JA, De Bruyne T, De Backer JP, Vauquelin G, Vlietinck AJ (1997). Cirsimarin and cirsimaritin, flavonoids of Microtea debilis (Phytolaccaceae) with adenosine antagonistic properties in rats: leads for new therapeutics in acute renal failure. J. Pharm. Pharmacol. 49(11):1150-1156.

Hasrat JA, Pieters L, Claeys M, Vlietinck A, De Backer JP, Vauquelin G (1997). Adenosine-1 active ligands: cirsimarin, a flavone glycoside from Microteadebilis. J. Nat. Prod. 60(6): 638-641.

Ibañez E, Kubátová A, Señoráns FJ, Cavero S, Reglero G, Hawthorne SB (2003). Subcritical water extraction of antioxidant compounds from rosemary plants. J Agric Food Chem. 51(2): 375-382.

Isobe T, Doe M, Morimoto Y, Nagata K, Ohsaki A (2006). The anti-Helicobacter pylori flavones in a Brazilian plant, Hyptis fasciculata, and the activity of methoxyflavones. Biol. Pharm. Bull. 29(5): 1039–1041.

Isobe T, Doe M, Morimoto Y, Nagata K, Ohsaki A. The anti-Helicobacter pylori flavones in a Brazilian plant, Hyptis fasciculata, and the activity of methoxyflavones.Biol Pharm Bull 2006;29(5):1039-1041.

Kanetis L, Exarchou V, Charalambous Z, Goulas V (2017). Edible coating composed of chitosan and Salvia fruticosa Mill extract for the control of grey mould of table grapes. J. Sci. Food Agric. 97(2): 452-460.

Kavvadias D, Monschein V, Sand P, Riederer P, Schreier P (2003). Constituents of sage (Salvia officinalis) with in vitro affinity to human brain benzodiazepine receptor. Planta Med. 69(2): 113-117.

Kawase M, Motohashi N (2004). Plant-Derived Leading Compounds for Eradication of Helicobacter pylori. Curr. Med. Chem. Antiinfect. Agents. 3(2): 89-100.

Kelm MA, Nair MG, Strasburg GM, DeWitt DL (2000). Antioxidant and cyclooxygenase inhibitory phenolic compounds from Ocimum sanctum Linn. Phytomedicine. 7(1): 7-13.

Kelm MA, Nair MG, StrasburgGM, DeWitt DL (2000). Antioxidant and cyclooxygenase inhibitory phenolic compounds from Ocimum sanctum Linn. Phytomedicine. 7(1): 7-13.

Khaliq S, Volk FJ, Frahm AW (2007). Phytochemical investigation of *Perovskia Abrotanoides*. Planta Med. 73(1): 77-83.

Kim HJ, Kim IS, Dong Y, Lee IS, Kim JS, Kim JS, Woo JT, Cha BY (2015). Melanogenesis-inducing effect of cirsimaritin through increases in microphthalmia-associated transcription factor and tyrosinase expression.

Int. J. Mol. Sci. 16(4): 8772-8788.
Kim HJ, Kim IS, Dong Y, Lee IS, Kim JS, Kim JS, Woo JT, Cha BY (2015). Melanogenesis-inducing effect of cirsimaritin through increases in microphthalmia-associated transcription factor and tyrosinase expression. Int J Mol. Sci. 16(4): 8772-8788.
Kuo CF, Su JD, Chiu CH, Peng CC, Chang CH, Sung TY, Huang SH, Lee WC, Chyau CC (2011). Anti-inflammatory effects of supercritical carbon dioxide extract and its isolated carnosic acid from Rosmarinus officinalis leaves. J. Agric. Food Chem. 59(8): 3674-385.
Lin S, Zhang QW, Zhang NN, Zhang YX (2005). Determination of flavonoids in buds of HerbaArtemisiaescopariae by HPLC. Zhongguo Zhong Yao Za Zhi. 30(8): 591-594.
Liu YL, Ho DK, Cassady JM, Cook VM, Baird WM (1992). Isolation of potential cancer chemopreventive agents from Eriodictyoncalifornicum. J. Nat. Prod. 55(3): 357-363.
Maia GL, Falcão-Silva Vdos S, Aquino PG, de Araújo-Júnior JX, Tavares JF, da Silva MS, Rodrigues LC, de Siqueira-Júnior JP, Barbosa-Filho JM (2011). Flavonoids from Praxelis clematidea R.M. King and Robinson modulate bacterial drug resistance. Molecules. 16(6): 4828-435.
Malmir M, Gohari AR, Saeidnia S, Silva O (2015). A new bioactive monoterpene-flavonoid from Satureja khuzistanica. Fitoterapia. 105: 107-112.
Marino A, Zengin G, Nostro A, Ginestra G, Dugo P, Cacciola F, Miceli N, Taviano MF, Filocamo A, Bisignano G, Aktumsek A (2016). Antimicrobial activities, toxicity and phenolic composition of Asphodeline anatolica E. Tuzlaci leaf extracts from Turkey. Nat. Prod. Res. 30(22): 2620-2623.
Markham KR (1983). Revised structures for the flavones cirsitakaoside and cirsitakaogenin. Phytochem. 22(1): 316-317.
Miski M, Ulubelen A, Johansson C, Mabry TJ (1983). Antibacterial activity studies of flavonoids from Salvia palaestina. J. Nat. Prod. 46(6): 874-875.
Miski M, Ulubelen A, Johansson C, Mabry TJ (1983). Antibacterial activity studies of flavonoids from Salvia palaestina. J. Nat. Prod. 46(6): 874-875.
Moghaddam G, Ebrahimi SA, Rahbar-Roshandel N, Foroumadi A (2012). Antiproliferative activity of flavonoids: influence of the sequential methoxylation state of the flavonoid structure. Phytother. Res. 26(7): 1023-1028.
Mujovo SF, Hussein AA, Meyer JJ, Fourie B, Muthivhi T, Lall N (2008). Bioactive compounds from Lippiajavanica and Hoslundiaopposita. Nat. Prod. Res. 22(12): 1047-1054.
Namba T, Hattori M, Takehana Y, Tsunezuka M, Tomimori T, Kizu H, Miyaichi Y (1983). A flavone from Artemisia capillaris. Phytochemistry. 22(4): 1057-1058.
Nyiligira E, Viljoen AM, Van Heerden FR, Van Zyl RL, Van Vuuren SF, Steenkamp PA (2008). Phytochemistry and in vitro pharmacological activities of South African Vitex (Verbenaceae) species. J. Ethnopharmacol.119(3): 680-685.
Nyiligira E, Viljoen AM, van Heerden, FR, van Zyl, RL, van Vuuren, SF, Steenkamp, PA (2008). Phytochemistry and in vitro pharmacological activities of South African Vitex (Verbenaceae) species. J. Ethnopharmacol. 119(3): 680–685.
Ono M, Morinaga H, Masuoka C, Ikeda T, Okawa M, Kinjo J, Nohara T (2005). New Bisabolane-Type Sesquiterpenes from the aerial parts of Lippia dulcis. Chem. Pharm. Bull. (Tokyo). 53(9): 1175-1177.
Peter SR, Peru KM, Fahlman B, McMartin DW, Headley JV (2015). The application of HPLC ESI MS in the investigation of the flavonoids and flavonoid glycosides of a Caribbean lamiaceae plant with potential for bioaccumulation. J. Environ. Sci. Health B. 50(11): 819-826.
Polatoğlu K, Karakoç OC, Demirci F, Gökçe A, Gören N (2013). Chemistry and biological activities of Tanacetum chiliophyllum var. oligocephalum extracts. J. AOAC Int. 96(6): 1222-1227.
Quan Z, Gu J, Dong P, Lu J, Wu X, Wu W, Fei X, Li S, Wang Y, Wang J (2010). Reactive oxygen species-mediated endoplasmic reticulum stress and mitochondrial dysfunction contribute to cirsimaritin-induced apoptosis in human gallbladder carcinoma GBC-SD cells. Cancer Lett. 295(2): 252–259.
Quan Z, Gu J, Dong P, Lu J, Wu X, Wu W, Fei X, Li S, Wang Y, Wang J, Liu Y (2010). Reactive oxygen species-mediated endoplasmic reticulum stress and mitochondrial dysfunction contribute to cirsimaritin-induced apoptosis in human gallbladder carcinoma GBC-SD cells. Cancer Lett. 295(2): 252-259.
Rijo P, Simões MF, Duarte A, Rodríguez B (2009). Isopimarane diterpenoids from Aeollanthus rydingianus and their antimicrobial activity. Phytochemistry. 70(9): 1161-1165.
Saleh NAM, El-Negoumy SI, Abou-Zaid MM (1987). Flavonoids of Artemisia judaica, A. Monosperma and A. herba-alba. Phytochemistry. 26(11): 3059-3064.
Sans JF, Barbera, O, Marco JA (1989). Sesquiterpene lactones from Artemisia hispanica. Phytochemistry. 28: 2163-2167.
Sen A, Ozbas Turan S, Bitis L (2017). Bioactivity-guided isolation of anti-proliferative compounds from endemic Centaurea kilaea. Pharm. Biol. 55(1): 541-546.
Shafiq N, Riaz N, Ahmed S, Ashraf M, Ejaz SA, Ahmed I, Saleem M, Touseef MI, Tareen RB, Jabbar A (2013). Bioactive phenolics from *Seriphidium Stenocephalum*. J. Asian Nat. Prod. Res. 15(3): 286-93.
Shen XL, Nielsen M, Witt MR, Sterner O, Bergendorff O, Khayyal M (1994). Inhibition of methyl-3H]diazepam binding to rat brain membranes in vitro by dinatin and skrofulein. Zhongguo Yao Li Xue Bao. 15(5): 385-388.
Shen XL, Nielsen M, Witt MR, Sterner O, Bergendorff O, Khayyal M (1994). Inhibition of methyl-3H diazepam binding to rat brain membranes in vitro by dinatin and skrofulein. Zhongguo Yao Li Xue Bao. 15(5):385-388.
Shilin Y, Roberts MF, Phyllipson JD (1989). Methoxylated flavones and coumarins from Artemisia annua. Phytochemistry. 28(5): 1509-1511.
Srivedavyasasri R, Hayes T, Ross SA (2017). Phytochemical and biological evaluation of Salvia apiana. Nat. Prod. Res. 31(17): 2058-2061.
Stefkov G, Kulevanova S, Miova B, Dinevska-Kjovkarovska S, Mølgaard P, Jäger AK, Josefsen K (2011). Effects of Teucrium polium spp. capitatum flavonoids on the lipid and carbohydrate metabolism in rats. Pharm. Biol. 49(9): 885-892.
Suleimenov EM, Raldugin VA, Adekenov SM (2008). Cirsimaritin from Stizolophusbalsamita. Chem. Nat. Compd. 44: 3-7.
Tahtah Y, Wubshet SG, Kongstad KT, Heskes AM, Pateraki I, Møller BL, Jäger AK, Staerk D (2016). High-resolution PTP1B inhibition profiling combined with high-performance liquid chromatography-high-resolution mass spectrometry-solid-phase extraction-nuclear magnetic resonance spectroscopy: Proof-of-concept and antidiabetic constituents in crude extract of Eremophilalucida. Fitoterapia. 110: 52-58.
Tundis R, Nadjafi F, Menichini F (2013). Angiotensin-converting enzyme inhibitory activity and antioxidant properties of Nepeta crassifolia Boiss & Buhse and Nepetabinaludensis Jamzad. Phytother. Res. 27(4): 572-580.
Vieira RF, Grayer RJ, Paton A, Simon JE (2001). Genetic diversity of Ocimum gratissimum L. based on volatile oil constituents, flavonoids and RAPD markers. Biochem. Syst. Ecol. 29(3): 287-304.
Wang JP, Chang LC, Hsu MF, Chen SC, Kuo SC (2002). Inhibition of formyl-methionyl-leucyl-phenylalanine-stimulated respiratory burst by cirsimaritin involves inhibition of phospholipase D signaling in rat neutrophils. Naunyn Schmiedebergs Arch Pharmacol. 366(4): 307-314.
Wang JP, Chang LC, Hsu MF, Chen SC, Kuo SC (2002).Inhibition of formyl-methionyl-leucyl-phenylalanine-stimulated respiratory burst by cirsimaritin involves inhibition of phospholipase D signaling in rat neutrophils, Naunyn Schmiedebergs Arch Pharmacol. 366(4): 307-314.
Wang RF, Yang XW, Ma CM, Liu HY, Shang MY, Zhang QY, Cai SQ, Park JH (2004). Trollioside, a new compound from the flowers of Trolliuschinensis. J. Asian Nat. Prod. Res. 6(2):139-144.
Wang TY, Li Q, Bi KS (2017). Bioactive flavonoids in medicinal plants: Structure, activity and biological fate. Asian J. Pharm. Sci. 13: 12-23.
Weimann C, Goransson U, Pongprayoon-Claeson U, Claeson P, Bohlin L, Rimpler H, Heinrich M (2002). Spasmolytic effects of Baccharis conferta and some of its constituents. J. Pharm. Pharmacol. 54(1): 99–104.
Weimann C, Goransson U, Pongprayoon-Claeson U, Claeson P, Bohlin L, Rimpler H, Heinrich M (2002). Spasmolytic effects of baccharis conferta and some of its constituents. J. Pharm. Pharmacol. 54(1): 99-104.
Yin Y, Gong FY, Wu XX, Sun Y, Li YH, Chen T, Xu QJ (2008). Anti-inflammatory and immunosuppressive effect of flavones isolated from Artemisia vestita. Ethnopharmacol. 120(1): 1-6.
Yokozawa T, Dong E, Kawai Y, Gemba M, Shimizu M (1999). Protective effects of some flavonoids on the renal cellular membrane. Exp. Toxicol. Pathol. 51(1): 9-14.
Youssef D, Frahm AW (1995). Constituents of the Egyptian Centaurea scoparia. III. Phenolic constituents of the aerial parts. Planta Med. 61(6): 570-573.
Yu ZW, Zhu HY, Yang XS, Sun QY, Hao XJ (2005). Study on chemical

constituents from Incarvillea arguta and their accelerating PC-12 cell differentiation. Zhongguo Zhong Yao Za Zhi. 30(17): 1335-1338.
Zhang QW, Zhang YX, Zhang Y, Xiao YQ, Wang ZM (2002). Studies on chemical constituents in buds of Artemisia scoparia. Zhongguo Zhong Yao Za Zhi. 27(3): 202-204.
Zhang W, Zhao DB, Li MJ, Liu XH, Wang HQ (2006). Studies on flavonoid constituents from herbs of Artemisia ordosica II. Zhongguo Zhong Yao Za Zhi. 31(23): 1959-1961.
Zhong J, Huang CG, Yu YJ, Li ZQ, Wang W, Huang XZ, Liu WX, Yuan Y, Jiang ZY (2015). Chemical constituents from Perovskiaatriplicifolia. Zhongguo Zhong Yao Za Zhi. 40(6): 1108-1113.
Zhu M, Phillipson JD, Greengrass PM, Bowery NG (1996). Chemical and biological investigation of the root bark of *Clerodendrum Mandarinorum*. Planta Med. 62(5): 393-396.