



Review Article

## Bioactive biflavonoids from *Wikstroemia indica* (L.) C.A. Mey. (Thymelaeaceae): A review

CHRISTIAN BAILLY

OncoWitan, Scientific Consulting Office. Lille (Wasquehal), 59290, France

### ABSTRACT

The roots of the plant *Wikstroemia indica* (L.) C.A. Mey., also known as Radix *Wikstroemiae* or Liaogewanggen in China, are used in traditional medicine as decoctions for the treatment of diverse inflammatory diseases, such as arthritis, bronchitis, and many other conditions. A large diversity of bioactive natural products have been characterized in *W. indica* including flavonoids, lignans, coumarins and sesquiterpenes. A scoping review was designed to identify the variety of biflavonoids isolated to date from the plant (mostly but not exclusively from the roots) and to depict their mode of action, based on database retrieval and a detailed analysis of all the relevant scientific literature. A focus has been made on two important series of C-3 linked dimeric compounds, sikokianins and wikstroflavones, and their anticancer properties and mechanism of action. Sikokianins A-D are atypical C-3/C-3'' biflavonoids, with sikokianin C as a lead molecule acting as an inhibitor of cystathionine  $\beta$ -synthase (CBS) and exhibiting marked anticancer properties *in vivo*. Wikstroflavones A-B and wikstaiwanones A-B are unusual flavone/flavanol dimers with a C-3/C-6'' linkage. Wikstroflavone B can potentiate the antiproliferative and antimetastatic activity of anticancer products. A few other biflavonoids have been isolated from the rhizomes of *W. indica*, such as daphnodorin derivatives. A biflavonoid-oriented survey of *Wikstroemia indica* is provided to highlight the potential benefit of the roots of *Wikstroemia indica* for the treatment of cancer.

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### 1. Introduction

The plant *Wikstroemia indica* (L.) C.A. Mey. (Thymelaeaceae), also known as "Salago" or "Tie bush", is native to (sub)tropical Asia to the south-west Pacific area. It can be found in many countries such as Australia, Bangladesh, China, India, Indonesia, Malaysia, Myanmar, Philippines, Thailand, and Vietnam. In China, the plant is essentially distributed in middle and southeast provinces. The name of the genus *Wikstroemia* was given by the Austrian botanist Stephan Ladislaus Endlicher (1804-1849) in honor of the Swedish botanist Johan Emanuel Wikström (1789-1856). There are more than 80 species with an accepted name in this genus (WFO, 2021). The species *W. indica* is a shrub growing in forests and on rocky slopes. It can grow between 50 and 200 cm in height and sometimes taller. It has glossy leaves and small green/yellow flowers and unpalatable red fruits (Fig. 1). Mass cultivation of *W.*

*indica* has been introduced in China. The inner bark can be used to make a high-quality paper.

The roots of *W. indica*, known as Radix *Wikstroemiae* (or Liaogewanggen or Liao Ge Wang in China, and Ryokao in Japan), are used in Chinese herbal medicine to treat various inflammatory diseases and conditions, including bronchitis, pneumonia, tonsillitis, parotitis and mastitis (Huang et al., 2010). The whole plant is also referred to as Nan-Ling-Jao-Hua in China (Suzuki et al., 1982). Radix *Wikstroemiae* is chronicled in the Chinese Pharmacopoeia (2015) as an essential herbal material. In particular, Liao Ge Wang is commonly used in Miao nationality of South China to treat multiple diseases, such as pneumonia, hepatitis, nephritis, traumatic injury and cancer (Feng et al., 2018). A Chinese product designated Pu Yin (Indian stringbush) and corresponding to Radix *Wikstroemia indica* is recommended to clear heat-toxins, to break masses, and to dispel water (reduce accumulations) to address a variety of conditions such

✉ Corresponding author: Christian Bailly  
 Tel: +33 622 66 18 17; Fax: +33 622 66 18 17

E-mail address: [christian.bailly@oncowitan.com](mailto:christian.bailly@oncowitan.com), doi: 10.30495/tpr.2021.1942441.1225



**Fig. 1.** The plant *Wikstroemia indica* (L.) C. A. Mey. (Thymelaeaceae), also known as Salago or Tie bush. The glossy leaves, with yellow flowers and the red fruits (not palatable). Most natural products discussed here have been isolated from the roots of the plant. There are many synonyms for this plant, such as *Wikstroemia ovalifolia* (Meisn.) Decne., *Wikstroemia pachyphylla* Merr., *Wikstroemia purpurata* (L.) Druce, *Wikstroemia rotundifolia* (L. f.) C.A. Mey., *Wikstroemia viridiflora* Wall. ex Meisn. and others (for details see: <http://www.theplantlist.org/tpl1.1/record/tro-32000565>). The photos were kindly provided by Mrs Gillian Gutridge, Sidney, Australia (<https://nbplantareas.com/wikstroemia-indica/>).

as pneumonia, tonsillitis, parotitis, scrofula, ascites, abdominal swellings, and toxic swelling due trauma (Best Chinese Medicines, 2021). Radix *Wikstroemiae* is also included in a multiterbal preparation designated Qi-Wei-Xiao-Yan-Tang (XYT) used as an anti-inflammatory and antimicrobial agent (He et al., 2013). The anti-inflammatory activity of *W. indica* extracts has been well characterized. Ethanolic extracts can be useful to treat cutaneous inflammation, notably in cases of atopic dermatitis (Lee et al., 2020). In traditional Chinese medicine, the plant has long been employed as antipyretic, detoxicant, expectorant, and vermifuge (Li et al., 2009). Leave extracts could be used to treat and reduce diarrheal episodes (Rahman et al., 2015). Many bioactive compounds, including flavonoids, coumarins, lignans, sterols and sesquiterpenes have been isolated from the root of *W. indica* (Li et al., 2009; Yao et al., 2010; Wei et al., 2015; Wang et al., 2019, 2021; Liu et al., 2021). Diverse guaiane-type sesquiterpenes have been found (Kato et al., 2014; Liu et al., 2020), such as the anti-inflammatory compound indicanone (Wang et al., 2005) and its isomers, namely  $\beta$ -hydroxypropiovanillone and *epi*-procurcumenol (Wang et al., 2019). Lignans were isolated such as wikstromol (also known as nortrachelogenin) (Yao et al., 2021), wikstronins A-B along with wikstresinol (Chang et al., 2017) and the anticancer agent arctigenin (Suzuki et al., 1982). Daphnane diterpenoids can also be found, such as genkwanine M endowed with anticancer properties (Zimmerman et al., 2013), as well as coumarins such as the dimeric compound daphnoretin (Ko et al., 2013; Chen et al., 2017). Most of these compounds have revealed anticancer properties. Common mono-flavonoids such as myricetin, luteolin, apigenin, thevetiaflavone and kaempferol can be found in the roots of the plant (Lu et al., 2012; Sun et al., 2015; Yao et al., 2017). However, the main characteristic of *W. indica* is the presence of biflavonoids, which are

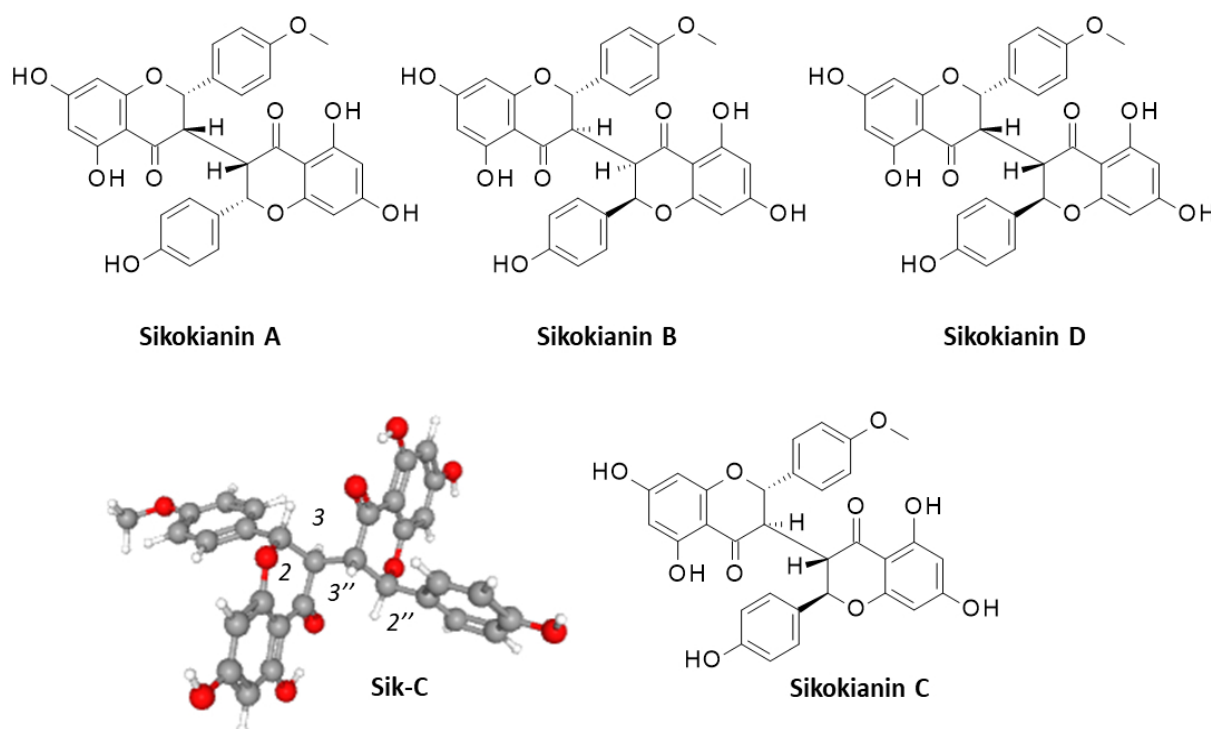
abundant and structurally diversified in the roots of the plant. The present review provides a survey of the various biflavonoid compounds isolated from *W. indica* roots to date and discusses their pharmacological properties. From a methodological perspective, extensive database retrieval, such as SciFinder and PubMed, was performed by using keywords like "*Wikstroemia indica*", "*Radix wikstroemiae*", and "biflavonoid". Relevant textbooks, patents, reviews, and digital documents were consulted to collate all available scientific literature and to provide a complete science-based survey of the topic. A better knowledge of the bioactive bioflavonoids found in the roots of *W. indica* is important. Some of these molecules may serve as chemotaxonomic markers for species assignment, as proposed with other plants of the Thymelaeaceae family (Andary et al., 2019) and with other specific *Wikstroemia* species (Lei et al., 2017).

## 2. Biflavonoids isolated from *W. indica*

Biflavonoids can be divided in two broad classes, C-C-type and C-O-C-type with an ether linkage between the two connected flavonoid units (Goossens et al., 2021). All biflavonoids isolated thus far from *W. indica* are C-C-type compounds, with a carbon-carbon linkage between the two units. There are different series of compounds, evoked below.

### 2.1. Sikokianins

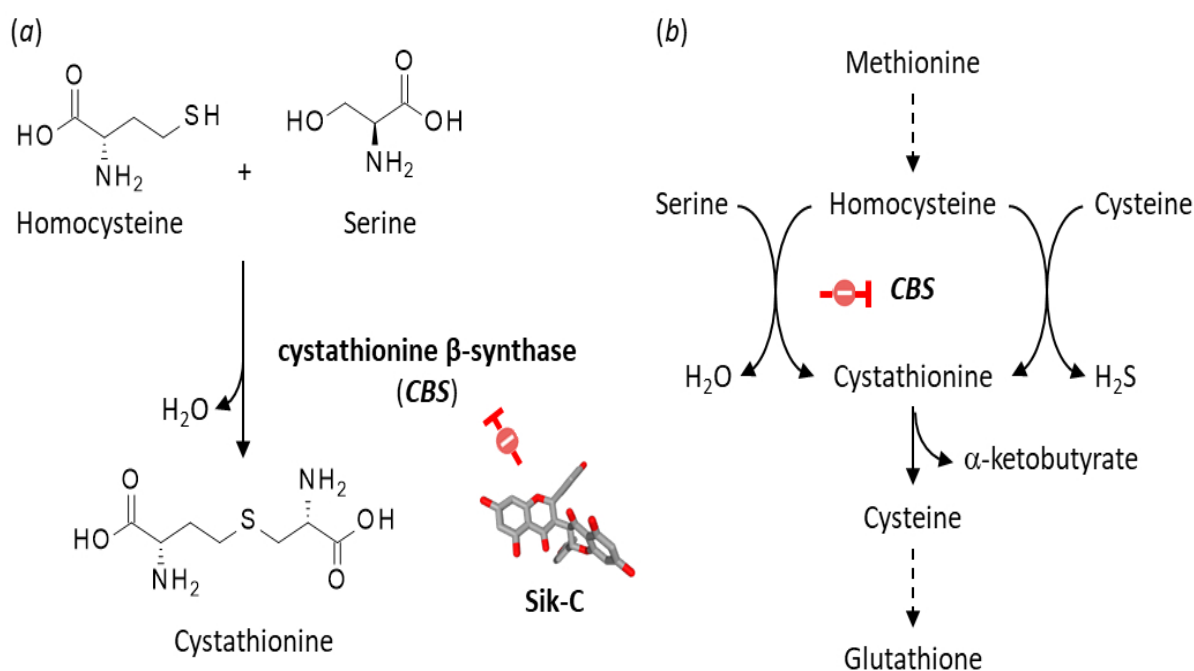
Phytochemical studies on the roots of *W. indica* have led to the isolation and characterization of the compounds called sikokianins A-D which are C-3/C-3" biflavanones (Fig. 2). Sikokianins A, B and C were initially isolated from *Wikstroemia sikokiana* Franch. & Sav. (known as "Gampi") and later found in *W. indica* (Niwa et al., 1986; Baba et al., 1994). Sikokianin A is an antioxidant agent capable of activating



**Fig. 2.** Chemical structures of sikokianins A-D. The two flavanone units are linked via the C-3 position. The compounds are stereoisomers ( $C_{31}H_{24}O_{10}$ , Mol. Weight: 556.5g/mol). They differ by the position of substituents at positions 2-3 and 2'-3'. A stereochemical model of Sik-C (2R,2'S,3S,3'R) is shown.

the Nrf2/HO-1 signaling pathway and probably at the origin of the neuroprotective effects of *W. indica* extracts (Yao et al., 2019). This compound bears a strong structural analogy with another type of C-3/C-3''-biflavonones: chamaejasmenin A-C isolated from the roots of *Stellera chamaejasme* L. (Yang et al., 2005). This is not surprising because the two plants *W. indica* and *S. chamaejasme* (both from the Thymelaeaceae family) are very close phylogenetically (Qian et al., 2019, 2020). Sikokianin A has revealed weak antifungal and antiviral activities *in vitro* (minimum inhibitory concentration (MIC) >100  $\mu\text{g}/\text{mL}$ ) (Yang et al., 2005; Yang and Chen, 2008) and a marked antioxidative action, protecting pheochromocytoma PC-12 cells (a classical injury cell model) from oxygen glucose deprivation/reperfusion-induced injury. At 1 mM, sikokianin A was found to protect PC-12 cells from oxidative damage and to reduce the rate of cell death (Yao et al., 2019). In other assays, this compound contributes to the pro-apoptotic activity of *S. chamaejasme* extracts (Liu et al., 2012). Sikokianins B and C were first isolated from a *n*-butanol extract of the roots of *W. indica* and initially characterized as antimalarial agents, active against a chloroquine-resistant strain of *Plasmodium falciparum* ( $IC_{50} = 0.54$  and  $0.56$   $\mu\text{g}/\text{mL}$ , respectively) (Nunome et al., 2004). Subsequently, these two compounds were found to present anti-inflammatory properties. They both inhibited nitric oxide (NO) production in RAW 264.7 macrophages stimulated by lipopolysaccharide

(LPS) and interferon-g (IFN-g) (Wang et al., 2005). Sikokianin C (Sik-C) is particularly interesting because it was found to display marked anticancer effects, with an innovative mechanism of action. This compound targets the enzyme cystathionine  $\beta$ -synthase (CBS) which is a key pyridoxal-5'-phosphate-dependent heme enzyme in the *trans*-sulfuration pathway. This enzyme is frequently overexpressed in colon cancer cells (Phillips et al., 2017; Zhu et al., 2018). CBS is directly implicated in the metabolism of homocysteine and the generation of hydrogen sulfide, as represented in Fig. 3. Sik-C functions as a potent CBS competitive inhibitor ( $IC_{50} = 0.9$   $\mu\text{M}$ ) (Niu et al., 2017). A molecular modeling analysis of the Sik-C/CBS complex indicated that five key amino acid residues of the CBS enzyme (Thr-193, Asn-194, His-203, Tyr-223 and Tyr-308) were essential to stabilize the complex via H-bond interactions with the phenolic hydroxyl groups and the carbonyl group of Sik-C. Point mutations of each of these key amino acids markedly decreased the capacity of the compound to inhibit CBS. For example, the inhibitory potency decreased considerably upon point mutation of residue His-203. The  $IC_{50}$  value increased from 0.9  $\mu\text{M}$  with the wild-type CBS enzyme to 43.0  $\mu\text{M}$  with the H203A (His -> Ala) CBS mutant, attesting of the major influence of this residue for the drug interaction. CBS was found to play a partial role in colon cancer (HT29) cell growth inhibition induced by Sik-C *in vitro*. Moreover, this biflavonoid revealed an antitumor activity *in vivo*, reducing partially



**Fig. 3.** The enzyme cystathionine  $\beta$ -synthase (CBS) targeted by sikokianin C. (a) CBS (EC 4.2.1.22) catalyzes the synthesis of cystathionine from serine and homocysteine. It is a L-serine hydrolyase. (b) CBS is implicated in homocysteine metabolism and its conversion to cysteine, in the frame of the *trans*-sulfuration pathway.

(50%) the growth of HT-29 tumor in mice, when injected daily at 3 and 10 mg/kg (Niu et al., 2017). Although the compound is not extraordinarily potent as an anticancer agent, the discovery that Sik-C targets CBS is important because this enzyme is dysregulated in different pathologies, including the Down syndrome which is a chromosomal disorder causing intellectual disability in children (Zuhra et al., 2020). CBS is not a unique target for Sik-C, but the compound could be used to design more potent anticancer analogues. It would be interesting to compare the capacity of the different sikokianins to inhibit CBS, notably sikokianin D (Sik-D) which has been isolated from an ethanolic extract of roots of *W. indica* (Li et al., 2012) and can be found also in *S. chamaejasme* extracts. Sik-D displays marked antiproliferative activities against cancer cell lines, notably a sub-micromolar activity against HT29 colon cancer cells ( $IC_{50} = 0.75 \mu M$ ) (Wang et al., 2014). At this point, it is worth mentioning that two related natural products, named sikokianin D and E have been isolated from the plant *Coreopsis tinctoria* Nutt. (genus *Coreopsis*; family Compositae), but they are bis-glycosylated biflavonones, with one C7-glucose residue on each flavonoid unit (Yan et al., 2017). They are thus distinct from the above discussed sikokianins which are not glycosylated. Non-glycosylated sikokianin derivatives can be found in other plants, such as sikokianin B isolated from the Kenyan medicinal plant *Ormocarpum kirkii* S.Moore (Xu et al., 2011).

Parenthetically, the term sikokianin should not be confused with shikokianin which refers to an ent-kaurane diterpenoid, with a totally distinct structure (Zhang et al., 2009).

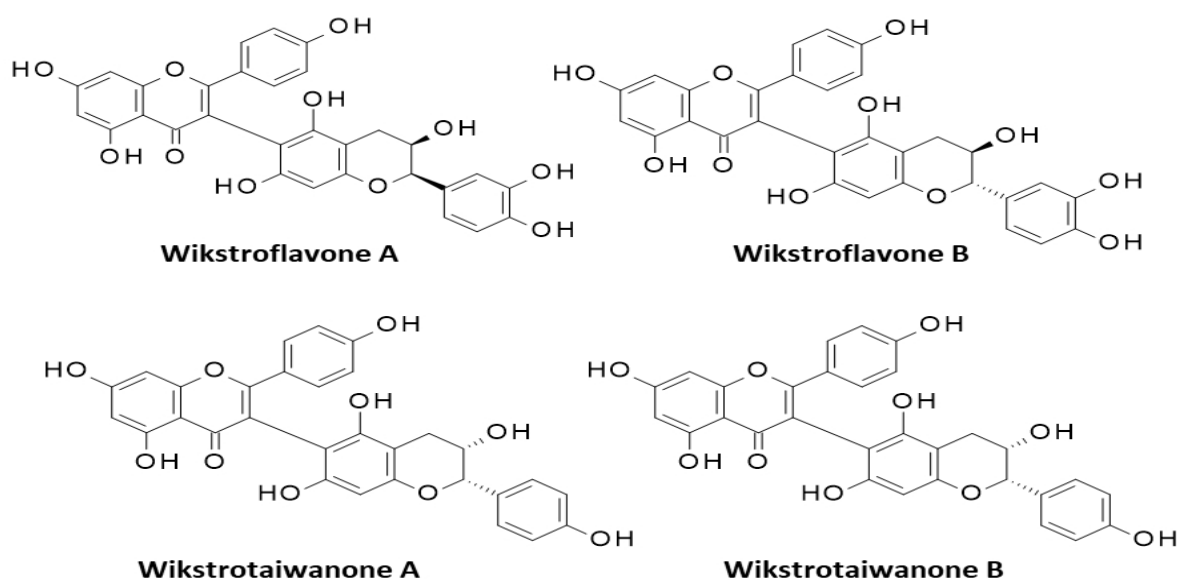
## 2.2. Wikstroflavones and wikstaiwanones

Four biflavonoid compounds designated wikstroflavones A-B and wikstaiwanones A-B have been isolated from the rhizome of *W. indica* (Wang et al., 2018; Shao et al., 2020). Wikstaiwanones were initially isolated from the stem of the related plant *W. taiwanensis* C.E. Chang which also contains sikokianin derivatives (Chen et al., 2012). Wikstaiwanones A-B are constituted by a flavone and a flavan-3-ol moieties, connected by a relatively rare C-3/C-6" linkage (Fig. 4). Wikstaiwanone B has been also isolated from the plant *Thymelaea hirsuta* (L.) Endl. (a traditional medicinal plant known as "Methnane" in North Africa) and the compound has revealed a very modest antiproliferative activity against HepG2 hepatocellular carcinoma cells *in vitro* ( $IC_{50} = 51 \mu g/mL$ ) (Badawy et al., 2021). Wikstroflavones and wikstaiwanones were found to exhibit moderate cytotoxic activities against different cancer cell lines, with  $IC_{50}$  in the 17-35  $\mu M$  range for wikstaiwanones A-B and  $IC_{50}$  in the range of 71-88  $\mu M$  for wikstroflavone A with the same cancer cell lines (Wang et al., 2018). In contrast, a recent study indicated that wikstroflavone B (Wf-B) is a more potent and



interesting compound. Wf-B modestly inhibited the growth of human nasopharyngeal carcinoma (NPC) cell lines *in vitro* but showed a marked synergistic activity in the presence of the polyphenol curcumin (from *Curcuma*). For example, the  $IC_{50}$  dropped from 55.1  $\mu$ M for Wf-B alone (and 31 mM for curcumin alone) to less than 8 mM when the two compounds were added together to limit the proliferation of CNE1 NPC cells.

The combination drastically reduced the migration and invasion of CNE1 cancer cells and repressed the expression of key proteins implicated in cell motility, notably matrix metalloproteinases MMP-2 and MMP-9, as well as the FAK/STAT3 signaling pathway (Shao et al., 2020). Wf-B warrants further investigations, but at present no molecular target has been evidenced for this biflavonoid.



**Fig. 4.** Chemical structures of wikstroflavones A-B and wikstrotaiwanone A-B.

### 2.3. Other biflavonoids

Daphnodorins form a heterogeneous group of compounds principally isolated from *Daphne* species, such as the medicinal plant *D. genkwa* Sieb. et Zucc. (Zheng et al., 2007; Zhou et al., 2021). They can be found in many plants, including *W. indica* which contains 3'-hydroxydaphnodorin A (Fig. 5), a chalcone-flavone hybrid with a weak cancer cell growth inhibitory capacity (Shao et al., 2016). Other daphnodorin derivatives have been isolated from *W. indica* such as daphnodorins D1 and D2, and their 4-methoxy analogues, as well as 4'-methoxydaphnodorin E (Huang et al., 2012), and the atypical spirobiflavonoid daphnodorin M (Zhang et al., 2011) (Fig. 5). Other minor products have been identified from the root bark of the plant (Ko et al., 2013). 4'-Methoxydaphnodorin E is a polycyclic furanspirobiflavonoid capable of inhibiting the multiplication of the respiratory syncytial virus (RSV) in cells ( $IC_{50} = 2.8 \mu$ M) (Huang et al., 2012). Genkwanol A-C are stereo isomers of spirobiflavonoids with antiviral effects (Huang et al., 2010). The present phytoanalysis is focused on the biflavonoid profile of *W. indica* but, of course, the plant contains many other bioactive substances including

monoflavonoids, coumarins, sesquiterpenes, etc.. The phytochemical footprint of *Wikstroemia* species is very broad, as observed in other medicinal plants (Mohammadhosseini et al., 2021a, 2021b; Nahar et al., 2021).

### 3. Concluding remarks

The plant *W. indica* is a commonly used herbal medicine in China, and in a few other Asian countries. It is a relatively non-toxic herb, frequently used as root decoctions to treat inflammatory problems, arthritis, pneumonia, genital infections, cancers and other diseases. The plant has the reputation to be poisonous (at least the fruits, non-palatable) but a specific toxicological assessment revealed that it is a relatively nontoxic plant. Aqueous and ethanolic extracts prepared from dried and powdered roots of *W. indica* showed no obvious acute toxicity in mice. Different extracts have been tested (upon boiling of the plant material in the solvent for 1 to 10 hours), but the extracts administered orally were well tolerated, causing no major toxicities. In all cases, the maximum tolerated dose was  $>10$  g/kg (Huang et al., 2009). Nevertheless, caution must be exercised with the red fruits considered as toxic (possibly inducing

dizziness, blurred vision, nausea, vomiting, abdominal pain and diarrhea) (Alchetron Encyclopedia, 2018). Robust scientific or medical data to support the supposed toxicity of the fruits are lacking. But this assumption is likely because the closely related plant *Stellera chamaejasme* L. is viewed as one of the most toxic weeds in north and west China (Yan et al., 2015). The ethnobotanical and traditional usage of the plant, essentially the dried rhizomes, are extended and a plethora of secondary metabolites has been isolated from *W. indica* (Suroowan and Mahomoodally, 2020). *W. indica* is phylogenetically close to *Stellera chamaejasme*, a plant known for its high content in cytotoxic biflavones, notably the chamaejasmenins (Yang et al., 2005; Zhang et al., 2013; Wang et al., 2014; Li et al., 2014). It is therefore not entirely surprising to find a diversity of related anticancer biflavonoids in the roots of *W. indica*. Extracts of the roots of *W. indica* contain a panoply of bioactive biflavonoids evoked here. One of the most interesting biflavonoids is sikokianin C (Sik-C), characterized as an inhibitor of cystathionine  $\beta$ -synthase (CBS), a key enzyme of the *trans*-sulfuration pathway. As a CBS inhibitor, Sik-C is more potent than other biflavonoids such as cupressuflavone and agasthisflavone (Zuhra et al., 2020). Therefore, it would be useful to investigate further the targeting of CBS by all four sikokianins (A-D) and other structurally related C3/C3'' biflavonoids such as chamaejasmin A and chamaejasmenin C (also known as ruixianglangdusu A and B). Chamaejasmins belong to a family of guaiane sesquiterpenes from the root of *Stellera chamaejasme* L. (Wang et al., 2014; El-Desoky et al., 2020) and chamaejasmins A and B are potent anticancer agents but their mechanism of action is not well-defined at present (Zhao et al., 2012; Wang et al., 2015; Qian et al., 2017; Si et al., 2020). These different C3/C3'' biflavonoids should be considered further as potential

CBS inhibitors. This type of biflavonoid compounds may be useful to combat cancer, and microbial diseases as well (Menezes and Campos, 2021). Collectively, the present literature survey shed light on the rich biflavonoid content of the roots of *W. indica* (Liaogewanggen). Notably, the presence of relatively rare C3/C3'' biflavonoids is highlighted. Compounds such as sikokianin C targeting the CBS enzyme and wikstroflavone B are potent anticancer natural products derived from Liaogewanggen. The traditional usage and health benefits of the plant roots warrant further consideration.

### Abbreviations

CBS, cystathionine  $\beta$ -synthase; Sik-C, sikokianin C; Wf-B, wikstroflavone B

### Funding

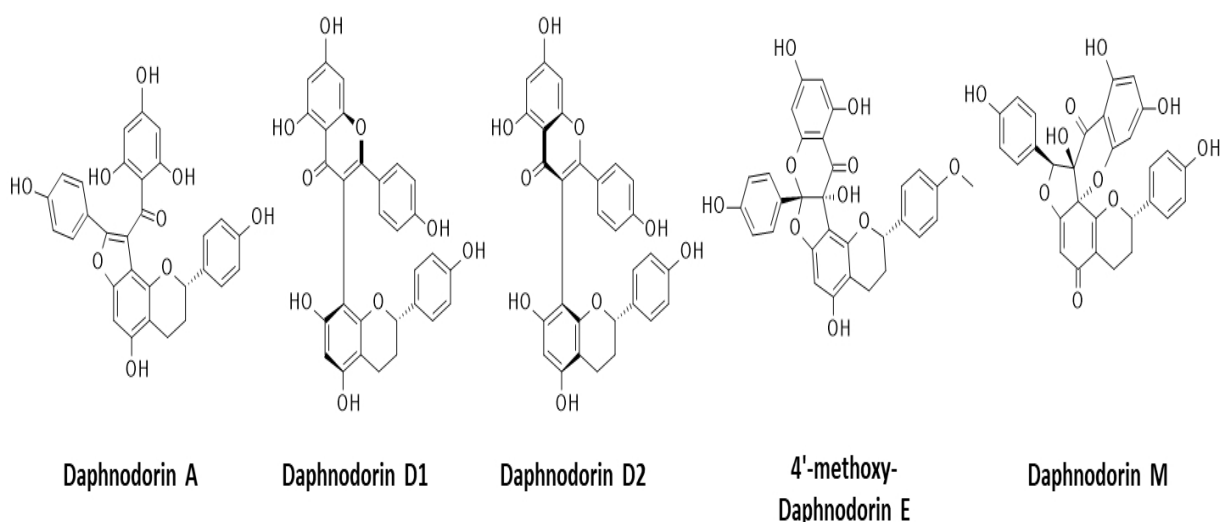
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### Conflict of interest

The authors declare that there is no conflict of interest.

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**Fig. 5.** Chemical structures of five daphnodorin derivatives which can be found in *Wikstroemia indica*.



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