Traditional Use, Pharmacology and Toxicology of the Lignans in Genus Kadsura: A Systematic Review

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Abstract: The genus Kadsura is an important part of traditional Chinese medicine, it has the functions of promoting wind, eliminating dampness, activating blood circulation. Modern pharmacological studies have shown that lignans are one of the main components to possess these medicinal effects. This review aimed to provide a systematic summary on the traditional use, phytochemistry, pharmacology, toxicology and other aspects of lignans in genus Kadsura. In this paper, we collected the relevant literature on Kadsura lignans from 1973 to the present, and isolated more than 337 lignans from this genus, including dibenzocyclooctadienes, aryltetralins, tetrahydrofurans, diarylbutanes, 7,8-seco-lignans, bisepoxylignans, neolignans, seco-dibenzocyclooctadienes, sesqu lignan and coumarin-containing lignan. Previous pharmacological studies have shown that lignans of the genus Kadsura have antitumor, anti-inflammatory, antibacterial, anti-HIV, anti-platelet aggregation, immunomodulatory and antioxidant effects. In clinical practice, it is commonly used to treat Alzheimer's disease, inflammation and insomnia. Kadsura is an important part of the field of Chinese medicine and is widely used in traditional medicine. However, further clarification of its active ingredients and mechanism of action and the establishment of a complete quality standard system are needed in order to provide a scientific basis for in-depth studies of this genus.

Keywords: Kadsura; traditional uses; lignans; pharmacology; toxicity. © 2022 ACG Publications. All rights reserved.

1. Introduction

The genus Kadsura is one of the subgenera of the family Schisandraceae, which is mainly distributed in eastern and southeastern Asia, eight species and four endemic species are recorded in China [1]. It is a

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Traditional use of genus *Kadsura*

widely used Chinese herb among Chinese folklore and was first described in Shennong’s Herbal Classic, where it was recorded to have the effects of moving qi and relieving pain, activating blood circulation and removing blood stasis, dispelling wind and dampness, and was used to treat headaches and hypertension [2].

In recent years, a great deal of research has been conducted on the phytochemical and biological activities of plants of the genus *Kadsura*. Several new compounds with unprecedented structures have been isolated, further enriching the range of natural products. The results showed that lignans are the main pharmacological substance base for exerting clinical efficacy. Therefore, the study of lignin monomer composition should draw attention. The in vitro antitumor activity evaluation test confirmed that biphenyl cyclooctene lignans extracted from *K. oblongifolia* have significant antitumor activity and can be used for the preparation of antitumor drugs, especially for lung, nasopharyngeal and colorectal cancers. In addition, this class of components has shown its excellent immunoprotected effects in immunomodulation and organ transplantation. Studies have shown that they possess a variety of beneficial biological activities, such as anti-HIV, anti-tumor, anti-hepatitis, antioxidant, anti-platelet aggregation activity and neuroprotective effects. Research on the development of the genus *Kadsura* does not stop here, as the development of wine, health products and cosmetics has been welcomed by many countries and regions, showing far-reaching market potential [3-5].

In order to assess the medicinal potential of lignans in the genus *Kadsura*, this article presents a systematic structural classification of lignans. Additionally, a comprehensive summary of the development of lignans, including their traditional usage, pharmacological activity, and toxicity evaluation, was presented. The aim of this analysis was to provide a thorough understanding of the current state of research and exploitation of lignans, as well as to offer insights into their future potential for use in the medical field.

2. Search strategy

In this paper, a comprehensive study and analysis of previously published literature was carried out to investigate the traditional uses, phytochemical and pharmacological activities of lignans from the genus *Kadsura*. All literature on the genus *Kadsura* was collected by using databases such as Medline PubMed, Science Direct, Sci Finder, Baidu Scholar, Google Scholar and CNKI, and finally 175 references were selected for use in the article. The keywords searched included: genus *Kadsura*, *Kadsura longipedunculata*, *Kadsura cocinea*, patent reports, *Kadsura* uses and toxicity assessment. Some of the analysed studies were obtained by manually searching articles in the reference lists of the included studies. Chemical structures were drawn with Chem Draw Professional 20.0 software.

3. Botany, description, and distribution

Currently, about 8 species (four endemic) of the genus *Kadsura* have been reported in China, including *Kadsura ananosma*, *Kadsura cocinea* (Variety name *Kadsura cocinea* var. Sichuanensis), *Kadsura heteroclita*, *Kadsura induta*, *Kadsura japonica*, *Kadsura longipedunculata*, *Kadsura oblongifolia* and *Kadsura renchangiana* [6]. Meanwhile, In the *Flora of China*, *Kadsura interior* and *Kadsura ploysperma* are clearly classified as *K. heteroclita*. The following are the main characteristics of this genus. Vines, woody, glabrous (except *K. induta*). Leaf blade elliptic, ovate, or obovate, papery to leathery, base cuneate (especially when young), broadly cuneate, truncate, or subcordate, margin denticulate to entire, apex acute to acuminate. Staminate flowers: stamens 13-80, distinct but basally connate or sometimes tightly aggregated into a sub globose mass. Pistillate flowers: carpels 17 to ca. 300, distinct; stigmatic crest forming subulate or laterally flattened "pseudostyle" or modified as sub peltate or irregular "pseudo stigma"; ovary with 1-5(-11) pendulous or ventrally attached ovules. Fruit aggregates of apocarps; receptacle ellipsoid or clavate; apocarps
ripening red or yellow, sub globose, obovoid, or elongate-obovoid. Seeds 1-5(-11) per apocarp, smooth. They mostly grow on mountain slopes, along streams or in dense forests at altitudes of 500-2000 m [7-11].

4. Traditional use

Genus *Kadsura* is an herb widely used in ancient China, giving birth to many Chinese medical prescriptions due to its good effects. It is recorded in the *Chinese Materia Medica* and *Shennong’s Herbal Classic*. It is written that it can be used to treat rheumatism, inflammation, traumatic injury and burns. Furthermore, it is recorded in *Zhejiang folk herbal medicine* that the leaves of *K. longipedunculata* can be used to treat knife wounds by pounding them and applying [12-13]. It is worth mentioning that *K. longipedunculata* is one of the "Shi ba zuan" of Yao medicines, which refers to it as "Xiao zuan". Meanwhile, *K. coccinea* (Da zuan), *K. heteroclite* (Da hong zuan), *K. oblongifolia* (Xiao hong zuan) and *K. renchangiana* (Tie zuan) also belong to the "Shi ba zuan" group. Because of its traditional and regional nature, it has gradually formed a Yao medicine with ethnic characteristics [14-16].

In modern times, plants of the genus *Kadsura* are also used in clinical treatment, mainly for digestive disorders, bone and joint diseases and for the treatment of various pains [17-18]. In this article, we have collected proprietary Chinese medicines or preparations of the genus *Kadsura*, including empirical prescriptions for folk use and in-hospital preparations (Table 1, Figure 8)

### Table 1. Traditional uses of the genus *Kadsura*

<table>
<thead>
<tr>
<th>Species</th>
<th>Local name</th>
<th>Part</th>
<th>Dosage form</th>
<th>Traditional clinical uses</th>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Xiao zuan,</td>
<td>roots</td>
<td>Powder (orally)</td>
<td>chronic cough</td>
</tr>
<tr>
<td></td>
<td>Hong mu xiang,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zi jin pi,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Xiao xue teng,</td>
<td></td>
<td>Decoction (orally)</td>
<td>Pulitations, night sweating, rheumatism, chronic gastritis, acute gastrointestinal ascites</td>
</tr>
<tr>
<td></td>
<td>Tu mu xiang.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>K. coccinea</em></td>
<td></td>
<td>roots and stems</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Da zuan,</td>
<td></td>
<td>Powder (orally)</td>
<td>postpartum hemorrhage, chronic gastritis, stomachache, cirrhotic ascites, dysmenorrhea, amenorrhea, acute gastroenteritis, gastric ulcer, gastrointestinal ulcer</td>
</tr>
<tr>
<td></td>
<td>Leng fan tuan,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Guo shan long teng,</td>
<td></td>
<td>Vinum (orally)</td>
<td>labor Injuries</td>
</tr>
<tr>
<td></td>
<td>Chou fan tuan,</td>
<td></td>
<td>Decoction, vinum (orally)</td>
<td>rheumatism</td>
</tr>
<tr>
<td></td>
<td>Xue teng.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mash (External application)</td>
<td>traumatic injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tablets (orally)</td>
<td>dysentery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Injections</td>
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</table>
5. **Lignans in genus Kadsura**

In recent years, scholars have isolated a variety of active ingredients from the genus *Kadsura*, and found that its fruits, rhizomes mainly contain lignans, triterpenes, volatile oils, polysaccharides and other...
components. Among them, lignans are the main components, and 337 lignans have been isolated from this genus, according to its structure it is divided into dibenzocyclooctadienes, aryltetralins, dibenzylbutanes, monoepoxy lignans, 7,8-seco-lignans, bisepoxy lignans, neolignans, seco-dibenzocyclooctadienes, sesquilignan and coumarin-containing lignan. The specific compound names and structures are shown in Table 2 and Figures 1-7.

Table 2. Lignans from Kadsura genus

<table>
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Traditional use of genus *Kadsura*

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**Bisepoxylignans**

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5.1. *Dibenzocyclooctadienes*

Scholars have isolated a large number of dibenzocyclooctadienes from the genus *Kadsura*. A summary analysis of the components of this group shows that these lignans have two aromatic protons at C4 and C11 of the biphenyl ring, and positions 1~3 and 12~14 of the benzene ring on both sides of the structure are mainly substituted with hydroxyl, methylenedioxy or methoxy groups. In addition, a series of new spirobenzofuranoid-dibenzo cyclooctadiene-type lignans were identified Table 3 and Figure 1.
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Traditional use of genus *Kadsura*

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| 102 | kadheterin G | OCH$_2$O | OMe | OH | OMe | OMe | β-Olsobut | β-Me, α-OH | a-Me | a-OAng | [47] | A |
| 103 | kadheterin H | OCH$_2$O | OMe | OH | OMe | OMe | β-OAng | β-Me, α-OH | a-Me | a-Olsoval | [47] | A |
| 104 | 9-benzyloxy-gomisin B | OCH$_2$O | OMe | OMe | OMe | OMe | β-OAng | β-Me, α-OH | a-Me | a-OBz | [47] | A |
| 105 | kadsuphilol R | OCH$_2$O | OMe | OH | OMe | OMe | β-OAng | β-Me, α-OH | a-Me | a-OAng | [47] | A |
| 106 | kadsuphilol T | OCH$_2$O | OMe | OH | OMe | OMe | β-OBz | β-Me, α-OH | α-Me | a-OAng | [47] | A |
| 107 | kadsuphilin F | OCH$_2$O | OMe | OH | OMe | OMe | a-Me | α-Me, β-OH | a-OBz | [47] | A |
| 108 | heteroclitin A | OCH$_2$O | OMe | OMe | OMe | OMe | a-Me | α-Me | α-Olsobut | [48] | A |
| 109 | heteroclitin B | OCH$_2$O | OMe | OMe | OMe | OMe | a-Me | α-Me | a-OAng | [48] | A |
| 110 | heteroclitin C | OCH$_2$O | OMe | OMe | OMe | OMe | a-Me | α-Me | a-OTig | [48] | A |
| 111 | kadsuralignan I | OCH$_2$O | OMe | β-OAng | OMe | OMe | α-Me | α-Me | a-OH | [49] | A |
| 112 | kadsuralignan K | OCH$_2$O | OMe | β-OBz | OMe | OMe | a-Me | α-Me | α-OH | [49] | A |
| 113 | ananinon A | OCH$_2$O | OMe | OMe | OMe | OMe | β-OBz | a-Me | a-Me | α-OH | [50] | A |
| 114 | ananinon B | OCH$_2$O | OMe | OMe | OMe | OMe | β-OBz | a-Me | α-Me | a-OAc | [50] | A |
| 115 | ananinon C | OCH$_2$O | OMe | OMe | OMe | OMe | β-OBz | α-Me | a-Me | a-OProp | [50] | A |
| 116 | ananinon D | OCH$_2$O | OMe | OMe | OMe | OMe | β-OBz | a-Me | a-Me | a-OBut | [50] | A |
| 117 | ananinon E | OCH$_2$O | OMe | OMe | OMe | OMe | β-OBz | a-Me | α-Me | a-Olsobut | [50] | A |
| 118 | ananinon F | OCH$_2$O | OMe | OMe | OMe | OMe | β-OBz | a-Me | a-Me | a-Olsoval | [50] | A |
| 119 | ananinon G | OCH$_2$O | OMe | OMe | OMe | OMe | β-OAng | a-Me | a-Me | a-Olsoval | [50] | A |
| 120 | ananinon H | OCH$_2$O | OH | OMe | OMe | OMe | β-OAng | a-Me | a-Me | a-OAc | [50] | A |
| 121 | ananinon I | OCH$_2$O | OH | OMe | OMe | OMe | β-OAng | a-Me | a-Me | a-OProp | [50] | A |
| 122 | ananinon J | OCH$_2$O | OH | OMe | OMe | OMe | β-OAng | a-Me | a-Me | a-Olsoval | [50] | A |
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| 124 | ananinon L | OH | OMe | OMe | OMe | OMe | β-OAng | a-Me | a-Me | a-OAc | [50] | A |
| 125 | ananinon M | OH | OMe | OMe | OMe | OMe | β-OBz | a-Me | a-Me | a-OH | [50] | A |
| 126 | ananinon N | OH | OMe | OMe | OMe | OMe | β-OBz | a-Me | a-Me | a-OAc | [50] | A |
| 127 | kadsuralignan B | OCH$_2$O | OMe | OMe | OMe | OMe | β-OAc | β-Me, α-OH | a-Me | a-OAc | [45] | A |</p>
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Traditional use of genus *Kadsura*

Figure 1. Structure of dibenzocyclooctadienes lignans in the genus *Kadsura*
5.2. Aryltetralins

Aryltetralins are formed by the cyclization of the C6 position in one phenylpropanoid unit with the C7 position of another phenylpropanoid. The common characteristic absorbing groups of this class of lignin are hydroxyl and carbonyl groups, etc. (Figure 2).

![Figure 2. Structure of aryltetralins lignans in the genus Kadsura](image)

5.3. Dibenzylbutanes

The conformation of this group of compounds (86~97) is feature by a borated methyl group or an exocyclic double bond at C-12, which are currently isolated only from plants such as K. induta, K. coccinea and K. polysperma, the specific structures of which are shown in Figure 3.

This group is characterized by the presence of tetrahydrofuran structures based on simple lignan, with 7-O-7', 9-O-9' or 7-O-9' types of structure being more common and the structures often having symmetry (Figure 3).
5.4. Monoepoxylignans

The compounds in this group (98–124) are formed by breaking C-13 and C-14 in the structure of lanostane-type triterpenoids and forming a new ring between C-12 and C-14, generated via Wagner-Milwyn rearrangement, as shown in Figure 4.

Monoepoxylignans is formed by linking two molecules of phenylpropanoid (Figure 4). In addition, this type of lignan is also a biogenic precursor for a number of other types of lignan.
Figure 4. Structure of monoepoxylignans in the genus *Kadsura*

5.5. 7,8-seco-lignans

This group of compounds is derived from the oxidative cleavage of the C7, C8 bond of the aryl tetrahydrofuran lignan. See Table 1 and Figure 5 for specific structures and names.

5.6. Bisepoxylignans

The bisepoxylignans are also formed by the interconnection of two groups of phenylpropanoids, in most cases with a skeleton of four chiral carbon spin isomers (Figure 5). Due to the symmetry of the structure, the hydrogen and carbon spectra often show overlapping signals.
5.7. Neolignans

It is formed from two phenylpropanoids linked by side chains, in addition, neolignans can also be C6-C3 monomers consisting of two monomers linked as oxygen bonds via an oxyether bond (Figure 6).
5.8. Seco-dibenzocyclooctadienes

Qi et al. [79] isolated four structurally novel seco-dibenzocycloctadiene lignans from the roots of *K. longipedunculata* and elucidated their structures by wave spectroscopy techniques (Figure 7).

5.9. Sesquilignan

Guo et al. [82] isolated a sesquilignan (pinobatol) with a spirodienone structure from *K. longipedunculata* (Figure 7), and it was reported that only one sesquilignan with a helical skeleton has been reported to date.

5.10. Coumarin-containing lignan

Compound 337 with a unique coumarin-contain lignan skeleton which was isolated from stems of *K. heteroclita* (Figure 7).

![Figure 7. Structure of dibenzocyclooctadienes, sesquilignans and coumarin-containing lignan in the genus *Kadsura*](image)

6. Pharmacological activities

6.1. Hepatoprotective and Anti-inflammation Activity

Oh et al. [84] found that gomisin J, gomisin N and schisandrin C were able to reduce nitric oxide (NO) production in LPS-stimulated Raw 264.7 cells. All three lignans had a low cytotoxic effect on Raw 264.7 cells. Pretreatment of Raw 264.7 cells with gomisin J, gomisin N and schisandrin C reduced mRNA expression and secretion of pro-inflammatory cytokines. These inhibitory effects were induced by blocking p38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase 1 and 2 (ERK 1/2), and c-Jun N-terminal kinase (JNK) phosphorylation for the prevention of inflammation. The researchers isolated two new dibenzocyclooctane lignans kadsurindutin A and B, and known lignans schisantherin L, schisantherin P, kadsulignan L and neokadsuranin from *K. induta* stems and tested these six compounds for the anti-HBV activity of these six compounds was tested in vitro. The compounds
kadsurindutin A, kadsulignan L and neokadsuranin were found to have in vitro antiviral effects against hepatitis B virus. The compounds kadsulignan L and neokadsuranin (concentration 0.1 mg/ml) are known to have some antiviral activity with inhibition of HBsAg and HBeAg of 32.6 and 36.5%, 14.5 and 20.2%, respectively. Compound kadsurindutin A at 0.2 mg/ml concentration showed HBsAg and HBeAg effects of 35.4 and 15.4%, respectively [25]. The compounds longipedlignan F and schiarisanrin B were found to have moderate hepatoprotective activity against N-acetaminophen-induced HepG2 cells using the hepatoprotective drug dicyclanol as a positive control. Cell survival was 52.2% and 50.2% at a concentration of 10 μM (49.0% with dicyclomine), respectively [26]. In addition, longipedlignan M was found to have similar hepatoprotective activity, with a cell survival rate of 50.8% at a concentration of 10 μM [71].

The potential anti-RA activity of four compounds, heilaohuusus A-D, isolated from K. coccinea, was measured on RA-FLS cells. It was found that heilaohusu A had potential anti-RA activity on RA-FLS cells with an IC50 value of 14.57 μM [34]. Jia et al. [70] examined the cellular activity of the isolated compounds heilaohugousus A-N and showed that heilaohugousu A and heilaohugousu L had good hepatoprotective activity against APAP-induced HepG-2 cells, with 10 μM cell survival rates of 53.5 ± 1.7% and 55.2 ± 1.2%, respectively (positive control, dicyclomine, 52.1±1.3%). Huang et al. [73] found that only angeloyl-binankadsurin A, angeloyl-binankadsurin B and acetyl-binankadsurin A had anti-HBV activity during the screening of anti-HBV active substances. Among them, angeloyl-binankadsurin A showed the strongest activity with 51.85% inhibition of HBeAg and an IC50 of 48.0 μg/mL. By comparing their structural features, the hydroxyl group at the 1 position may be the key group for the anti-HBV activity of these compounds. Liu et al. [86] reported the effects of K. longipedunculata on serum indices in mice with acute liver injury caused by D-GalN. The results pointed out that ALT and AST activities were significantly lower in the K. longipedunculata high-dose group compared with the model group, indicating that the drug group had a protective effect on D-GalN-induced liver injury. Moreover, it was also found that all dose groups of K. heteroclita alcohol extract reduced AST and ALT activity in rat serum, alleviated CCl4-induced liver histopathological changes, and significantly increased GSH content in liver homogenate while reducing liver coefficients, indicating its protective effect on CCl4-induced acute liver injury, and it is speculated that its anti-liver injury mechanism may be related to enhancing the ability of rats to scavenge free radicals [87].

6.2. Anticancer Activity

Huang et al. [20] isolated four new dibenzocyclooctadiene lignans from K. oblongifolia and performed in vitro toxicity assays on these four compounds to evaluate the cytotoxic activity against tumors including A549, DU145, KB and HCT-8. Kadsufolin D exhibited strong cytotoxic activity against A549 and HCT-8. The GI50 values were 5.1 mg/ml and 5.7 mg/ml, respectively, while kadsufolin A showed only weak cytotoxic activity against these cell lines, with GI50 values ranging from (10.55-20.0) mg/ml. Wang and co-workers investigated a series of lignans from K. interior, initially using short-term in vitro experiments on EBV-EA activation, to observe the inhibitory effect of these compounds on TPA-induced EBV-EA activation and the associated viability of Raji cells. The results showed that all compounds had an inhibitory effect on EBV-EA activation but no cytotoxic effect on Raji cells. The experimental data suggest that neokadsuranin and schisandrin C may be potentially valuable antitumor promoters [19].

Shehla et al. [35] performed a systematic isolation of K. heteroclita and evaluated the cytotoxic
effects of these compounds. It was learned that only (+)-1-hydroxy-2,6-bis-epi-pinoresinol was cytotoxic against human gastric cancer cells (BGC-823) and human cervical cancer cell line (HeLa) with IC50 values of 11.0 and 23.8 μM, respectively, compared to the positive control paclitaxel. It was shown that Heilaohulignan C prevented the development of BGC-823 cells in vitro and induced apoptosis through the P53 and mitochondrial apoptotic pathways, while Bax was upregulated and cleaved caspase-3 and p53, thus blocking the p53 and mitochondrial apoptotic pathways. In addition, the movement of BGC-823 cells was prevented. Indicates that the compound has a potential natural compound for the treatment of human gastric cancer [88-89]. In vitro studies have shown that schizandrin A exhibits some inhibitory effects on a variety of tumor cells, and it is speculated that the mechanism may be related to the inhibition of heat shock factor 1 activation, inhibition of NF-κB, PI3K/AKT pathway [90]. Zhang et al. [91] found that schisandrin B could inhibit the growth and metastasis of liver cancer, gallbladder cancer, melanoma, prostate cancer and glioma by regulating the Trfa/TAK1, MAPK and Wnt/β-catenin signaling pathways, blocking cell cycle, inducing apoptosis, preventing tumor cell invasion and metastasis, inhibiting tumor angiogenesis and promoting oxygen free radical scavenging. Furthermore, schisandrin B inhibits the expression of drug resistance-associated proteins, reduces drug efflux and enhances the sensitivity of anti-tumor drugs [92]. In vitro studies have shown that heteroelicitin D can promote apoptosis and inhibit the growth of gastric cancer cells, as well as effectively down-regulate the levels of chemokines such as chemokine IL-8 and intercellular adhesion factor ICAM-1 in the serum of gastric cancer nude mice [93-94]. Xu et al [95] performed in vitro cellular assays on compounds isolated from K. heteroclitus and showed that longipedlactones A and F significantly inhibited the proliferation of human hepatocellular carcinoma HepG2 cells and Bel-7402 cells.

Chen et al. [19] isolated 14 lignans from the vine stems of K. interior and screened them for their ability to inhibit Epstein-Barr virus early antigens, with neokadsuranin and schisandrin C showing stronger antitumour-promoting effects. The results suggest that such lignans may be used as antitumour promoters. Tan et al. [96] studied the inhibitory effect of ethanolic extract of K. longipedunculata on four tumor cells (human colorectal cancer cells LOVO, human breast cancer cells MCF-7, human liver cancer cells HepG2, mouse melanoma cells B16). The inhibition rate increased with increasing concentration of the drug, and the inhibitory effect was dose dependent. Liu et al. [97] screened the compounds isolated from K. oblongifolia for antitumor activity, among which schizanrin B showed significant inhibitory activity against colorectal cancer HCT-15 and oral epithelial cancer KB-3-1 tumor strains.

6.3. Anti-HIV

Chen et al. [98] evaluated lignans isolated from K. interior for anti-HIV viral activity. The results showed that interiotherin A and schisantherin D had a strong inhibitory effect on HIV [29]. Subsequently, in further experiments, gomisin G was also found to have strong anti-HIV activity, which is a highly valuable anti-HIV natural product and lead compound. Pu et al. [99] found that kadsurin and heteroelicitin F showed weak anti-HIV activity and interiorin and interiorin B showed moderate anti-HIV activity by anti-HIV assay analysis. Sun et al. [100] screened the anti-HIV activity of longipedunins A-C and the data showed that longipedunin A had stronger inhibitory activity against HIV-1 protease than the other compounds. A study has shown that lignans from K.coccinea have an inhibitory effect on the reverse transcription of HIV-1 [101]. In addition, some scholars have applied HIV protease (HIVPR) to screen them for preliminary anti-HIV activity and
found that *K. longipedunculata* showed some anti-HIV activity [102]. Liu et al. [103] showed that kadsulignan M had significant anti-HIV activity.

6.4. Antioxidant Activity

Modern pharmacological studies have found that some lignans have significant protective effects on tissue models of oxidative stress injury both in vivo and in vitro. The researchers investigated the antioxidant capacity of anthocyanins and polyphenols extracted from *K. coccinea* fruit using the DPPH method. The results showed that the total polyphenol extract from the peel of the fruit had better antioxidant capacity compared to the pigment extract and the pulp polyphenol extract [104]. Lin et al. [105] found that the antioxidant capacity of ethanolic extracts from different parts of *K. longipedunculata* was in the following order: old roots, young roots, old stems, young stems and leaves. The morphology showed a decreasing trend from bottom to top. Scholars found that the combination of *K. coccinea* extract with cyclodextrins enhanced its antioxidant effect and also enhanced its thermal stability [106]. During the study of *K. interior*, gomisin J was found to have a significant anti-lipid peroxidation effect. It was reported that gomisin J had a significant inhibitory effect on calcium overload and other induced lipid peroxidation in liver mitochondria and oxidative modification of LDL induced by copper ions and endothelial cells, as well as a scavenging effect on superoxide anion radicals [107]. In addition, experiments by Gu et al. [108] showed that gomisin J has a stronger scavenging effect on hydroxyl radicals. Studies have reported that the active ingredients of *K. heteroclita* (Da Hong Zuan) significantly reduced the production of lipid peroxidation products in mouse liver, restored superoxide dismutase (SOD) activity and induced oxygen radical scavenging by liver enzymes [109].

Wu et al. [110-111] explored the scavenging ability and antioxidant effect of different solvent extracts of *K. longipedunculata* on oxygen radicals and found that its ethanolic extract had the strongest scavenging ability on DPPH, and it was hypothesized that the stronger the extract solvent polarity, the higher the scavenging rate on DPPH. The heteroclitins F-G extracted from *K. heteroclita* significantly restored SOD activity and induced oxygen radical scavenging by liver enzymes [112]. Ai et al. [113] used modern pharmacological methods to study the pharmacological activity of *K. coccinea* and found that its active ingredients significantly reduced the production of lipid peroxidation products such as thio barbituric reactive substances in the liver of mice and induced liver enzymes to scavenge oxygen free radicals. Additionally, Yan et al. [114] examined the free radical scavenging effect of compounds in *K. coccinea* in vitro. The results revealed that the ethyl acetate extracted part of its ethanolic extract had in vitro antioxidant effects. The ethanolic extract of *K. longipedunculata* significantly inhibited the degree of autoxidation and hydrogen peroxide-induced erythrocyte hemolysis in rat liver homogenates in vitro and showed significant antioxidant activity [115].

6.5. Anti-platelet Aggregation

Jiang et al. [116-117] investigated the effects of heteroclitin D and (+)-anwulignan on platelet aggregation and improvement of blood microcirculation. The study showed that as the concentration of heteroclitin D increased, its inhibitory effect on ADP-induced platelet aggregation became more pronounced and the inhibitory effect was comparable to that of aspirin. It also has the effect of shortening the time to maximum platelet aggregation induced by ADP. (+)-anwulignan had an inhibitory effect on ADP and PAF-induced platelet aggregation but had no significant effect on the
time to aggregation. It was found that tigloylgomisin B, angeloylgomisin P and R-(+)-gomisin M1 all had competitive antagonistic effects on platelet activating factors [38]. Li et al. [118] studied the effects of gomisin J and heteroclitin D on vasoconstriction caused by hyperkalemic depolarization contractions, CaCl2 and norepinephrine through pharmacological experiments. The data show that both of them act similarly to verapamil, inhibiting the vasoconstriction caused by high potassium depolarization, CaCl2 and norepinephrine, and have a stronger inhibitory effect on CaCl2-induced vasoconstriction. Studies have shown that aqueous extracts of the Yao medicine Da Zuan (K. coccinea) have a significant inhibitory effect on thrombosis in mice. Compared with the model group, the aqueous extract of K. coccinea significantly prolonged the bleeding time of tail breakage and reduced the extent of carrageenan-induced black tail in mice [119-120]. In addition, isovaleroylb inankadsurin A and acetylbinankadsurin A have also been reported to have an inhibitory effect on platelet aggregation [121].

6.6. Cardiovascular Protective Effect

It was found that isovaleroylbinankadsurin A could directly agonize the glucocorticoid receptor, activate the RISK signaling pathway, inhibit oxidative stress and apoptosis, and improve myocardial ischemia-reperfusion injury [122]. Ye et al. [123] investigated the vasodilatory activity of gomisin J through pharmacological experiments and found that gomisin J could inhibit angiotensin II-induced hypertension in mice. In Furthermore, Park et al. [124] speculated that the vasodilating effect of gomisin J might be through the promotion of endothelial nitric oxide synthase activation and AKT phosphorylation to promote NO (nitric oxide) production. Zhou et al. [125] found Schizandrin A to be effective against cerebral ischemia-reperfusion injury. Xu et al. [126] treated K. interior and found that its ethanolic extract significantly increased hematocrit, hemoglobin and red blood cell levels, as well as serum levels of interleukin 3 and macrophage-stimulating factor, demonstrating its good homotonic efficacy. According to the literature, K. coccinea seeds contain 17 amino acids required by the human body, as well as three functional amino acids, namely glutamic acid, arginine and proline, and therefore have cardiovascular disease prevention and immunomodulatory effects [127]. Schisandrin B and schisandrin C can regulate keap/Nrf2, AMPK signaling and ATR, TGF-β/Smad signaling pathways. Reduce oxidative stress and apoptosis, improve Ang-II-induced myocardial remodeling and prevent oxidative damage in the heart in mice [128-130].

6.7. Antibacterial Activity

In the course of their study on K. coccinea, Duan et al. [131] found that neglectalignan D, yunnankadsurin B and arisantetralone B inhibited Staphylococcus aureus, with arisantetralone B also exhibiting an inhibitory effect on Escherichia coli. Shi and Li [132] studied the antibacterial activity of K. coccinea fruit peel and found that it had strong antibacterial activity against Salmonella typhi and strong stability of the inhibitory component. Research shows that, both the ethanolic extract and the aqueous extract of K. longipedunculata inhibited Escherichia coli, Staphylococcus aureus and Salmonella typhi. The antibacterial effect of the ethanolic extract was slightly stronger than that of the aqueous extract [133]. In subsequent experiments, the ethanol extract of K. longipedunculata was found to have the strongest inhibitory effect on Salmonella when the pH was acidic or normal and had good thermal stability [134]. Another study showed that the inhibitory activity of K. longipedunculata extracts treated with Fe3+ and Fe2+ was significantly
Traditional use of genus *Kadsura*

increased [135]. Furthermore, Zhao et al. [136] found that *K. longipedunculata* extracts showed stronger antibacterial activity under weakly acidic conditions. According to Aldo and Miyazawa's experiments, t extracts of *K. longipedunculata* showed good inhibitory effects on *Mycobacterium tuberculosis* H37Rv and *Salmonella typhi* [137-138].

6.8. Lipid-regulating and Anti-diabetic Effects

Pharmacological studies have shown that *K. coccinea* fruit can significantly reduce cholesterol levels in mice and delay the synthesis or accelerate the breakdown of blood lipids in mice [139]. Gomisin M1 has been reported to be effective in scavenging DPPH, ABTs free radicals and inhibiting the synthesis of glycosylation end products, thereby reducing the risk of cardiovascular disease in patients [140]. Hsu et al. [141] showed that schiarisanrin A and schiarisanrin B have insulin-promoting effects and that the mechanism may be related to the inhibition of apoptosis in rat pancreatic BRIN-BD11 cells and that there is a dose-dependent protective effect.

6.9. Immunomodulation

The results of Li et al. [142] showed that anwulignan has immunomodulatory functions, inhibiting the inflammatory response and increasing the levels of immunoglobulins IgG, IgM and IgA in mice by regulating the Nrf2/HO-1 signaling pathway. It also regulates the expression of calpain I and Bax in splenocytes and reduces lymphocyte death. Liu et al. [143] conducted a preliminary study on the anti-immune liver fibrosis of *K. coccinea* alcohol extract and its mechanism of action. The results showed that the serum levels of PCIII, IV-C, LN and HA were significantly increased in rats, suggesting that it has the effect of reducing the degree of liver fibrosis in rats. It also significantly increased the serum TGF-β1 and TNF-α levels in rats and had a regulatory effect on cytokines. Wang et al. [144] reported that the fruits of *K. japonica* have a wide range of immunomodulatory effects and can significantly promote the proliferation of T lymphocytes and the production of ND antibodies in normal chickens, enhancing the body's immune function and keeping the body's antibody level at a high level.

6.10. Neuroprotective Effects

Reports indicate that *K. heteroclita* extract promotes the growth and development of hippocampal neurons and has some anti-aging effects on neuronal cells. The coumarinlignan extract from *K. heteroclita* has also been reported to have a neuroprotective effect [145-146]. Zhou et al. [147] showed that schisandrins could reduce neurological deficits caused by ischemic brain injury in mice by modulating the expression of small soluble α-synuclein in the presynaptic membrane of the central nervous system. It can also prevent cognitive impairment caused by ischemia-reperfusion injury in the central nervous system and improve the learning and memory ability [148-149]. Yang et al. [30] demonstrated that ananolignan F and ananolignan L, isolated from *K. ananosma*, had significant neuroprotective effects through in vitro experiments. It was reported that polysperlignans A、B、D and F showed significant neuroprotective effects in these in vitro assays[21].

6.11. Insecticidal Effect

Jiang [150] found that the lignans (-)-machilusin and schisantherin D had strong insecticidal activity against *plutella xylostella* with a 99% mortality rate of the pest, which warrants further study. During the screening process for insecticidal herbs, *K. longipedunculata* and *K. heteroclita*
were found to have strong insecticidal activity and the potential to be natural insecticides [151-152]. In addition, schisandrol A and schisandrin B have also been reported to have insecticidal effects [153].

6.12. Others

The ethanol extract of *K. longipedunculata* effectively inhibited gastric mucosal damage induced by hydrochloric acid-ethanol solution and cold-water immersion in rats and reduced diarrhea symptoms [151]. In another study, its ethanolic extract showed better protection against pyloric ligation ulcer model in rats [154]. Anwulignan has a fatigue-relieving effect by regulating Nrf2 and p38/MAPK-PGC-1α signaling pathways, preventing apoptosis, improving biochemical indicators related to fatigue and increasing endurance in mice [155]. The pharmacological effects of the monomeric compounds of this genus are detailed in Table 4.

### Table 4. Pharmacological Activities of *Kadsura*

<table>
<thead>
<tr>
<th>Pharmacological Action</th>
<th>Effective Fraction/Compounds</th>
<th>Model</th>
<th>Dose or Critical Assessment</th>
<th>Target or Possible Mechanism</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatoprotective and Anti-inflammatory</td>
<td>gomisin J</td>
<td>Raw 264.7 cells</td>
<td>low activity positive control (dexamethasone) inhibited HBsAg secretion by more than 32.6%</td>
<td>Inhibiting NO CYP2E1, CPY1A2 and CYP3A11↓</td>
<td>[84]</td>
</tr>
<tr>
<td></td>
<td>gomisin N</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>schisandrin C</td>
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<tr>
<td></td>
<td>kadsulignan L</td>
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<tr>
<td></td>
<td>neokadsuranin</td>
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<tr>
<td></td>
<td>kadsurindutins A</td>
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<tr>
<td></td>
<td>gomisin G</td>
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<tr>
<td></td>
<td>longipedlignan F</td>
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<tr>
<td></td>
<td>schiarisanrin B</td>
<td>in vitro/HepG2 cells</td>
<td>Inhibition of 76.3%</td>
<td>Regulation of YAP1, Bcl-2, Bax and other proteins expression</td>
<td>[25]</td>
</tr>
<tr>
<td></td>
<td>longipedlignan M</td>
<td>APAP-induced toxicity in HepG2 cells</td>
<td>Inhibition of 52.2%</td>
<td>Regulation of YAP1, Bcl-2, Bax expression</td>
<td>[71]</td>
</tr>
<tr>
<td></td>
<td>heilaohusu A</td>
<td>RA-FLS cell line</td>
<td>14.57 µM 11.70 µM (positive control indomethacin IC50=4.10) Inhibition of 53.5±1.7%</td>
<td>SSH1L/Cofilin-1 signaling pathway</td>
<td>[34]</td>
</tr>
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<td></td>
<td>angeloy-lbinankadsurin A</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>heilaohuguosu A</td>
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<tr>
<td></td>
<td>heilaohuguosu L</td>
<td>APAP-induced toxicity in HepG2 cells</td>
<td>Inhibition of 55.2±1.2% positive control bicyclol (52.1±1.3%, 10 µM)</td>
<td>Reduces ALT, AST levels and inhibits ROS</td>
<td>[70]</td>
</tr>
<tr>
<td></td>
<td>gomisin C</td>
<td></td>
<td>3.77 µmol/L</td>
<td></td>
<td>[156]</td>
</tr>
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</table>
Traditional use of genus *Kadsura*

<table>
<thead>
<tr>
<th>Compound</th>
<th>Origin</th>
<th>IC$<em>{50}$/EC$</em>{50}$/EC$<em>{25}$/EC$</em>{10}$</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>kadsurin</td>
<td>Rat liver microsomes</td>
<td>6.18 μmol/L</td>
<td>Inhibits CYP3A1/2 activity</td>
</tr>
<tr>
<td>heterolitin D</td>
<td>Raw 264.7 cells</td>
<td>20.67 μmol/L</td>
<td></td>
</tr>
<tr>
<td>interiorin</td>
<td></td>
<td>16.43 μmol/L</td>
<td></td>
</tr>
<tr>
<td>angeloyl-binankadsurina A</td>
<td></td>
<td>23.07 μmol/L</td>
<td></td>
</tr>
<tr>
<td>gomisin O</td>
<td>LPS-induced RAW264.7 cells</td>
<td>0.5, 2.5, 12.5μmol/L (Significant activity)</td>
<td>TNF-α, IL-6, IL-1β [157]</td>
</tr>
<tr>
<td>deoxyschisandrin</td>
<td>RAW 264.7 cells</td>
<td>20.67 μmol/L</td>
<td></td>
</tr>
<tr>
<td>(+)-anwulignan</td>
<td>RAW 264.7 cells</td>
<td>IC$_{50}$ = 1.00 μM</td>
<td>COX-2 [159]</td>
</tr>
<tr>
<td>kadsuralignan C</td>
<td>LPS-induced RAW264.7 cells</td>
<td>IC$_{50}$ = 21.2 μM</td>
<td>Inhibiting NO [160]</td>
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<tr>
<td>kadsuralignan H</td>
<td>RAW264.7 cells</td>
<td>IC$_{50}$ = 19.6 μM</td>
<td></td>
</tr>
<tr>
<td>meso-dihydroguaiaretic acid</td>
<td>murine macrophage cell lines</td>
<td>1 mg/kg</td>
<td>LXR-α [161]</td>
</tr>
<tr>
<td>Isovaleroylbinankadsurin A</td>
<td>Hydrogen peroxide-induced hepatocyte injury</td>
<td>EC$_{50}$ = 26.1</td>
<td>lactate dehydrogenase (LDH) [70]</td>
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<tr>
<td>binankadsurin A</td>
<td>RAW264.7 cells</td>
<td>EC$_{50}$ = 26.1</td>
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<td>acetylepigomisin R</td>
<td>RAW264.7 cells</td>
<td>EC$_{50}$ = 79.3</td>
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<td>Anti-cancer</td>
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<tr>
<td>heteroclitin D</td>
<td>SGC-7901 cells</td>
<td>1.25, 2.5, 5, 10mg/L</td>
<td>Caspase3, Bax, P53, Bcl-2 [162]</td>
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<tr>
<td>heilaohusu C</td>
<td>HepG-2, HCT-116, BGC-823 and Hela cell line</td>
<td>13.04 to 21.93 μm</td>
<td>Regulation of bcl-2, bax protein [34]</td>
</tr>
<tr>
<td>neglignan G</td>
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<td>angeloylbinankadsurin A</td>
<td>MCF10A cell line</td>
<td>IC$_{50}$ = 85 μM</td>
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<td>gomisin M2</td>
<td>MDA-MB-231 cell line</td>
<td>IC$_{50}$ = 60 μM</td>
<td>Wnt/β-catenin [89]</td>
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<td>meso-dihydroguaiaretic acid</td>
<td>MCF-7 cell line</td>
<td>IC$_{50}$ = 15.1 μM</td>
<td>Src/EGFR/intergrin β3 [161]</td>
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<td>H358 cell line</td>
<td>IC$_{50}$ = 16.9 μM</td>
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<td></td>
<td>IC$_{50}$ = 10.1 μM</td>
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<tr>
<td>Compound</td>
<td>Cell Line</td>
<td>IC₅₀/EC₅₀/μM/µg/mL</td>
<td>Pathway/Activity</td>
</tr>
<tr>
<td>------------------</td>
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<td>-------------------------------------------</td>
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<tr>
<td>Anwulignan</td>
<td>A549, H1299, H1650 and H1975 cells</td>
<td>Not mentioned</td>
<td>JAK1/STAT3, cyclin D1/3</td>
</tr>
<tr>
<td>Neokadsuranin</td>
<td>Raji cells</td>
<td>Survival rate 92.6 ± 0.4%</td>
<td>EBV-EA activation</td>
</tr>
<tr>
<td>Schisandrin C</td>
<td>BGC-823 cell line</td>
<td>IC₅₀ = 16 ± 0.38 μM</td>
<td>p53 apoptotic pathway, BAX, Bcl-2</td>
</tr>
<tr>
<td>Heilaohusu C</td>
<td>HCT-116 cell line</td>
<td>IC₅₀ = 16.59 ± 0.51 μM</td>
<td>EBV-EA activation</td>
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<tr>
<td>Schisandrin A</td>
<td>HeLa cell line</td>
<td>IC₅₀ = 22 ± 0.65 μM</td>
<td>EBV-EA activation</td>
</tr>
<tr>
<td>Schisandrin B</td>
<td>HCC827/GR and HCC827 cells</td>
<td>IC₅₀ = 0.558, 14.62</td>
<td>EBV-EA activation</td>
</tr>
<tr>
<td>Schisandrin B</td>
<td>SW116 cells</td>
<td>apoptosis rate of 14.5-39.8%</td>
<td>EBV-EA activation</td>
</tr>
<tr>
<td>Gomisin J</td>
<td>SD rats</td>
<td>IC₅₀ = 0.95(0.14~6.54) μmol/L</td>
<td>Fe²⁺-Vit C, ADP/NADPH</td>
</tr>
<tr>
<td>Isolariciresinol</td>
<td>Human whole blood</td>
<td>IC₅₀ = 36.38 μM</td>
<td>ROS</td>
</tr>
<tr>
<td>(+)-1-hydroxy-2,6-bis-epi-pinoresinol</td>
<td></td>
<td>IC₅₀ = 34.41 μM</td>
<td></td>
</tr>
<tr>
<td>(+)-lariresinol</td>
<td>Neutrophils</td>
<td>IC₅₀ = 35.97 μM</td>
<td></td>
</tr>
<tr>
<td>Evofolin B</td>
<td>UMR106 cells</td>
<td>IC₅₀ = 3.84-14.43 μg/ml</td>
<td>against ABTS free radicals</td>
</tr>
<tr>
<td>Pinobatol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matairesinol 4′-O-glucoside</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-)-secoisolariciresinol-O-a-L-rhamnopyranoside</td>
<td>UMR106 cells</td>
<td>IC₅₀ = 3.84-14.43 µg/ml</td>
<td>against ABTS free radicals</td>
</tr>
<tr>
<td>(-)-secoisolariciresinol 9-O-a-L-arabinopyranoside</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(-)-Catechin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isorhamnetin-3-O-β-D-glucoside</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HIV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longipedunin A</td>
<td>T cell line</td>
<td>Inhibition rate 47.3%-77.8%</td>
<td>Inhibition of HIV-1 protease</td>
</tr>
<tr>
<td>Longipedunin B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longipedunin C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kadsuranin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gomisin J</td>
<td>H9 T cell line</td>
<td>EC₅₀ = 0.006~1.5 µg/mL</td>
<td>HIV-1 RT, RNaseH</td>
</tr>
<tr>
<td>Schisandrin C</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Traditional use of genus *Kadsura*

<table>
<thead>
<tr>
<th>Anti-platelet aggregation</th>
<th>heteroclitin D</th>
<th>New Zealand white rabbits</th>
<th>(ADP-) Inhibition of 36.35%, 19.57%</th>
<th>TXA-2, blocking L-type calcium channels [116]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>schisanhenol</td>
<td>(ADP- and PAF-induced platelet aggregation)</td>
<td>(PAF-) Inhibition of 17.55%, 18.44%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>isovaleroyl-binankadsurin A</td>
<td>diabetict rabbits</td>
<td>Inhibition of 16.64%, 21.96%</td>
<td>Inhibition of platelet aggregation [121]</td>
</tr>
<tr>
<td>Cardiovascular protection</td>
<td>Isovaleroylbilan-kadsurin A</td>
<td>H9c2 cells</td>
<td>mitochondrial dysfunction increased from 12.4% to 80.3%</td>
<td>Bcl-2, BAX [122]</td>
</tr>
<tr>
<td></td>
<td>gomisin J</td>
<td>Male C57BL/6 mice</td>
<td>the vasodilatory effect of GJ was 99 ± 12 μM</td>
<td>NO, eNOS, ROS [123]</td>
</tr>
<tr>
<td></td>
<td>schizandrin A</td>
<td>C57BL/6J mice</td>
<td>50 or 100 mg/kg</td>
<td>AMPK/Nrf2 pathway, Bcl-2, BAX [125]</td>
</tr>
<tr>
<td></td>
<td>schisandrin B</td>
<td>male sprague dawley rats</td>
<td>25 and 50 mg/kg</td>
<td>NO, cyclooxygenase-2, IL-1β, IL-6, tumor necrosis factor α [129]</td>
</tr>
<tr>
<td></td>
<td>schisandrin C</td>
<td>C57BL/6 mice</td>
<td>48.59 ± 2.301%</td>
<td>Nrf2, ROS, HO-1, NQO-1 [130]</td>
</tr>
<tr>
<td></td>
<td>meso-dihydroguaiaretic acid</td>
<td>PDGF-BB</td>
<td>186.07 ± 346.5 ± 111.7<del>3864.17 at 1</del>20 μM</td>
<td>ERK1/2, p38, JNK, PDGFR β [166]</td>
</tr>
<tr>
<td>Antibacterial</td>
<td>neglectalignan D</td>
<td>Staphylococcus aureus and escherichia coli</td>
<td>antibacterial ring diameter of 7.83 ± 0.13 to 10.25 ± 0.11 mm</td>
<td>Disruption of bacterial cell membranes [131]</td>
</tr>
<tr>
<td></td>
<td>yunnankadsurin B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>arisanteralone B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>meso-dihydroguaiaretic acid</td>
<td>Salmonella typhimurium</td>
<td>ID₅₀ = 0.08 μmol/ml</td>
<td>TA1535/ pSK1002 [137]</td>
</tr>
<tr>
<td></td>
<td>schisandrin</td>
<td></td>
<td>minimum inhibitory concentration: E. coli (0.0625 g/mL ~ 0.125 g/mL), A. niger (0.125 g/mL ~ 0.25 g/mL)</td>
<td>Free radical scavenging effect [167]</td>
</tr>
<tr>
<td></td>
<td>schisandrin B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-diabetic</td>
<td>tigloylgomisin P</td>
<td>1.08 mg/mL</td>
<td>MOD↑, SOD ↓</td>
<td>[140]</td>
</tr>
</tbody>
</table>
### Inhibitory activity of AGEs formation.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>Concentration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzoyliso gomisin O</td>
<td></td>
<td>7.42 mg/mL</td>
<td></td>
</tr>
<tr>
<td>schiarisanrin A</td>
<td>BRIN-BD11 cells</td>
<td>20 μg/mL</td>
<td>SAPK/JNK, p38MAPK and STAT-1α, Ca^{2+}</td>
</tr>
<tr>
<td>schiarisanrin B</td>
<td></td>
<td>20 μg/mL</td>
<td></td>
</tr>
</tbody>
</table>

### Immunomodulatory activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>Concentration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>anwulignan</td>
<td>Clean-grade healthy male ICR mice</td>
<td>4 mg/kg</td>
<td>Nrf2/HO-1 pathway, IgG, IgM and IgA, Calpain I and Bax</td>
</tr>
<tr>
<td>Alcohol extract from <em>K. coccinea</em></td>
<td>SD male rats</td>
<td>1.68, 0.84, 0.42 g·kg⁻¹</td>
<td>PCIII, IV-C, LN, HA, TGF-β1 and TNF-α, IFN-γ, TGF-β1</td>
</tr>
<tr>
<td>gomisin M2</td>
<td>Male ICR mice</td>
<td>0.1 ~ 10 mg/kg</td>
<td>Lyn and Fyn pathways, Ca2+, caspase-1, RIP-2, IgE, IgG1, TNF-α and IL-1β</td>
</tr>
<tr>
<td>schizandrin</td>
<td>Mice (5-week Balb/c)</td>
<td>10 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

### Neuroprotective activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>Concentration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>extract of <em>K. heteroclita</em></td>
<td>wistar rats</td>
<td>0.2 ~ 8 mg/ml</td>
<td>NGF, TBA-RS, SOD</td>
</tr>
<tr>
<td>schisandrin</td>
<td>APP/PS1 double transgenic dementia mice</td>
<td>10 mg·kg⁻¹·d⁻¹</td>
<td>SYP, α-syn</td>
</tr>
<tr>
<td>polysperlignan A</td>
<td>PC12 cells</td>
<td>test concentration (1 and 10μM)</td>
<td>Against H2O2- or Aβ25-35-induced neurotoxicity</td>
</tr>
<tr>
<td>polysperlignan B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>polysperlignan D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>polysperlignan F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>heteroclitin D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>schiarisanrin A</td>
<td>LPS-induced BV-2 cells</td>
<td>IC_{50} = 18.6±1.0, 9.6±0.5, 26.4±3.2</td>
<td>Inhibiting NO</td>
</tr>
<tr>
<td>schiarisanrin B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>schisandrol A</td>
<td>Myzus persicae Sulzer</td>
<td>LC_{50} = 295.62 mg/L</td>
<td>Regulation of intracellular Ca^{2+} levels</td>
</tr>
<tr>
<td>schisandrin B</td>
<td>Plutella xylostella Linnaeus</td>
<td>LC_{50} = 586.22 mg/L</td>
<td></td>
</tr>
</tbody>
</table>

### Anti-ulcer activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>Concentration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>k. longipedunculata</em> ethanol extract</td>
<td>Wistar female rats</td>
<td>100 mg/kg</td>
<td>Regulates levels of relevant inflammatory factors</td>
</tr>
</tbody>
</table>

### Anti-fatigue activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>Concentration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>anwulignan</td>
<td>mice</td>
<td>4 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>
7. Toxicity

Jin et al. [173] explored the toxicity studies of periwinkle on zebrafish embryo development. The results found that meso-dihydroguaiaretic acid (1 µg/mL) treated group exhibited severe pericardial oedema and yolk sac oedema, while embryos in the kadsulignan O and kadsufolin A (100 µg/mL) treated groups exhibited mild pericardial oedema, yolk sac oedema and slowed heart rate. Indicating that all three compounds were toxic to both embryonic development and cardiac development in zebrafish, and speculating that the target organ of toxicity may be the heart. Li et al. [139] investigated the acute toxicity test of *K. coccinea* fruit by taking the maximum gavage volume (40 ml/kg) for 30 days. During the experimental period, the mice showed normal activity, feeding, good growth and development, and no significant changes in their blood biochemical parameters and organism ratio. The above characteristics indicate that *K. coccinea* has no obvious toxic effects and is a safe fruit for consumption. Furthermore, Xia et al. [174] evaluated the toxicity of *K. coccinea* roots and stems using zebrafish as a model. *K. coccinea* alcohol extracts were found to cause hepatocyte damage and liver dysfunction in zebrafish larvae, in addition to inducing developmental hepatotoxicity. These results suggest that alcohol extracts of *K. coccinea* and stems are the main toxic extracts in zebrafish embryos and larvae. Deng et al. [175] used rats as a model to explore the pharmacological and toxicological safety of the extracts of *K. heteroclita*. The rats were divided into three groups and administered once daily at low, medium and high (1, 3 and 6 mg/kg) doses to observe the physiological changes during administration. The results showed that the high dose group showed coarse liver cell granules during the administration period, which returned to normal after discontinuation of the drug; the medium and low dose groups did not show any abnormalities during the experiment. In addition, there was no mortality in the rats of all dosing groups during the test period. This indicates that the extract is safe at medium and low doses, while the high dose needs to be further studied.

8. Discussion and Prospects

The genus *Kadsura* has a history of thousands of years of development in China, with the earliest recorded use dating back to *Shennong's Classic of Materia Medica* and has the effect of dispels wind and dampness and moving Qi and blood. Due to its wide distribution, it has formed a variety of uses with ethnic characteristics, such as Dong and Yao medicine (*K. coccinea*), Wa, Hani and Yao medicine (*K. heteroclita*), etc. Today, modern techniques and methods have revealed that the genus *Kadsura* contains more than 337 structurally diverse lignans, of which biphenyl cyclooctene-type lignans are considered to be the main bioactive components of the genus, See figure 9 for the percentage of major components. Pharmacological studies have confirmed its anti-inflammatory, hepatoprotective, neuroprotective, anti-HIV and anti-platelet aggregation pharmacological activities. Compared to the previous reviews, this paper further adds and refines the information about the species, pharmacological activities and related applications of lignans.
from the genus *Kadsura*. Although some results have been achieved in the current understanding of the genus *Kadsura*, there are still some questions that deserve to be explored.

**Figure 8.** Traditionally used plant parts of genus *Kadsura*


**Figure 9.** Percentage of various types of lignans in the genus *Kadsura*

First, the genus *Kadsura* is abundant and widespread, but most of the studies to date have
reported *K. coccinea* and *K. longipedunculata* (Figures 10 and 11), while there are few other species. According to the literature, all plants in the genus *Kadsura* have medicinal value. In addition, *K. coccinea* and *K. japonica* can be used as fruit and have cough suppressant effects, and *K. longipedunculata* and *K. oblongifolia* can be used for ornamental purposes. The next step is to explore this genus in its entirety and to give full play to its value for exploitation. Secondly, the genus *Kadsura* can also be used clinically to treat rheumatic diseases, bone and joint diseases and various kinds of pain, and has achieved certain therapeutic effects. However, there is compatibility in the use of Chinese medicine for clinical applications, so the therapeutic mechanism of the genus in combination with other drugs should be studied in depth. At the meantime, the development of new clinical therapies should also receive attention. Third, to date, the genus has been identified as having more than 337 lignan-like constituents, and due to its diverse biological activities, considerable progress has been made in pharmacology (Figure 12), with anti-inflammatory, hepatoprotective and antitumor aspects in particular being the most extensively studied. Although there is a large body of literature reporting progress in the study of their pharmacological effects, there is still a lack of research on their mechanisms of action and targets. In the future, the mechanism and targets can be studied from compounded herbal formulations or with the help of network pharmacology. Fourthly, genus *Kadsura* has a long history of folk medicine use in China and has formed a variety of ethnic-specific medicine use, however, there are differences in each medicine use and dosage, and there is a lack of uniform standards. Moreover, only a small number of toxicity assessment experiments have been conducted, and a large number of experiments are needed to fill this gap.

![Figure 10. Percentage of all published reports on the chemistry and biology of species of the genus *Kadsura*](image-url)
On balance, the genus *Kadsura* is still lacking in comprehensive research and development, so this paper collates the existing studies and suggests a few noteworthy directions for development, in the hope of providing a valuable reference for subsequent exploration.
Traditional use of genus *Kadsura*

**Author contributions**

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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**Competing Interests**

The authors declare that there is no conflict of interest.

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Dongdong Zhang: 0000-0003-0956-1261

**References**

Xu et al., Rec. Nat. Prod. (20XX) X:X XX-XX


Traditional use of genus Kadsura


Sin compounds from stems of *L. japonica*, *L*. *J. H. Heteroclite* *L.* *L.* *J.* *W. H. Lignans from *Kadsura japonica* from *K. japonica* and *K. coccinea* longipedunculata *renchangiana* *M. Chim* *J. S.* *I.* *L.* *L.* *Li*, *H. Y.* *Z. X.* *M. D.* *H. Y.* *S.* *S.* *W.* *Wang*, *D. F.* *Chen*, *G. J.* *Xu*, *X. W.* *Yang*, *M.* *Hattori*, *Y.* *Tezuka* and *T.* *Kikuchi* (1992). Dibenzocyclooctadiene lignans from *Kadsura heteroclite*, *Phytochemistry*. 31, 629-632.


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