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Review

A review of lignans from genus *Kadsura* and their spectrum characteristics

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ABSTRACT

Kadsura belongs to the Schisandroideae subfamily of Magnoliaceae. Plants from genus *Kadsura* are widely distributed in the South and Southwest of China. The plants of the genus are widely used as folk medicine for a long time in history, with the functions of relieving pain, promoting '*qi*' circulation, activating blood resolve stasis, and applications in the treatment of rheumatoid arthritis and gastroenteric disorders. Lignans are the primary characteristic constituents with various biological activities of plants from genus *Kadsura*. This paper summarized 81 lignans isolated from the plants of genus *Kadsura* over the past eight years (from 2014 to 2021), which belong to five types: dibenzocyclooctadienes, spirobenzofuranoid dibenzocyclooctadienes, aryltetralins, diarylbutanes and tetrahydrofurans. Each type of these lignans possess typical characteristics in proton magnetic resonance (^{1}H NMR) and carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra, the NMR regularities of these types of lingans were summarized, which provided a useful reference for the structural analysis of lignans. The relationships between lignans and pharmacodynamics were also systematically analyzed, lignans were predicted to be the quality markers (Q-marker) of *Kadsura* genus.

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1. Introduction

Kadsura contains about 29 plant species, and 10 species of this genus mainly distributed among the South and Southwest of China. Among these species of the genus *Kadsura*, lignans are the dominant constituents. Refers to Dong's article (Dong, Shu, Liu, He, & Yan, 2014), the present paper aims to provide an up-to-date review of the structures of the lignans isolated from the genus *Kadsura* during 2014 to 2021. About 81 lignans have been isolated and identified, including 46 dibenzocyclooctadiens, 19 spirobenzofuranoid-dibenzocyclooctadienes, six aryltetralins, one tetrahydrofuran, three diarylbutanes and six new lignans. The lignan structures in the genus *Kadsura* have typical characteristics in their nuclear magnetic spectrum. Thus, this paper summarizes the structure types of lignans and the NMR regularities of each type, so as to provide reference for the future identification of lignan chemical structure.

2. Chemical constituents

A large number of compounds have been isolated from *Kadsura* genus, including lignans, triterpenoids, flavonoids, sesquiterpenoids, etc, with lignans and triterpenoids as the mainly chemical constituents. All these isolates enriched the diversity of constituents in Schisandraceae plants (Liu et al., 2014).

2.1. Lignans

Lignans, as significant characteristic class of secondary metabolites, were found in genus *Kadsura*. The lignans isolated from the *Kadsura* genus can be divided into five categories, including dibenzocyclooctadienes, spirobenzofuranoid dibenzocyclooctadienes, aryltetralins, diarylbutanes and tetrahydrofurans.

2.1.1. Dibenzocyclooctadiene

Dibenzocyclooctadiene lignans constitute more than half of the total lignans, they contain a basic skeleton biphenyl ring octene lignans which are divided into two series of biphenyl *S* and *R* configurations (I and II). Due to the existence of other chiral centers in molecules, there are many stereoisomers in this type of compound. There are three conformations of octet ring, including twisted boat chair type (TBC, III), twisted boat type (TB, IV) and 6,9 oxbridge biphenyl cyclooctadiene (V), the twisted boat chair type is the main conformation among the three ones. The main structural types and conformations of diphenylcyclooctene lignans in *Kadsura* are shown in Fig. 1.

Except for the presence of two aromatic protons at C-4 and C-11 positions on the biphenyl ring, all other positions (C-1–3 and C-12–14) were substituted by oxygen-containing substitutions, including methoxyl, methylenedioxy, hydroxyl and ester groups (Chen, Qin, & Xie, 2000). Most hydroxyl groups are shown on C-1, C-12, C-14, and some are attached to the C-3. Biphenyl rings usually have one phenolic hydroxyl group, and a few have two phenolic hydroxyl groups or one phenolic hydroxyl group and one ester group. The most common substituents for the C-1, C-6 and C-9 are acetyl, angeloyl, tigloyl, propanoyl, benzoyl, isovaleryl and isobutyryl.

The recent published structures of biphenylcyclooctene lignans from *Kadsura* plants are shown in Fig. 2 and Table 1.

2.1.2. Spirobenzofuranoid dibenzocyclooctadiene

Spirobenzofuranoid dibenzocyclooctadiene lignan contains a new C-16 centric furan nucleus as compared with dibenzocyclooc-

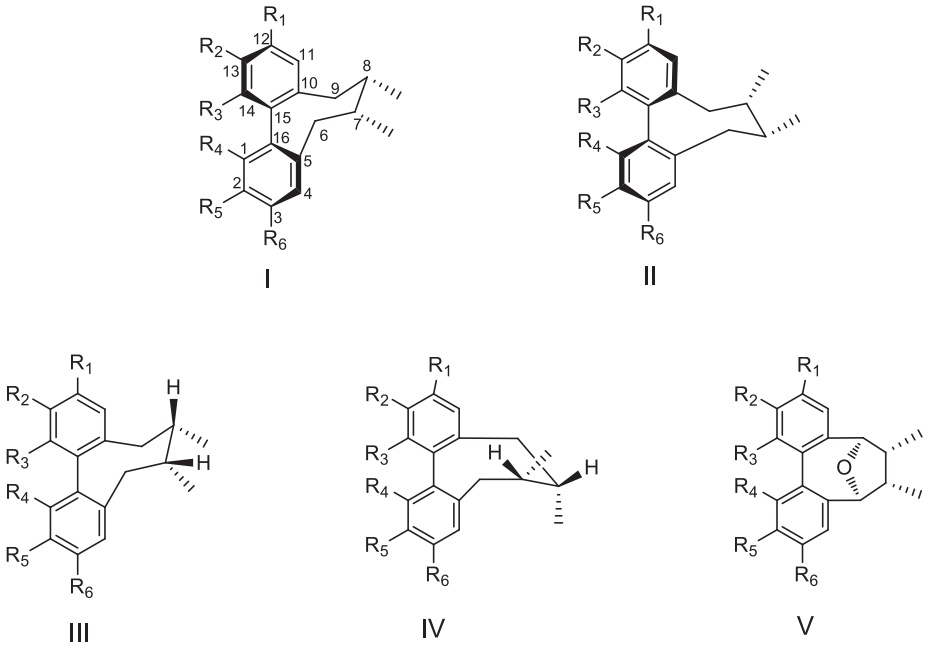


Fig. 1. Structural skeletons and conformations of dibenzocyclooctadiene lignans (I: *S* configuration, II: *R* configuration, III: twisted boat chair, IV: twisted boat, V: 6, 9 oxbridge biphenyl cyclooctadiene) from plants of *Kadsura*.

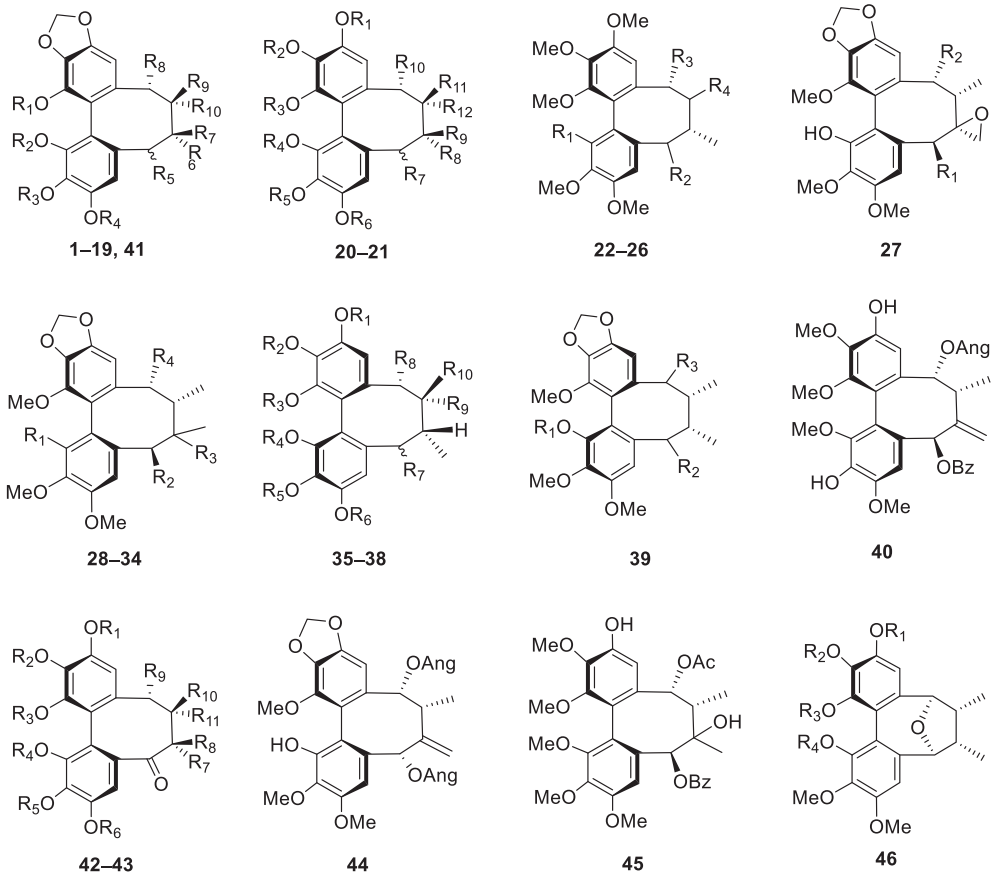


Fig. 2. Structures of dibenzocyclooctadiene lignans in plants of *Kadsura*.

tadiene lignans, which forms by adding other oxygen-containing substituents to it. Meanwhile, it also has an enketonation on the aromatic ring of C-16. This kind of compounds were isolated from *Kadsura* plants. Most screw rings are formed from the oxygen-containing substituents of C-14 and C-16. There are two types of enketonations (Fig. 3) on the aromatic ring of these chemical compounds, the α, β, γ, δ-dienone (VI) and α, β, α', β'-dienone (VII) (Kuo, Wu, Huang, Kuo, & Ong, 2005; Kuo, Wu, Hung, Huang, YangKuo et al., 2015). The compositions of spirobenzofuranoid dibenzocyclooctadienes isolated from *Kadsura* plants in recent years are shown in Fig. 4 and Table 2.

2.1.3. Aryltetralin

Six lignans of aryltetrahydrothalene type (Table 3) were isolated and identified from *Schisandra* in rencent seven years, there are (7′S, 8′S, 8R)-(8β, 8′α)-dimethyl-4, 4′-dihydroxy-5, 3′-dimethoxy-5′- cyclolignan glucoside (**66**) (Yeon, Cheng, He, & Kong et al., 2014), heilaohusu E (**67**) (Yang, Liu, Daniyal, Yu, & Wang, 2019), and Heilaohuguosus O-R (**68–71)** (Jia et al., 2021)**.** Their structures are shown in Fig. 5.

2.1.4. Diarylbutane

In recent years, three dibenzylbutane type lignans, such as kadsurindutin E (**72**) (Fang, Xie, Wang, Jin, Xu, Guo, & Ma, 2014), coccilignan A (**73**) (Fang et al., 2014), kadsuphilin J (**74**) (Shen et al., 2008) were isolated from Schisandrae. Structures are shown in Fig. 5.

2.1.5. Tetrahydrofurans

Only one tetrahydrofuran type lignan (Fig. 5), heilaohuguosu S (**75**) (Jia et al., 2021) was isolated from Schisandrae.

2.1.6. New lignans

Six new lignans have been found from the plants of the genus Kadsura. longipedlignan R **(76)** (Liu, Pandey, Wang, Adams, & Li, 2019), kadlongilignan A–D (**77**–**80**) (Qi, Liu, Chen, Hou, & Li, 2020), coumarinlignan (**81**) (Su et al., 2015). Their structures are shown in Fig. 5.

3. ^{1}H NMR and ^{13}C NMR spectrum characteristics of lignans from genus *Kadsura*

Lignans are dominant constituents of genus *Kadsura*, and a large number of ^{13}C and ^{1}H NMR chemical shift data of lignans have been reported, but these data are scattered in the literatures, we collected and analysis these NMR data, and it will be of value to provide easy access to elucidate the sturctures of lignans isolated from *Kadsura*. This paper reports the NMR data compilation of the main skeletons of these compounds.

3.1. ^{13}C NMR characteristics of lignans

3.1.1. Biphenyclooctene lignans

3.1.1.1. Aromatic carbon (C-4 and C-11). The chemical shift of carbon on biphenyl ring conforms to the empirical rule that substituent's chemical effects of the carbon atom on benzene ring (Chen, Qin, & Xie, 2001). Taking the structure of Fig. 6 as an example, the chemical shift of C_4 and C_{11} is shown in Table 4.

3.1.1.2. Aromatic quaternary carbon. The chemical shift of aromatic quaternary carbon is mainly affected by its own substituents, and the change of chemical shift is shown in Table 5.

Table 1
Dibenzocyclooctadiene lignans in plants of *Kadsura*.

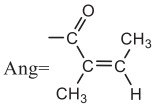
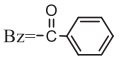
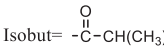
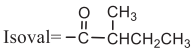
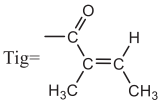
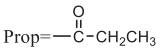
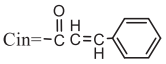
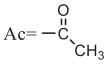
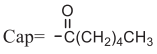
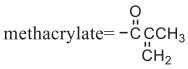
No.	Compound	Substituent groups	Structures of specific substituents	Sources	References
1	Kadheterin C	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, $R_5 = \beta$-OAng, $R_6 = CH_3$, $R_7 = OH$, $R_8 = OAng$, $R_9 = H$, $R_{10} = CH_3$		*K. heteroclita*	(Luo et al., 2017)
2	Kadheterin D	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, $R_5 = \beta$-OBz, $R_6 = CH_3$, $R_7 = OH$, $R_8 = OAng$, $R_9 = H$, $R_{10} = CH_3$		*K. heteroclita*	(Luo et al., 2017)
3	Kadheterin E	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, $R_5 = \beta$-OAng, $R_6 = CH_3$, $R_7 = OH$, $R_8 = OBz$, $R_9 = H$, $R_{10} = CH_3$		*K. heteroclita*	(Luo et al., 2017)
4	Kadheterin F	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, $R_5 = \beta$-OBz, $R_6 = OH$, $R_7 = CH_3$, $R_8 = OBz$, $R_9 = H$, $R_{10} = CH_3$		*K. heteroclita*	(Luo et al., 2017)
5	Kadheterin G	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, $R_5 = \beta$-OIsobut, $R_6 = OH$, $R_7 = CH_3$, $R_8 = OAng$, $R_9 = H$, $R_{10} = CH_3$		*K. heteroclita*	(Luo et al., 2017)
6	Kadheterin H	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, $R_5 = \beta$-OAng, $R_6 = OH$, $R_7 = CH_3$, $R_8 = OIsoval$, $R_9 = H$, $R_{10} = CH_3$		*K. heteroclita*	(Luo et al., 2017)
7	kadsutherin E	$R_1 = R_2 = H$, $R_3 = R_4 = CH_3$, $R_5 = H$, $R_6 = CH_3$, $R_7 = H$, $R_8 = OBz$, $R_9 = H$, $R_{10} = CH_3$		*K. interior*	(Liu, & Yang et al., 2018; Liu, & Zhang et al., 2018)
8	14-*O*-Demethyl polysperlignan D	$R_1 = H$, $R_2 = R_3 = R_4 = CH_3$, $R_5 = \beta$-OAng, $R_6 = CH_3$, $R_7 = H$, $R_8 = OTig$, $R_9 = H$, $R_{10} = CH_3$		*K. coccinea*	(Fang et al., 2014)
9	Heilaohulignan A	$R_1 = R_3 = R_4 = CH_3$, $R_2 = OIsobut$, $R_5 = H$, $R_6 = H$, $R_7 = CH_3$, $R_8 = OH$, $R_9 = H$, $R_{10} = CH_3$		*K. coccinea*	(Liu et al., 2018)
10	Heilaohulignan B	$R_1 = R_3 = R_4 = CH_3$, $R_2 = OIsval$, $R_5 = H$, $R_6 = CH_3$, $R_7 = H$, $R_8 = O$, $R_9 = CH_3$, $R_{10} = OH$		*K. coccinea*	(Liu et al., 2018)
11	Heilaohulignan C	$R_1 = R_3 = R_4 = CH_3$, $R_2 = \beta$-H, $R_5 = H$, $R_6 = CH_3$, $R_7 = H$, $R_8 = OTig$, $R_9 = CH_3$, $R_{10} = H$		*K. coccinea*	(Liu et al., 2018)
12	Schizanrin O	$R_1 = R_2 = R_3 = R_4 = CH_3$, $R_5 = OBz$, $R_6 = OH$, $R_7 = CH_3$, $R_8 = OProp$, $R_9 = H$, $R_{10} = CH_3$		*K. induta*	(Minh et al., 2014)
13	Heilaohusu C	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, $R_5 = H$, $R_6 = CH_3$, $R_7 = H$, $R_8 = O$, $R_9 = OAng$, $R_{10} = CH_3$		*K. coccinea*	(Yang et al., 2019)
14	Longipedlignan A	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, $R_5 = H$, $R_6 = OH$, $R_7 = CH_3$, $R_8 = OBz$, $R_9 = H$, $R_{10} = CH_3$		*K. longipedunculata*	(Liu et al., 2018)
15	Longipedlignan B	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, $R_5 = H$, $R_6 = CH_3$, $R_7 = OH$, $R_8 = OBz$, $R_9 = H$, $R_{10} = CH_3$		*K. longipedunculata*	(Liu et al., 2018)
16	Longipedlignan C	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, $R_5 = H$, $R_6 = OH$, $R_7 = CH_3$, $R_8 = OCin$, $R_9 = H$, $R_{10} = CH_3$		*K. longipedunculata*	(Liu et al., 2018)
17	Longipedlignan D	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, $R_5 = H$, $R_6 = CH_3$, $R_7 = OH$, $R_8 = OCin$, $R_9 = H$, $R_{10} = CH_3$		*K. longipedunculata*	(Liu et al., 2018)
18	Longipedlignan E	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$, $R_5 = H$, $R_6 = OH$, $R_7 = CH_3$, $R_8 = OAng$, $R_9 = H$, $R_{10} = CH_3$		*K. longipedunculata*	(Liu et al., 2018)
19	Longipedunculatin D	$R_3 = R_5 = CH_3$, $R_4 = H$, $R_6 = OGlc$, $R_7 = H$, $R_8 = CH_3$, $R_9 = H$, $R_{10} = OH$, $R_{11} = H$, $R_{12} = CH_3$		*K. longipedunculata*	(Liu et al., 2019)
20	Renchangianin E	$R_1 = H$, $R_2 = R_3 = R_5 = R_6 = CH_3$, $R_4 = H$, $R_7 = OBz$, $R_8 = OH$, $R_9 = H$, $R_{10} = OBz$, $R_{11} = H$, $R_{12} = CH_3$		*K. renchangiana*	(Liu, Luo, Hu, Deng, & Chen, 2014)
21	Heilaohusus D	$R_1 = H$, $R_2 = R_3 = R_4 = R_5 = R_6 = CH_3$, $R_7 = OBz$,$R_8 = CH_3$, $R_9 = OH$, $R_{10} = OAc$, $R_{11} = CH_3$, $R_{12} = H$		*K. coccinea*	(Yang et al., 2019)
22	Heilaohuguosu H	$R_1 = OCap$, $R_2 = \beta$-OAc, $R_3 = OH$, $R_4 = \alpha$-CH_3		*K. coccinea*	(Jia et al., 2021)
23	Heilaohuguosu I	$R_1 = OAng$, $R_2 = \beta$-OAc, $R_3 = OH$, $R_4 = \alpha$-CH_3		*K. coccinea*	(Jia et al., 2021)
24	Heilaohuguosu J	$R_1 = OH$, $R_2 = \beta$-OCH_3, $R_3 = OAc$, $R_4 = \alpha$-CH_3		*K. coccinea*	(Jia et al., 2021)
25	Heilaohuguosu K	$R_1 = OCH_3$, $R_2 = \beta$-OCH_3, $R_3 = OH$, $R_4 = \alpha$-CH_3		*K. coccinea*	(Jia et al., 2021)
26	Heilaohuguosu L	$R_1 = OCH_3$, $R_2 = \beta$-OAc, $R_3 = OH$, $R_4 = \alpha$-CH_3		*K. coccinea*	(Jia et al., 2021)
27	Kadheterin B	$R_1 = OBz$, $R_2 = OAng$		*K. heteroclita*	(Luo et al., 2017)
28	Heilaohuguosu A	$R_1 = OCH_3$, $R_2 = H$, $R_3 = \beta$-OH, $R_4 = OAng$		*K. coccinea*	(Jia et al., 2021)
29	Heilaohuguosu B	$R_1 = OCH_3$, $R_2 = OAng$, $R_3 = \alpha$-OH, $R_4 = OH$		*K. coccinea*	(Jia et al., 2021)
30	Heilaohuguosu C	$R_1 = OH$, $R_2 = OAng$, $R_3 = \beta$-H, $R_4 = OAc$		*K. coccinea*	(Jia et al., 2021)
31	Heilaohuguosu D	$R_1 = OCH_3$, $R_2 = OAng$, $R_3 = \beta$-H, $R_4 =$ methacry		*K. coccinea*	(Jia et al., 2021)
32	Heilaohuguosu E	$R_1 = OCH_3$, $R_2 = OAng$, $R_3 = \beta$-H, $R_4 = OH$		*K. coccinea*	(Jia et al., 2021)
33	Heilaohuguosu F	$R_1 = OCH_3$, $R_2 = H$, $R_3 = \beta$-H, $R_4 = OIsobut$		*K. coccinea*	(Chen, Luo, Zou, Lang, & Chen, 2014)

Table 1 (*continued*)

No.	Compound	Substituent groups	Structures of specific substituents	Sources	References
34	Heilaohuguosu G	R_1 = OCH_3, R_2 = H, R_3 = β-H, R_4 = OBz		*K. coccinea*	(Jia et al., 2021)
35	Herteroclitin S	R_1 = R_2 = R_4 = CH_3, R_3 = H, R_5 + R_6 = CH_2, R_7 = O, R_8 = H, R_9 = CH_3, R_{10} = H		*K. heteroclita*	(Chen et al., 2014)
36	Longipedlignan K	R_1 = H, R_2 = R_3 = R_4 = R_5 = CH_3, R_6 = H, R_7 = H, R_8 = OBz, R_9 = CH_3, R_{10} = H		*K. longipedunculata*	(Liu et al., 2019)
37	Heilaohusu A	R_1 + R_2 = CH_2, R_3 = R_5 = R_6 = CH_3, R_4 = OAng, R_7 = H, R_8 = OH, R_9 = CH_3, R_{10} = H		*K. coccinea*	(Yang et al., 2019)
38	Heilaohusu B	R_1 + R_2 = CH_2, R_3 = R_5 = R_6 = CH_3, R_4 = OIsoval, R_7 = H, R_8 = OIsoval, R_9 = CH_3, R_{10} = H		*K. coccinea*	(Yang et al., 2019)
39	Heilaohuguosu M	R_1 = H, R_2 = α-OH, R_3 = H		*K. coccinea*	
40	Longipedunin E			*K. longipedunculata*	(Zhang et al., 2018)
41	Kadsulignan W			*K. heteroclita*	(Shehla et al., 2018)
42	Schisantherin R	R_1 + R_2 = CH_2, R_5 + R_6 = CH_2, R_3 = R_4 = R_7 = R_{10} = CH_3, R_8 = R_9 = R_{11} = H		*K. coccinea*	(Xu, Su, Wei, Zhang, & Li, 2018)
43	Schisantherin S	R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = R_7 = R_{10}=CH_3, R_8 = R_9 = R_{11} = H		*K. coccinea*	(Xu et al., 2018)
44	Kadheterin A			*K. heteroclita*	(Luo et al., 2017)
45	Longipedunin			*K. longipedunculata*	(Guo, Gao, Zhang, & Liu, 2016)
46	Heilaohuguosu N	R_1 = R_2 = CH_3, R_3 = R_4 = H		*K. coccinea*	(Jia et al., 2021)

3.1.1.3. Cyclooctene carbon (C-7 and C-8). When there are methyl groups on the C-7 and C-8 bits, the chemical shift of C-7 and C-8 methyl carbon are around δ_C 32.2–43.9 ppm, if the hydrogen on C-7 are replaced by hydroxyl, the chemical shift of C-7 shows 71.8–80.9 ppm and C-8 is about 42.1–49.2 ppm.

3.1.1.4. C-6 and C-9. When C-6 and (or) C-9 are carbonyl groups, their chemical shifts are related to whether they are conjugated with the benzene ring. When there are different ester groups substituted C-6 and (or) C-9, the chemical shifts are between 80.2 and 86.6 (Table 6) (Chen et al., 2001).

3.1.1.5. Methoxy carbon. The chemical shift of methoxy which has an unsubstituted ortho-carbon is bigger. For example, the chemical shift of methoxy group of C-3 and C-12 was 55.0 ppm, and the other methoxy group was around δ_C 60.0 ppm.

3.1.1.6. Methyl on cyclooctene (C_{17} and C_{18}). The chemical shift of methyl on the cyclooctene is affected by the relative configuration of methyl groups on the eight-member ring, when C-7, C-8 was only substituted by methyl, the chemical shift of α-methyl was between 8.2 and 15.7 ppm, β-methyl was 17.5–20.4 ppm. When the hydrogen on C-7 is replaced by hydroxyl group, the chemical shift of C-17 and C-18 is shown in Table 7.

3.1.1.7. Typical substituents. Benzoyl group: δ_C 65.6 (C═O), δ_C 129.9 (C-2', 6'), δ_C l28.1 (C-3 ', 5 '), δ_C 132.8 (C-1') (Chen, Zhang, Chen, Zhou, & Lee, 1996). acetyl group: δ_C 169.3 (C═O), δ_C 21.2 (-Me); angeloy group: δ_C l5.8 (α-Me), 20.8 (β-Me), δ_C l27.6, δ_C138.7 (C═C), δ_C l66.4 (C═O) (Luo et al., 2017); isobutyryl group: δ_C 176.6(C═O), δ_C 33.7(–CH); δ_C18.7 (α-Me), δ_C 19.2 (β-Me) (Yang et al., 2019), propanoyl group: δ_C 173.6(C═O), δ_C 27.3(–CH_2); δ_C 8.6 (-Me) (Hu et al., 2012).

3.1.2. ^{13}C NMR spectral characteristics of spirobenzofuranoid dibenzocyclooctadienes lignans

Chemical shift of α, β, α', β'-dienone carbonyl group is about 183.0 ppm, and that of α, β, γ, δ-dienone carbonyl group nears 196.0 ppm. The chemical shift of C-16 and C-17 in the spisobenzofuran ring are about 56.0–65.0 ppm and 78.0–85.0 ppm, respectively. When acyl groups were attached to C-6 and C-9, the chemical shifts of these two carbons are 78.0–85.0 ppm (Lin et al., 2013). Take the structure of Fig. 3 as example, the chemical shift is shown in Table 8.

3.2. ^1H NMR spectrum characteristics of lignans from genus Kadsura

3.2.1. Biphenylcyclooctene lignans

The chemical shift of hydrogen on biphenylcyclooctene lignans empirical rule is shown in Table 9.

3.2.1.1. Aromatic proton. The chemical shift of the two aromatic protons H-4 and H-11 in biphenyl ring is 5.9–7.0 ppm (each 1H, s). The two aromatic protons H-4 and H-11 are equivalent in symmetric planar struc-ture, and the chemical shift of these two aromatic protons is related to *ortho* substituent. The *ortho* proton of methylenedioxy appears in the higher field than ordinary proton, and *ortho* proton of hydroxyl appears in the lower field (Chen et al., 2000). If an ester is substituted at C-6 or C-9, H-4 or H-11 should be deshielded, and their chemical shift increment is 0.1 ppm, when 6-OH is α-orientation, the chemical shift of H-4 is bigger than that of β-orientation (Wang & Chen, 1985).

3.2.1.2. Methoxy proton. Chemical shift of the methoxy group on the aromatic ring is 3.2–3.9 ppm, and that of methoxy groups on C-14 and C-1 are lower than the methoxy groups on other positions of same benzene ring, because of the shielding effect of the adjacent aromatic ring. When the methylenedioxy group and methoxy groups are on the same aromatic ring, the chemical shifts of methoxy groups in the same ring move to the lower field (Chen et al., 2000).

3.2.1.3. Methylene dioxy proton. Chemical shift of methylenedioxy group on the aromatic ring is about 5.6–6.0 ppm.

3.2.1.4. Cyclooctent moiety methyl proton. CH_3-17 and CH_3-18 are *cis*-form when there is no hydroxyl group substituted on C-7 and C-8, signals of CH_3-17 and CH_3-18 are two non-equivalent doublets (δ_H 0.7–1.0 ppm, J = 7.0 Hz). When a hydroxyl group substituted on C-7, CH_3-18 is a singlet, δ_H 1.1–1.3 ppm.

3.2.1.5. H-6 and H-9. Chemical shift of H-6 and H-9 is about 2.0–2.7 ppm (each 2H, ABX), when there is no oxygen-containing substitution on C-6 and C-9. If there are hydroxyl or ester groups on C-

6 or C-9, when H-6/ H-7 (or H-9/H-8) are *trans*-form, H-6 or H-9 are doublets (4.0–6.0 ppm, J = 8.0 Hz) and C-6 hydroxyl or ester group is β-oriented, C-9 hydroxyl or ester group is α-oriented. And when H-6/H-7 (or H-9/H-8) are *cis*-form, H-6 (or H-9) is singlet, and C-6 hydroxyl is α-oriented (Chen et al., 2000). Therefore, the configurations of C-6, C-9 and cyclooctene can be inferred from the multiplets and coupling constants.

3.2.1.6. H-7 and H-8. Chemical shifts of H-7 and H-8 are generally in the range of 1.7–2.2 ppm, which is related to the substituent, configuration, and conformation of the cyclooctent ring.

3.2.1.7. Typical acyl substituents. Benzoyl group: δ_H 7.20–7.50 (5H, m); Angeloy group: There are three group of signals which are δ_H 1.78 (3H, dq, J = 7.5, 1.5 Hz), 1.30 (3H, q, J = 1.5 Hz) and 5.80–6.00 (1H, m); *Cis* angelyl group: δ_H1.64 (3H, d, J = 7.0 Hz), 1.54 (3H, s), 6.78 (1H, m).

3.2.2. ^{1}H NMR characteristics of spirobenzofuranoid dibenzocyclooctadienes lignans

Characteristic signal of spirobenzofuranoid dibenzocyclooctadienes lignans is the signal of 17-OCH_3, its chemical shift is 4.0–5.0 ppm (2H, dd, J = 9.0 Hz), indicating the C-17 was connected to C-16.

3.2.2.1. h-4. Characteristic proton spectra of olefinic proton H-4 is δ 5.8–7.3 ppm, singlet or doublet (J = 1.5 Hz).

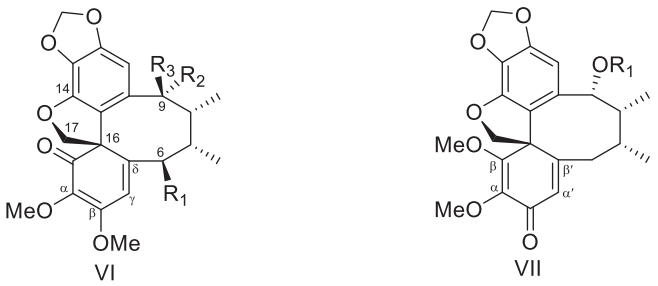


Fig. 3. Structural skeletons (VI: α, β, γ, δ-dienone, VII:α, β, α', β'-dienone) of spirobenzofuranoid dibenzocyclooctadiene lignans from plants of *Kadsura*.

3.2.2.2. H-6 and H-9. The orientation of acyloxy group or hydroxyl group at C-6 or C-9 can be determined from the coupling constants $J_{6,7}$, and $J_{8,9}$. acyloxy group or hydroxyl groups on C-6 are generally β oriented, if there is no hydroxyl on C-7, $J_{6,7}$ is around 10.0 Hz, and if there is a hydroxyl on C-7, H-6 is a doublet (J = 1.5 Hz), for the long-range coupling between H-4 and H-6. Acyloxy group on C-9 is generally α-oriented, when the cyclooctent ring is a boat chair conformation, $J_{8\beta,9\beta}$ is about 7.0 Hz or cyclooctent ring is a boat conformation $J_{8\beta,9\beta}$ is about 0 Hz (Kuo, Kuo, & Chen, 1997).

4. Prediction lignans as Q-marker of genus *Kadsura*

In recent years, researchers are increasingly concerned about TCM quality control system. A few years ago, the new concept of a TCM quality marker was proposed by Liu et al. (2016). Q-marker of TCM is intrinsic chemicals that exist in herbs and in products made from herbs. In order to be indicators of quality control, these compounds should be associated with the functions and properties of the TCM in question, so that they can reflect its safety and efficacy.

Q-marker of *Kadsura* was predicted by plant phylogenetic relationship, pharmacodynamics, identifiable chemical compositions, injectable compositions.

4.1. Q-marker prediction analysis based on original plant phylogeny and characteristic chemical components

Kadsura Kaempf. ex Juss., belonging to the family Schisandroideae, has 29 species of plants, mainly growing in east and southeast of Asia. There are 10 species of this genus in China, most of them are distributed in the southeast and southwest of China, including Yunnan, Guizhou, Sichuan, Guangdong, Guangxi, Fujian and other provinces (Dong et al., 2014), Chinese Pharmacopeia (2015 Edition) lists *Kadsura* species such as *K. interior*, *K. coccinea*, *K. longipedunculata*, and *K. heteroclita,* etc. Among these species of the genus *Kadsura*, lignans are the dominant constituents. At present, more than 300 lignans have been isolated from *Kadsura.* Lignans are biosynthesised from shikimic acid (or cinnamic acid) pathway, shikimic acid (or cinnamic acid) is generated from phenylalanine through deamination and oxidation, then lignans are synthesized from cinnamic acid and benzoic acid. Based on

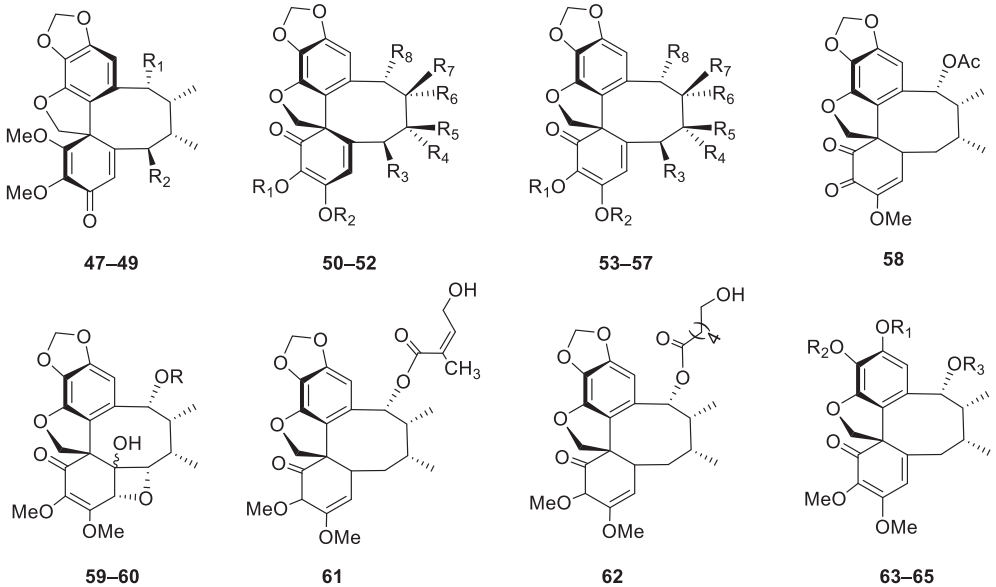
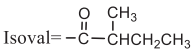
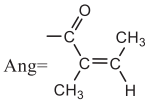
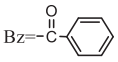
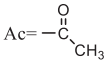
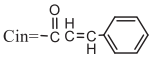
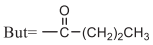


Fig. 4. Structures of spirobenzofuranoid dibenzocyclooctadiene lignans in plants of *Kadsura*.

Table 2
Spirobenzofuranoid dibenzocyclooctadiene lignans isolated from plants of *Kadsura*.

No.	Compound	Substituent groups	Structures of specific substituents	Source	References
47	Kadsutherin F	R_1 = OAng, R_2 = OH	Isoval= 	*K. interior*	(Liu et al., 2018a; Liu et al., 2018b)
48	Kadsutherin G	R_1 = OBz,R_2 = OH	Ang= 	*K. interior*	(Liu et al., 2018a; Liu et al., 2018b)
49	Kadsutherin H	R_1 = OAc,R_2 = OH	Bz= 	*K. interior*	(Liu et al., 2018a; Liu et al., 2018b)
50	Longipedlignan M	R_1 = R_2 = CH_3, R_3 = H, R_4 = OH, R_5 = CH_3, R_6 = CH_3, R_7 = H, R_8 = OCin	Ac= 	*K. longipedunculata*	(Liu et al., 2019)
51	Longipedlignan N	R_1 = R_2 = CH_3, R_3 = H, R_4 = CH_3, R_5 = OH, R_6 = CH_3, R_7 = H, R_8 = OCin	Cin= 	*K. longipedunculata*	(Liu et al., 2019)
52	Herteroclitin R	R_1 = R_2 = CH_3, R_3 = O, R_4 = CH_3, R_5 = H, R_6 = CH_3, R_7 = H, R_8 = OAng		*K. heteroclita*	(Chen et al., 2014)
53	Longipedlignan F	R_1 = R_2 = CH_3, R_3 = H, R_4 = OH, R_5 = CH_3, R_6 = CH_3, R_7 = H, R_8 = OBz		*K. longipedunculata*	(Liu et al., 2018c)
54	Longipedlignan G	R_1 = R_2 = CH_3, R_3 = H, R_4 = CH_3, R_5 = OH, R_6 = CH_3, R_7 = H, R_8 = OBz		*K.longipedunculata*	(Liu et al., 2018c)
55	longipedlignan H	R_1 = R_2 = CH_3, R_3 = OH, R_4 = CH_3, R_5 = H, R_6 = CH_3, R_7 = H, R_8 = OAc		*K. longipedunculata*	(Liu et al., 2018c)
56	Longipedlignan I	R_1 = R_2 = CH_3, R_3 = OH, R_4 = CH_3, R_5 = H, R_6 = CH_3, R_7 = H, R_{10} = Obutanoyl		*K. longipedunculata*	(Liu et al., 2018c)
57	Longipedlignan J	R_1 = R_2 = CH_3, R_3 = OH, R_4 = CH_3, R_5 = H, R_6 = CH_3, R_7 = H, R_8 = OAng	But= 	*K. longipedunculata*	(Liu et al., 2018c)
58	Longipedlignan L			*K. longipedunculata*	(Liu et al., 2018c)
59	Longipedlignan O	R = Bz		*K. longipedunculata*	(Liu et al., 2018c)
60	longipedlignan P	R = Ac		*K. longipedunculata*	(Liu et al., 2018c)
61	Kadlongilignan E				(Shao, Qi, Sun, & Li, 2020)
62	Kadlongilignan F				(Shao et al., 2020)
63	Longipedunculatin A	R_1 = H, R_2 = Glc, R_3 = Ang			(Liu et al., 2018c)
64	Longipedunculatin B	R_1 = Glc, R_2 = H, R_3 = Ang			(Liu et al., 2018c)
65	Longipedunculatin C	R_1 = H, R_2 = Glc, R_3 = 2-Methybutyryl			(Liu et al., 2018c)

the above analysis lignans are considered as Q-marker of *Kadsura* plants.

4.2. Q-marker prediction analysis based on chemical compositions and pharmacodynamics

Q-marker is the main index for evaluating and controlling the effectiveness of traditional Chinese medicine, it closely related to the effectiveness. The reported lignans from *Kadsura* plant possess a series of pharmacological activities, such as anti-cancer (Kuo, Wu, Huang, Kuo, & Ong, 2005a; Kuo, Wu, Hung, Huang, YangKuo, Shen, Ong. 2005b), anti-tumor (Xu, Peng, Chen, Wang, & Xiao, 2010), anti-HIV (Pu et al., 2008; Sun et al., 2011), anti-inflammatory (Lin, Shen, Shen, & Tsai, 2006), anti-platelet aggregation (Lu & Chen, 2009), nitric oxide inhibition (Awale, Tezuka, Banskota, Adnyana, & Kadota, 2003; Mulyaningsil et al., 2010) and neuroprotective effects (Dong, Pu, Zhang, Du, & Sun, 2012).

The stem of *Kadsura* plant is mainly used for promoting blood circulation, relieving pain, removing wind and dehumidifying. Heilaohulignan C from *Kadsura coccinea*, showed good cytotoxicity

Tabe 3
Aryltetralin lignanoids isolated from plants of *Kadsura*.

No.	Compound	Substituent groups	Source	References
66	(7′S, 8′S, 8R)-(8β, 8′α)-dimethyl-4, 4′-dihydroxy-5, 3′-dimethoxy-5′- cyclolignan glucoside		*K. coccinea*	(Yeon et al., 2014)
67	Heilaohusu E	R_1 = R_2 = R_5 = R_6 = OCH_3, R_3 = R_4 = OH	*K. coccinea*	(Yang et al., 2019)
68	Heilaohuguosu O	R_1 = R_6 = OH, R_2 = R_3 = R_4 = R_5 = OCH_3	*K. coccinea*	(Jia et al., 2021)
69	Heilaohuguosu P	R_1 = R_2 = OCH_3, R_3 = R_6 = OH, R_4 = R_5 = OCH_3	*K. coccinea*	(Jia et al., 2021)
70	Heilaohuguosu Q	R_1 = R_2 = OCH_3, R_3 = H, R_4 = R_5 = OCH_3 R_6 = OH,	*K. coccinea*	(Jia et al., 2021)
71	Heilaohuguosu R	R_1 = R_3 = R_4 = R_6 = OCH_3, R_2 = R_5 = OH	*K. coccinea*	(Jia et al., 2021)

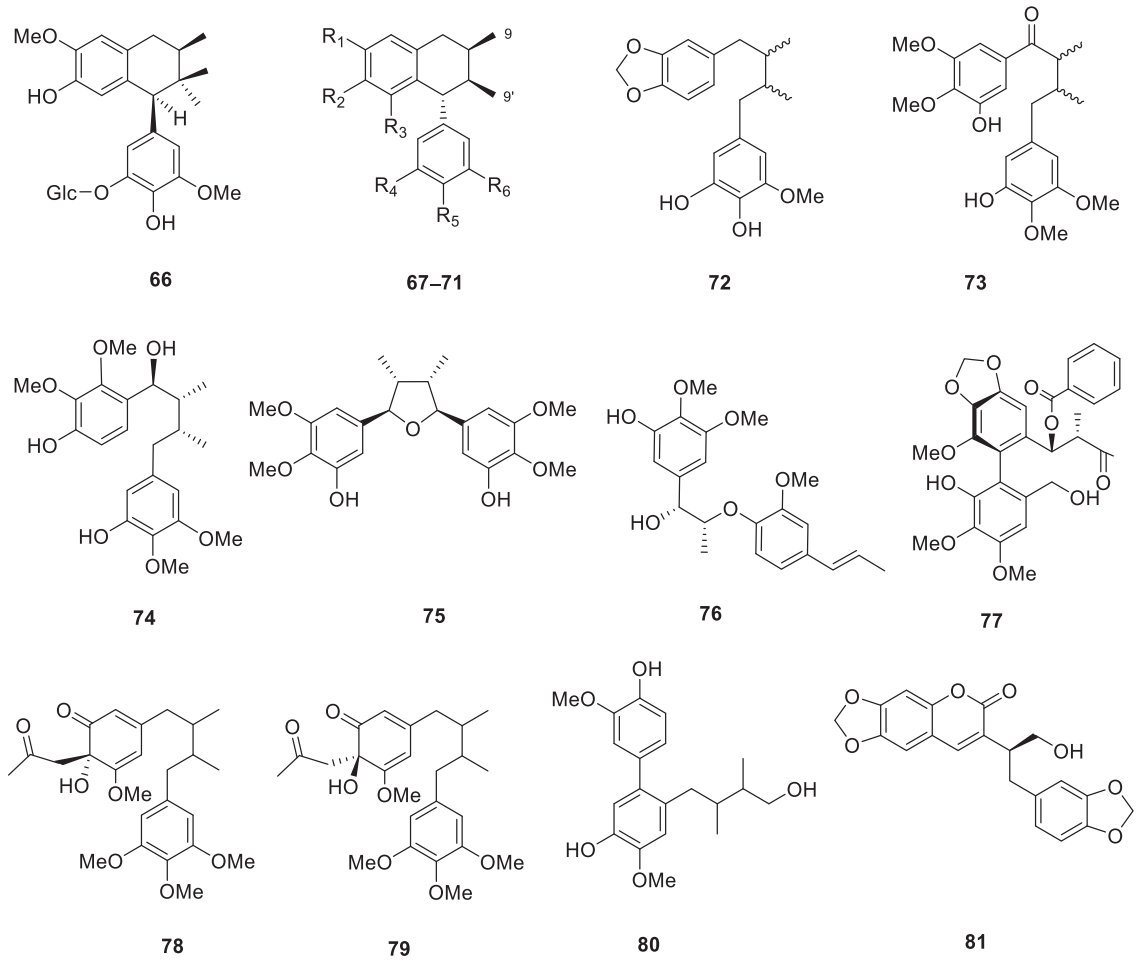


Fig. 5. Structures of aryltetralin, diarylbutane, tetrahydrofurans and new lignans in plants of *Kadsura*.

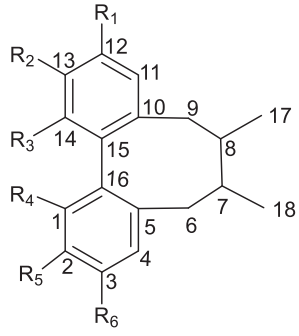


Fig. 6. Structures of biphenyclooctene skeletonwise.

Table 4
Chemical shift of C_4 and C_{11} at different substituents on benzene ring.

Substituent groups			δ_C (C_4 and C_{11})
$R_{1,6}$	$R_{2,5}$	$R_{3,4}$	
OMe	OMe	OMe	106.9–111.9
OH	OMe	OMe	109.9–110.2
OMe	OMe	OH	105.9–107.7
OCH_2O		OMe	101.1–103.1

Table 5
Aromatic quaternary carbon chemical shift.

Position of carbon	Substituents (R)	Chemical shift of carbon
C_{12}, C_3	OMe	153.3–150.2
	OCH_2O	147.9–149.6
C_{13}, C_2	OMe	133.6–142.1
	OCH_2O	132.8–136.9
C_1, C_{14}	OR	141.0–142.0
	OMe	135.2–151.4
	OH	146.7–149.0
C_{15}, C_{16}		115.2–124.8

Note: R = Ang, Tig, Isoval, Bz, Ac...

Table 6
Chemical shift of C_6 and C_9.

Substituent groups	δ_C (C6, C9)	
OR	80.2–86.6	
C=O	Conjugated to aromatic	200.4–203.7
	Not-conjugated to aromatic	208.3–210.4

Note: R = Ang, Tig, Isoval, Bz, Ac...

in HepG-2 human liver cancer cells with IC_{50} values of 9.92 μM (Kuo et al., 2005). Interiorin A and interiorin B isolated from *Kadsura heteroclita* showed anti-HIV activity with EC_{50} 1.6 and 1.4 μg/mL respectively (Pu et al., 2018). The *in vitro* anti-inflammatory assay of lignans longipedunculatin A, longipedlignan M, and longipedlignan J showed significant inhibitory effective

Table 7
Chemical shift of C_{17} and C_{18}.

Substituent groups	Corresponding substituents	Chemical shift
7α-OH	18-β-CH_3	28.8–31.5
	17-α-CH_3	16.8–17.9
7β-OH	18-α-CH_3	21.4–24.3
	17-β-CH_3	17.0–17.9

Table 8
^{13}C NMR spectral characteristics of spirobenzofuranoid dibenzocyclooctadienes lignans.

Structure types	Dienone carbonyl groups	Chemical shift		
		C_{17}	C_{16}	C_6 and C_9
α, β, α', β'	194.6–197.8	55.0–56.9	79.2–84.3	78.0–85.0
α, β, γ, δ	165.8–183.5	61.0–66.7	79.1–81.9	78.0–85.0

Table 9
^{1}H NMR chemical shift of biphenyclooctene lignans.

Positions		Chemical shift
H_4, H_{11}		5.9–7.0
H_7, H_8		1.7–2.8
H_6, H_9	Without substituents	2.0–2.7
	Oxygen-containing substituents	4.0–6.0
OCH_3		3.2–3.9
OCH_2O		5.6–6.0
Cyclooctent moiety methyl proton	C7 is substituted for OH	H_{17} (1.1–1.4) H_{18} (1.3–1.4)
H_{17}, H_{18}	C_7 only has methyl substitution	$H_{17,18}$ (0.6–1.1)

with inhibition rates in 55.1%, 74.9%, and 89.8% respectively (Dong et al., 2014). Acetylepigomisin R, isovaleroylbinankadsurin A and binankadsurin A isolated from *Kadsura coccinea* have the effect of protecting rat liver injury caused by *tert*-butyl hydrogen peroxide, with ED_{50} 135.7, 26.1 and 79.3 mol/L, respectively (Dong et al., 2014). The above studies indicate that lignans are important active substances of *Kadsura* plants and can be used as Q-marker.

4.3. Q-Marker prediction analysis of identifiable chemical composition

The identifiable of chemical components is basic conditions of Q-marker. The determination of chemical composition is mainly by chromatographic analysis. At present, the relevant literature on the chemical composition of *Kadsura* plants is summarized and found that lignans in *Kadsura* are qualitatively identified and determined by column chromatography, HPLC (Chen, Wang, & Song, 2018), UV spectrophotometry, infrared fingerprint method (Sun, Xu, Xu, Xin, & Huang, 2012), near infrared spectroscopy, ultra-high performance liquid chromatography (Deng, Wang, Yan, & Yin, 2017), liquid chromatography-ion trap mass spectrometric (LC-MS/MS) (Tian, Xu, Hu, Zhao, & Liu, 2012).

4.4. Q-Marker prediction analysis based on the injectable components

The complexity of the components of TCM is the basis on its various effects and pharmacological actions. Although the chemical composition is complex, it is only absorbed into the bloodstream and takes effect while reaching a certain blood concentration in the body (Shi et al., 2019). Studies have found that lignans are absorbed faster in the stomach than other organs. Lignans are mainly distributed in the liver, and exist in hepato-intestinal circulation, entero-intestinal circulation or gastro-intestinal circulation in the body (Wang et al., 2014). As Q-marker indicators, lignans provide significant reference for the quality control and surveillance research of genus *Kadsura*.

5. Conclusion and future perspectives

Lignans are the major effective components of genus Kadsura. Genus *Kadsura* plants are widely distributed in China, which possess unique resource superiority. Eighty-one lignans have been separated and identified from this genus in the past eight years, including dibenzocyclooctadienes, spirobenzofuranoid dibenzocyclooctadienes, aryltetralins, and neolignans. ^{1}H NMR and ^{13}C NMR spectral characteristics of lignans compounds are summarized in this paper. Based on Q-marker and the analysis of phylogenetic relationship and effective components of *Kadsura*, lignans were predicted to be one of the quality markers of *Kadsura* plants. Thus, the research and utilization of genus *Kadsura* based on lignans will have an extensive prospect.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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