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Phytochemistry and anti-inflammatory activities of *Piper kadsura* (Choisy) Ohwi – a review

[Actividades fitoquímicas y antiinflamatorias de *Piper kadsura* (Choisy) Ohwi - una revisión]

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Abstract: *Piper kadsura* (Choisy) Ohwi which belongs to the family Piperaceae, is a well-known medicinal plant possessing high medicinal and various therapeutic properties. It is widely used in traditional Chinese medicine for the treatment of asthma and rheumatic arthritis. Numerous studies on this species have also corroborated the significant anti-inflammatory potential of its extracts and secondary metabolites. The main chemical constituents which have been isolated and identified from *P. kadsura* are lignans and neolignans, which possess anti-inflammatory activities. The present article aims to provide a review of the studies done on the phytochemistry and anti-inflammatory activities of *P. kadsura*. The scientific journals for this brief literature review were from electronic sources, such as Science Direct, PubMed, Google Scholar, Scopus, and Web of Science. This review is expected to draw the attention of the medical professionals and the general public towards *P. kadsura* and to open the door for detailed research in the future.

Keywords: Piperaceae; *Piper kadsura*; Phytochemistry; Neolignan; Alkaloid; Anti-inflammatory

Resumen: *Piper kadsura* (Choisy) Ohwi, perteneciente a la familia Piperaceae, es una planta medicinal conocida que posee importantes propiedades medicinales y diversas propiedades terapéuticas. Es ampliamente utilizada en la medicina tradicional china para el tratamiento del asma y la artritis reumática. Numerosos estudios sobre esta especie también han corroborado el destacado potencial antiinflamatorio de sus extractos y metabolitos secundarios. Los principales componentes químicos que se han aislado e identificado de *P. kadsura* son los lignanos y los neolignanos, que poseen actividades antiinflamatorias. El presente artículo tiene como objetivo proporcionar una revisión de los estudios realizados sobre las actividades fitoquímicas y antiinflamatorias de *P. kadsura*. Las revistas científicas para esta breve revisión de literatura fueron de fuentes electrónicas, como Science Direct, PubMed, Google Scholar, Scopus y Web of Science. Se espera que esta revisión atraiga la atención de los profesionales médicos y el público en general respecto de *P. kadsura* y abra la puerta a una investigación detallada en el futuro.

Palabras clave: Piperaceae; *Piper kadsura*; Fitoquímica; Neolignano; Alcaloide; Anti-inflamatorio

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INTRODUCTION

Medicinal plants are considered as nature's blessings, as they have served mankind to preserve our health with their medicinal properties for centuries (Katkar *et al*., 2010). According to the World Health Organization (WHO), more than 80% of the world's population depends on traditional medicine (WHO, 1993). Of these, *Piper* is the largest genus within the Piperaceae family consisting of approximately 2000 species. They are widely distributed throughout the tropical and subtropical regions of the world and have multiple applications in different folk medicines. The high species diversity of *Piper* is of considerable evolutionary importance in the traditional Magnoliidae, a major group of basal angiosperms. Most *Piper* species vary from being locally endemic to widespread and can display different life forms such as shrubs, herbs, or lianas (Sanderson & Donoghue, 1994; Jaramillo and Manos, 2001; Wanke *et al*., 2007; Jaramillo *et al*., 2008; Salleh *et al*., 2014). *P. kadsura* (Choisy) Ohwi (**Figure No. 1**) locally known as *haifengteng*, are found in the East Asian warm-temperate forests and they maintain high endemism in such forests throughout the world (Qian & Ricklefs, 2000). The plant has different synonyms like; *Ipomoea kadsura* Choisy, *Piper arboricola* C.DC. *Piper futokadsura* Sieb., and *Piper subglaucescens* C.DC. (The Plant List, 2010). It also grows in the Fujian and Hainan, with other sporadic distributions in Southern China (Wu and Hong, 1982). The characteristics of *P. kadsura* are listed in **Table No. 1**. This species which has been widely used in medical treatment has attracted considerable attention due to many of its functions. According to the Chinese medicinal theory, *P. kadsura* is generally used to dredge meridian, expel wind-dampness, and relieve limb pain. It is also used for cooking and improving digestive function in Japan because its fruit is similar to pepper (Chinese Pharmacopoeia Commission, 2010). The stem is used in traditional Chinese medicine to treat asthma, anemofrigid-damp arthralgia, and traumatic injury. In addition, it is also useful in treating rheumatic arthritis and rheumatoid arthritis with joint pain. Moreover, it has also been used for the relief of muscular contraction and ankylosis (Parmar *et al*., 1997; Li *et al*., 2003). To date, various chemical constituents have been isolated from *P. kadsura*, including lignans, neolignans, amides, alkaloids, and miscellaneous compounds. Meanwhile, modern pharmacological tests have revealed that the plant can ameliorate the learning and memory deficiency of model mice with Alzheimer's disease (Xiao *et al*., 2004), by inhibiting the gene expression of the β-amyloid precursor protein related to Alzheimer's disease (Xing *et al*., 2011; Zheng *et al*., 2011) and exerting a protective effect on focal cerebral ischemia-aged rats by reducing delayed neuronal cell death and necrosis (Wang *et al*., 2003), along with anti-inflammatory activity (Li *et al*., 2006). The aim of this brief review is to summarise the available information on the traditional uses, phytochemistry and anti-inflammatory activities of *P. kadsura*. The literature used in the review comprises of scientific journals obtained from electronic sources, such as Science Direct, PubMed, Google Scholar, Scopus, and Web of Science.

Figure No. 1
***P. kadsura* (Choisy) Ohwi**

Table No. 1
Characteristics of *P. kadsura* (Wu & Hong, 1982)

Characters	Botanical Discription
Plant Habit	Lianas, rooted at nodes, sparsely hairy at young stage.
Leaf	Ovate to long ovate, diameter 12×3.5-7 cm, Leaf base is cordate to rounded and acute or obtuse at the apex. Leathery blade, occasionally hairy and sheath at the base. Petiole length between 1.0-1.5 cm and venation in 5 with the apical pair up to 1.5 cm above the base. Opposite type of leaf arrangement
Flower	Inflorescence: spike and leaf-opposed. Male spike is yellowish and in assending order, peduncle 0.6-1.5 cm. Rachis hispidulous, bract yellowish, orbicular, and about 1mmm wide. Subtend bract irregular margin, rough white hair at the abaxial and sessile. Stamens in 2-3 short filaments. Female spike shorter than the leaf blade and peduncle is about the length of the petiole. Rachis and bracts are somewhat similar to male spike. Ovary globose, stigma 3-4, linear and hairy.

Phytochemistry

A review of the literature revealed that the phytochemical properties of *P. kadsura* have long been carried out. Since 1975, compounds **1**–**62** (Figure No. 2) have been isolated from various parts of *P. kadsura*. The species is reported to contain several classes of natural products including lignans, neolignans, amides, alkaloids, and miscellaneous compounds which are listed in Table No. 2.

Lignans and neolignans

Lignans and neolignans are large groups of natural products characterised by the coupling of two C_6-C_3 units (Salleh *et al*., 2016). Both lignans and neolignans are common in some *Piper* species (Tyagi *et al*., 1993; Prasad *et al*., 1994). In the case of *P. kadsura*, thirty-nine (**1-39**) lignans and neolignans were isolated from the stem and aerial parts, mainly consisting of benzofuran and bicycle-(3,2,1)-octanoid type of neolignans (Matsui & Munakata, 1975; Ma *et al*., 1993a; Jiang *et al*., 2003; Lin *et al*., 2006; Kim *et al*., 2010). Of these, kadsurenone (**8**) was the first natural product isolated from the stems of *P. kadsura*. It has been demonstrated as a natural Platelet-Activating Factor (PAF) inhibitor that could stop or diminish all unwanted reactions induced by PAF (Huang *et al*., 2009).

Amides and alkaloids

Amides and alkaloids are not commonly isolated from this species but are known to be present in other *Piper* species (Salleh *et al*., 2019; Hashim *et al*., 2019). However, a total of ten compounds (**40-49**) were successfully isolated from three studies, mainly of aristolactams alkaloids (Lin *et al*., 2006; Kim *et al*., 2011; Xin *et al*., 2018).

Miscellaneous compounds

Twelve other compounds (**50-62**) belonging to other classes of natural compounds have also been isolated, such as phenolics, terpenes, and ketones. (+)-Crotepoxide (**12**) was isolated from the stems of *P. kadsura*, is also known as a tumour inhibitor (Takahashi, 1969; Takahashi, 1970; Lin *et al*., 2006). In addition, Kim *et al*. (2011) successfully isolated a new stereoisomer of guaiane sesquiterpene, kadsuguain A (**42**) and a new cyclohexadienone, kadsuketanone A (**51**) from the methanolic extract of the aerial parts. Compound (**51**) which is a rare analogue in natural sources have been found to significantly reduce PGE_2 production in the LPS-stimulated microglia in anti-neuroinflammatory effects.

Essential oil

Only one study has assessed the essential oil composition from fresh stems of *P. kadsura* collected from China. Forty-three components (72.01%) were detected in the stem oil, representing β-eudesmol (12.9%), laevojunenol (9.8%), espatulenol (6.0%), β-caryophyllene (6.0%), *cis*-asarone (5.8%), and valencene (5.4%), as their major components (Liu *et al*., 2015).

Table No. 2
Chemical constituents isolated from *P. kadsura*

No	Constituents	Parts	References
LIGNANS AND NEOLIGNANS			
1	Piperkadsin A	Stem	Lin *et al*., 2006
2	Piperkadsin B	Stem	Lin *et al*., 2006
3	Piperkadsin C	Aerial part	Kim *et al*., 2010
4	Futoquinol	Stem	Lin *et al*., 2006
		Stem	Strickler & Stone, 1989
		Aerial part	Kim *et al*., 2010
		Stem	Chen *et al*., 1993
5	Isofutoquinol A	Aerial part	Kim *et al*., 2010
6	Kadsurin A	Stem	Lin *et al*., 2006
		Stem	Chang *et al*., 1985
7	Kadsurin B	Stem	Lin *et al*., 2006
		Stem	Chang *et al*., 1985
8	Kadsurenone	Stem	Lin *et al*., 2006
		Stem	Strickler & Stone, 1989
		Aerial part	Kim *et al*., 2010
		Aerial part	Wang *et al*., 2002
		Aerial part	Xin *et al*., 2018
		Stem	Chen *et al*., 1993
		Stem	Shen *et al*., 1985
		Stem	Chang *et al*., 1985
9	Galgravin	Stem	Lin *et al*., 2006
		Aerial part	Xin *et al*., 2017
		Aerial part	Konishi *et al*., 2005
		Stem	Chen *et al*., 1993
10	Futoenone	Stem	Lin *et al*., 2006
11	Liliflone	Stem	Lin *et al*., 2006
12	(7*R*,8*R*,3′*R*)-7-acetoxy-3′,4′-dimethoxy-3,4-methylenedioxy-6′-oxo-Δ-$^{1',4',8'}$-8.3′-lignan	Stem	Lin *et al*., 2006
13	(7*S*,8*S*,1′*R*)-$\Delta^{8'}$-1′-methoxy-3,4-methylenedioxy-1′,6′-dihydro-6′-oxo-7-*O*-4′,8.3′-neolignan	Stem	Lin *et al*., 2006
14	Burchellin	Stem	Lin *et al*., 2006
15	Kadsurenin B	Aerial part	Ma *et al*., 1993b
16	Kadsurenin C	Aerial part	Jiang *et al*., 2003
		Aerial part	Ma *et al*., 1993b
17	Kadsurenin H	Aerial part	Jiang *et al*., 2003
18	Kadsurenin K	Aerial part	Ma *et al*., 1993b
19	Kadsurenin L	Aerial part	Kim *et al*., 2010
		Aerial part	Ma *et al*., 1993b
20	Kadsurenin M	Aerial part	Wang *et al*., 2002
21	Wallichinine	Aerial part	Kim *et al*., 2010
		Aerial part	Xin *et al*., 2018
22	Denudatin A	Aerial part	Kim *et al*., 2010
23	Denudatin B	Aerial part	Wang *et al*., 2002
		Aerial part	Xin *et al*., 2018
24	Futokadsurin A	Aerial part	Konishi *et al*., 2005
25	Futokadsurin B	Aerial part	Konishi *et al*., 2005
26	Futokadsurin C	Aerial part	Kim *et al*., 2010

		Aerial part	Konishi *et al*., 2005
27	(-)-Chicanine	Aerial part	Konishi *et al*., 2005
28	(-)-Zuonin A	Aerial part	Konishi *et al*., 2005
29	(-)-Galbacin	Aerial part	Konishi *et al*., 2005
30	Machilin F	Aerial part	Konishi *et al*., 2005
31	(-)-Machilusin	Aerial part	Konishi *et al*., 2005
32	2-(3′-allyl-2′,6′-dimethoxy-phenyloxy)-1-acetoxy-(3,4-dimethoxy-phenyl)-propyl ester	Aerial part	Kim *et al*., 2010
33	(+)-Acuminatin	Aerial part	Wang *et al*., 2002
		Aerial part	Konishi *et al*., 2005
34	(+)-Licarin A	Aerial part	Wang *et al*., 2002
35	Licarin D	Stem	Lin *et al*., 2006
36	Piperenone	Leaves	Matsui & Munakata, 1975
37	(-)-Galbelgin	Aerial part	Xin *et al*., 2017
		Aerial part	Konishi *et al*., 2005
		Stem	Chen *et al*., 1993
38	(-)-Ganschisandrin	Aerial part	Xin *et al*., 2017
39	(-)-Veraguensin	Aerial part	Xin *et al*., 2017
		Aerial part	Konishi *et al*., 2005
		Stem	Chen *et al*., 1993
AMIDES AND ALKALOIDS			
40	Piperlactam S	Stem	Lin *et al*., 2006
41	*N*-*p*-Coumaroyl tyramine	Stem	Lin *et al*., 2006
42	Aristololactam AIIIa	Stem	Lin *et al*., 2006
43	Aristolactam A II	Aerial part	Kim *et al*., 2011
44	Piperolactam A	Aerial part	Kim *et al*., 2011
45	Piperolactam B	Aerial part	Kim *et al*., 2011
46	Pellitorine	Aerial part	Xin *et al*., 2018
		Aerial part	Konishi *et al*., 2005
47	2*E*-Decenoic-acid *N*-isobutylamide	Aerial part	Xin *et al*., 2018
48	Piperlonguminine	Stem	Xia *et al*., 2015
49	Dihydropiperlonguminine	Stem	Xia *et al*., 2015
MISCELLANEOUS COMPOUNDS			
50	Stigmasterol	Stem	Lin *et al*., 2006
51	Kadsuguain A	Aerial part	Kim *et al*., 2011
52	*trans*-Phytol	Aerial part	Kim *et al*., 2011
53	Junenol	Aerial part	Kim *et al*., 2011
54	*ent*-Germacra-4(15),5,10(14)-trien-1β-ol	Aerial part	Kim *et al*., 2011
55	Germacra-5,10(14)-dien-1β,4β-diol	Aerial part	Kim *et al*., 2011
56	Blumenol A	Aerial part	Kim *et al*., 2011
57	Blumenol B	Aerial part	Kim *et al*., 2011
58	Benzyl benzoate	Aerial part	Kim *et al*., 2011
59	*trans*-2,3-diacetoxy-1-[(benzoy1oxy)methyl]-cyclohexa-4,6-diene	Aerial part	Kim *et al*., 2011
60	Kadsuketanone A	Aerial part	Kim *et al*., 2011
61	Isoasarone	Aerial part	Kim *et al*., 2011
62	(+)-Crotepoxide	Stem	Lin *et al*., 2006
		Aerial part	Xin *et al*., 2018

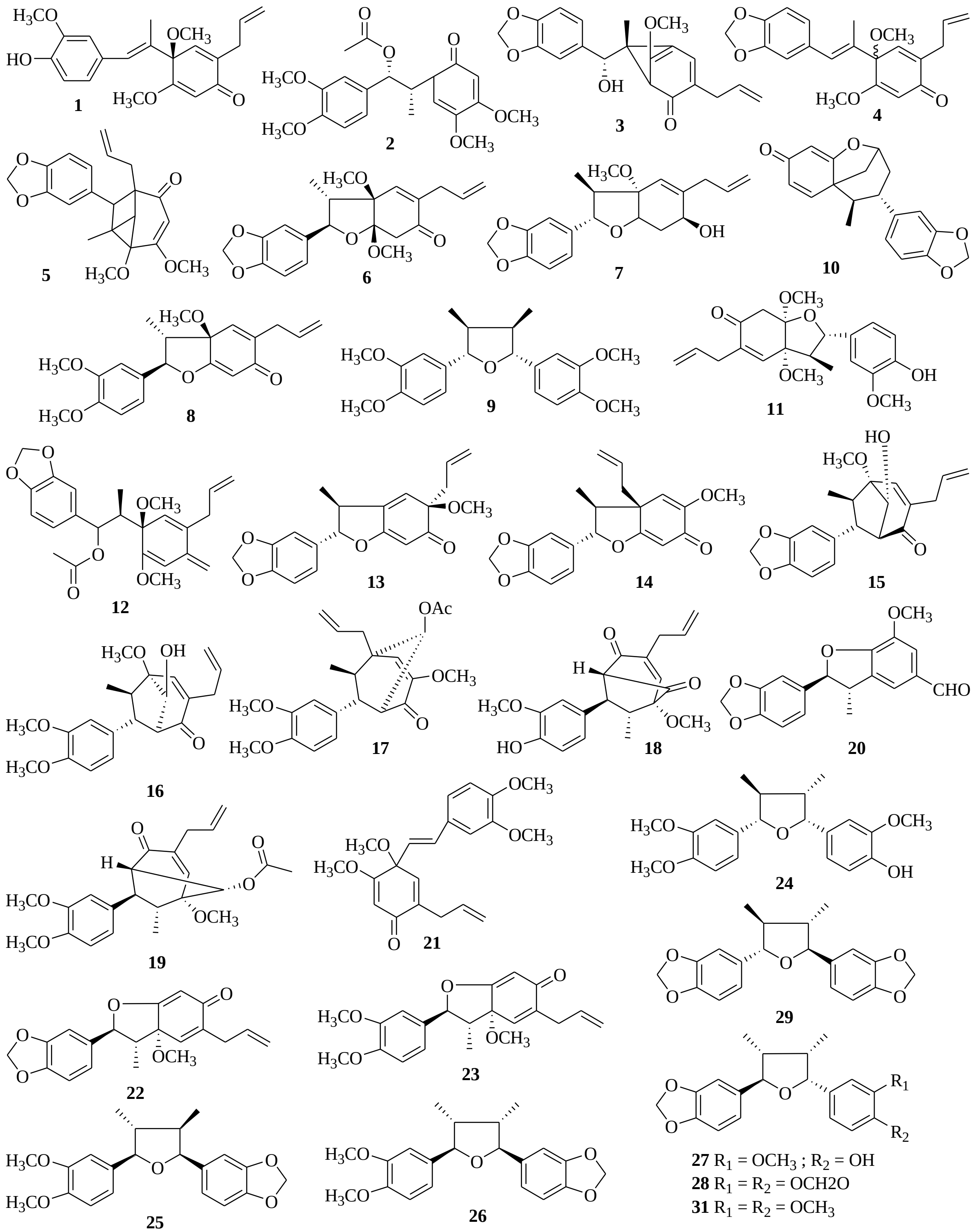

Figure No. 2
Chemical structures of the isolated phytochemicals from *P. kadsura*

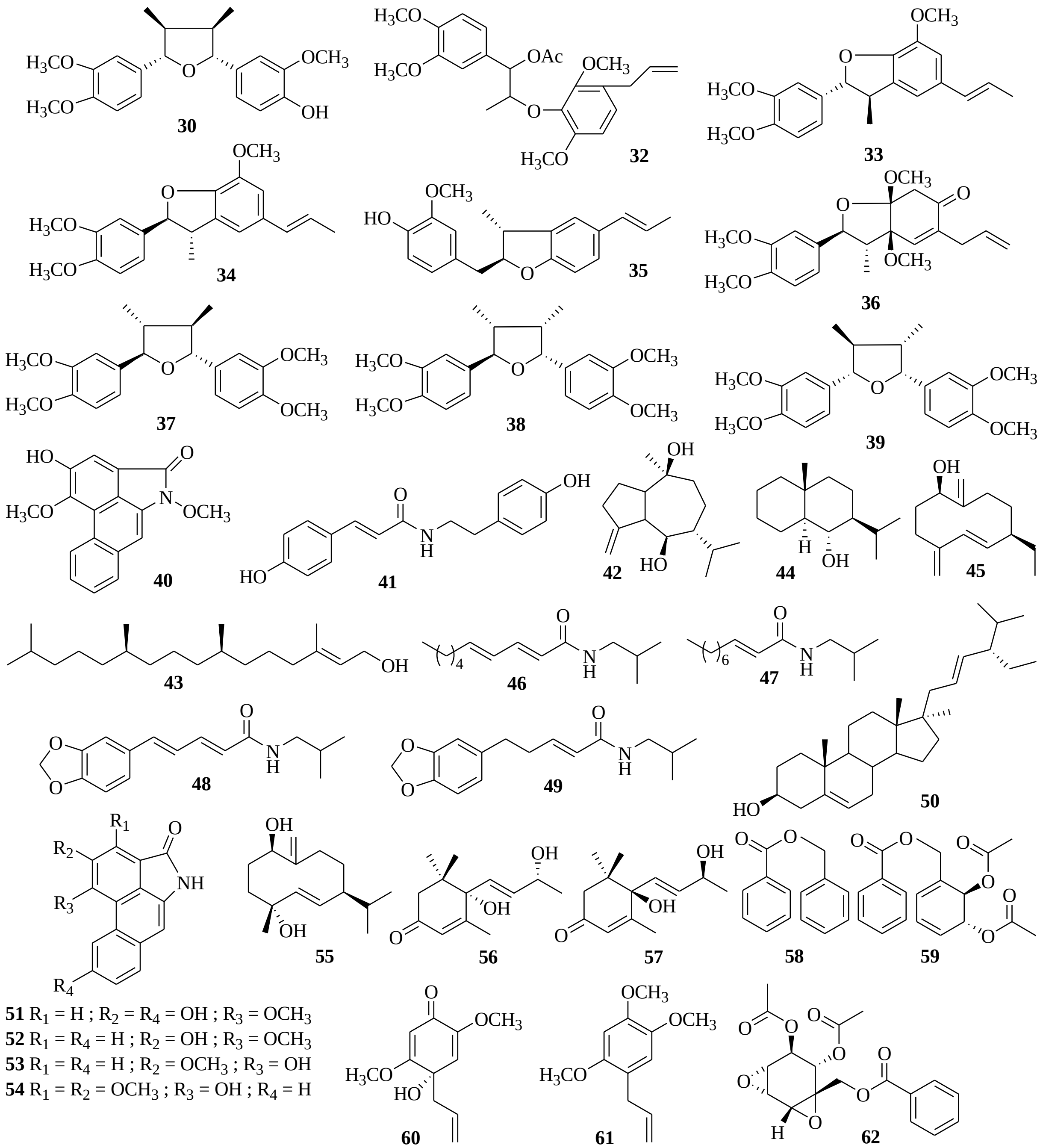

Figure No. 2 [cont.]
Chemical structures of the isolated phytochemicals from *P. kadsura*

Antiinflammatory activities

In the last few decades, several therapeutic options including non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) and glucocorticoids (GCs) have been approved for treating various anti-inflammatory diseases (Ong *et al*., 2007). However, it has been reported that the prolonged use of modern anti-inflammatory drugs are often responsible for producing undesirable side effects including cognitive dysfunction and depression (Hoppmann *et al*., 1991), myocardial infarction, heart failure

(Schmidt *et al*., 2016), gastrointestinal tract bleeding (Moore *et al*., 2015) and acute renal failure (Ejaz *et al*., 2004). Due to these unwanted side effects from existing modern anti-inflammatory therapies, natural anti-inflammatory compounds are becoming more popular with many scientific investigations being performed. Numerous extracts and isolated compounds from medicinal plant species have provided a foundation for modern pharmaceutical drug development. Natural products have been proven to be an essential source for drug discovery and drug design. However, these traditional practices are lacking scientific evidence to validate these medicinal practices (Attiq *et al*., 2017). Considering the above facts, there is a demand for exploring medicinal plants for the recognition of novel, safe and effective anti-inflammatory agents. Many studies have previously demonstrated *Piper* genus with an extensive range of anti-inflammatory activities including isolated compounds as well as primary crude extracts from various parts of the plants.

Li *et al*. (2003) reported the anti-inflammatory activity of the stem extract against a panel of key enzymes relating to inflammation. The enzymes included cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), phospholipase A_2 (PLA_2), 5-lipoxygenase (5-LO) and 12-lipoxygenase (12-LO). The extract exhibited potent inhibitory activities against COX-1, COX-2, PLA_2, and 12-LO with the IC_{50} values of 251, 631, 147, and 85 µg/mL, respectively. However, the stem extract was found inactive against 5-LO. In another study, the *n*-hexane extract of *P. kadsura* demonstrated considerable amount of effects in the 5-LOX and COX-1 assays with a percentage inhibition of 70 µg/mL (Stohr *et al*., 2001). The *n*-hexane and chloroform soluble fractions of the MeOH extract were also found to potently inhibit nitric oxide (NO) production in LPS-activated BV-2 cells, a microglial cell line (Kim *et al*., 2011). In addition, the leaves, stems, roots, and rhizomes of *P. kadsura* collected from Japan were tested for melanogenesis stimulation activity of aqueous ethanolic extracts in B16 melanoma cells. At a concentration of 10 ug/mL, the leaves, stems, roots, and rhizomes extracts demonstrated the percentage of cell proliferation at 99.6, 104.9, 106.1, and 100.4%, respectively (Matsuda *et al*., 2006).

The aqueous extract of Futokadsura stems alleviated the Aβ(25-35)-induced impairment of spatial learning and memory in the Alzheimer disease rats. Furthermore, the extract protected the neurons by decreasing the expression of Aβ, TNF-α and IL-6 and the content of NO and NOS in the brain, and increasing the expression of synaptophysin (SYP) in the hippocampus (Xia *et al*., 2015). Moreover, this mini-review also highlights the secondary metabolites that can serve as the potential candidates for anti-inflammatory regimen in the future. On the other hand, **Table 3** summarises the anti-inflammatory activity of several phytochemicals isolated from *P. kadsura*.

Table No. 3
Anti-inflammatory activities of several phytochemicals from *P. kadsura*

Constituents	Description
Piperkadsin A (**1**)	Potent inhibition of PMA-induced ROS production in human polymorphonuclear neutrophils with IC_{50} value 4.3 μM (Lin *et al*., 2006)
Piperkadsin B (**2**)	Potent inhibition of PMA-induced ROS production in human polymorphonuclear neutrophils with IC_{50} value 12.2 μM (Lin *et al*., 2006)
Piperkadsin C (**3**)	Potently inhibited NO production in LPS-activated BV-2 cells, a microglia cell line with IC_{50} value 14.6 μM (Kim *et al*., 2010)
Futoquinol (**4**)	Potently inhibited NO production in LPS-activated BV-2 cells, a microglia cell line with IC_{50} value 16.8 μM (Kim *et al*., 2010)
	Potent inhibition of PMA-induced ROS production in human polymorphonuclear neutrophils with IC_{50} value 13.1 μM (Lin *et al*., 2006)
Kadsurenone (**8**)	Inhibits PAF-induced aggregation of rabbit platelets and human neutrophils at 2.4-24 μM, without showing any PAF agonistic activity (Shen *et al*., 1985)
Galgravin (**9**)	Inhibited NO production by a murine macrophage-like cell line (RAW 264.7) with IC_{50} value 33.4 μM (Konishi *et al*., 2005)
Kadsurenin C (**16**)	Exhibit significant PAF antagonistic activity with IC_{50} value 5.1×10^{-6} mol/l

	(Jiang *et al*., 2003)
Kadsurenin H (**17**)	Exhibit significant PAF antagonistic activity with IC_{50} value 1.8×10^{-7} mol/l (Jiang *et al*., 2003)
Wallichinine (**21**)	Moderately inhibited NO production in LPS-activated BV-2 cells, a microglia cell line with IC_{50} value 45.6 μM (Kim *et al*., 2010)
Futokadsurin C (**26**)	Moderately inhibited NO production in LPS-activated BV-2 cells, a microglia cell line with IC_{50} value 43.1 μM (Kim *et al*., 2010)
N-*p*-coumaroyl tyramine (**34**)	Potent inhibition of PMA-induced ROS production in human polymorphonuclear neutrophils with IC_{50} value 8.4 μM (Lin *et al*., 2006)
Piperlactam S (**40**)	Potent inhibition of PMA-induced ROS production in human polymorphonuclear neutrophils with IC_{50} value 7.0 μM (Lin *et al*., 2006)
Piperolactam A (**44**)	Inhibited both nitric oxide (NO) and prostaglandin E2 (PGE2) production in the LPS-activated microglia cells with IC_{50} value 6.32 μM (Kim *et al*., 2011)
Piperlonguminine (**48**) and Dihydropiperlonguminine (**49**)	Inhibit the expression of amyloid precursor protein (APP) gene, which play an important role in Alzheimer disease pathogenesis (Xia *et al*., 2007)
Kadsuketanone A (**60**)	Inhibited both nitric oxide (NO) and prostaglandin E2 (PGE2) production in the LPS-activated microglia cells with IC_{50} value 5.62 μM (Kim *et al*., 2011)

CONCLUSION

In the present review, 62 chemical constituents have been isolated and identified from the stems and aerial parts of *P. kadsura*. Neolignans as the major characteristic constituents with significant anti-inflammatory activities hold great potential to be developed into new drugs, especially as anti-inflammatory agents. It can also be treated as a promising source of biologically active compounds for various diseases. Furthermore, ongoing and detailed research is required for the identification, cataloguing and documentation of this herb to provide scientific information for future exploration and necessary development of this herb for the pharmaceutical purposes.

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