Pharmaceutical Sciences Asia

Pharm Sci Asia 2021; 48(1), 1-24

DOI:10.29090/psa.2021.01.19.070

Review

A review on the ethnomedicinal uses, phytochemistry and pharmacology of plant species belonging to *Kaempferia* L. genus (Zingiberaceae)

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Keywords:
Kaempferia L.; *Kaempferia galanga; K. parviflora; K. pandurata; K. daklakensis*; Thailand; Vietnam; South East Asia

ABSTRACT

Kaempferia L. is a genus commonly distributed in Asian countries including China, India, Thailand, Myanmar, Malaysia, Indonesia, Laos, Cambodia and Vietnam, where these species are popularly used as traditional medicines for different ailments comprising infective diseases, wound infection, cough, pain and digestion disorders on chemical composition of *Kaempferia* plants revealed the presence of natural compounds classified in monoterpenoids, diterpenoids, flavonoids, phenolic glycosides, cyclohexane oxide derivatives, diarylheptanoids and essential oil with various biological properties, which are valuable for discovery of new natural-derived therapeutic drugs and applications for the human beings. This study is aimed to review the chemical, ethnobotanical and pharmacological properties of the plants belonging to *Kaempferia* genus growing in Asian countries and especially in South East Asia.

1. INTRODUCTION

Kaempferia, is a medium - sized genus of about 60 plant species belonging to Zingiberaceae[1] that is one of the major tropical plant families with many members commonly used as ornaments, spices and as medicinal herbs[2]. The generic name of the genus memorializes Engelbert Kaempfer (1651-1716), who was a known German naturalist and physician and explorer writer[3]. There are about 40 *Kaempferia* species names were officially accepted (Table 1S, Supporting information)[4]. The genus mainly distributes in East Asia to China, India, Bangladesh and Southeast Asia like Thailand, Myanmar, Malaysia, Indonesia, Philippines, Laos, Cambodia and Vietnam. The most widespread *Kaempferia* species are *K. galanga*, *K. parviflora*, and *K. rotunda*, *K. augustiflora*, etc. (Table 1). These species distribute in many countries and territories and are popularly used as traditional medicines for different ailments including infective diseases, wound infection, cough, pain and digestion disorders. Research on chemical composition of *Kaempferia* plants revealed the presence of natural compounds classified in monoterpenoids, diterpenoids, flavonoids, phenolic glycosides, cyclohexane oxide derivatives, diarylheptanoids and essential oil with various biological properties, which provide these species as a valuable medicinal resource for new natural-derived therapeutic applications for the human beings. This study is aimed to review the ethnobotanical uses, morphological, chemical, and pharmacological properties of the plants belonging to *Kaempferia* species. The application of the species in modern life is also reported.

2. MATERIALS AND METHODS

Different methods were used to collect information about ethnomedicinal uses, phytochemistry and pharmacological properties of *Kaempferia* species.

Accepted name of the plant was collected by using the website www.theplantlist.org (The Plant List, 2019). Worldwide databases including Science Direct, Scopus, Pubmed, Google Scholar and Google Search Engine with keywords of family name, genus name, plant name and isolated natural compound names were used for literature search. Related patents were acquired from Google Patents.

Only articles containing plants collected or purchased from certified medicinal/non medicinal stores with proper identification and voucher specimen were considered for this review in accordance with previously described methods for literature search[5].

3. RESULTS AND DISCUSSION

3.1. Ethnobotanical use of *Kaempferia* L. species

Many *Kaempferia* species have been reported to be used as medicinal plants in many folk medicines for treatment of various ailments including malaria, wound infection, urticarial, diabetes, cancer, herpes and allergy[6].

In almost Asian traditional systems, the most common *Kaempferia* species was *Kaempferia galanga* which plays a very special role as medicinal plant. In India, it is a component of over 59 in ayrurvedic drug formulations to cure asthma, malaria, skin disease, bronchitis, wounds and splenic disorders[7]. It is also used as perfumery, cosmetics and spice ingredients[8]. There are 15 *Kaempferia* enumerated for Thailand[9], of which 12/15 *Kaempferia* species were discovered by C. Picheansoonthon and his colleagues from 2008–2013 (Table 1)[10].

K. galanga is commonly used for the treatment of dysentery, diarrhea, stomachache, swelling, cough, and rheumatism[6]. The dried rhizome has been used as cardiotonic and CNS stimulant[8]. *K. roscoeana* Wall, known as "Pro pa", is used as a spice and food in Thai cuisine[1]. In the North and Northeast of Thailand, the rhizome of *K. parviflora* has been widely used as a traditional medicine for centuries[11]. The rhizomes of *K. parviflora* have been used to treat allergies, gastrointestinal disorders, and peptic ulcers[12]. Among local people in the northeast of Thailand, these rhizomes have been known as health-promoting herbs, and also frequently used for treatment of gout, abscesses, colic disorder, peptic- and duodenal ulcers[13].

There are 10 species in Cambodia, Laos and Vietnam[9]. In Vietnam, there are approximately 7 *Kaempferia* species which are widely cultivated and used as medicinal plants like *K. galanga* (local name Địa liền) for treatment of pains like stomach pain, abdominal pain, rheumatism, pain in the joints, headache, tooth pain, chest pain, also used for poor digestion, and pertussis; *K. angustifolia* is used for cough treatment; *K. rotunda* is for treatment of abdominal pain, menstrual disorder, less menstruation and dysmenorrhea (Table 1). Recently *Kaempferia* species have been found to demonstrate effective cancerpreventive properties. In previous papers, several *Kaempferia* species were described as new record of medicinal plant species for Viet Nam including *K. parviflora* Wall. ex Baker[14], *K. marginata* Carey ex Roscoe[15], *K. champasakensis* Picheans. & Koonterm.[16] and *K. laotica* Gagnep[17].

The ethnobotanical uses in different countries of *Kaempferia* species with their local names have been summarized in Table 1.

Table 1. Ethnobotanical uses of several *Kaempferia* species.

Species	Distribution[17]	Local name	Ethnobotanical / Traditional uses	Ref.
K. angustifolia Roscoe	Bangladesh, Assam, Vietnam, Thailand, Sumatra	VN: Địa liền lá thơm, Thiền liền lá hẹp Thai: townanghang	Vietnam: tuber is used for cough treatment. Root is eaten with *Piper betle* leaves for prevention of tooth decay.	18 19 2
K. elegans (Wall.) Baker	Sichuan, Indochina, Borneo, India, Burma, Malay Peninsula	VN: Ngải chúa	Vietnam: ornamental plant.	9 2 20
K. galanga L.	Yunnan, Assam, Bangladesh, India, Indochina, Vietnam, Thailand, Taiwan	Common name: Sand ginger, Resurrection lily Thai: Proh Hom (*waan horm)* Khmer: *prâh or prâh krâ-oup*	**Thailand:** Used as food spice. The stem is used for treatment of menstrual stimulation and dyspepsia, the leave are for the treatment of skin infected with fungus *Tinea versicolor*, and flower for eye diseases and seizures. The dried rhizome is used as cardiotonic and CNS. The extract causes CNS depression, a decrease in motor activity and a decrease in respiratory rate.	21 22

Table 1. Ethnobotanical uses of several *Kaempferia* species. (cont.)

Species	Distribution[17]	Local name	Ethnobotanical / Traditional uses	Ref.
			Philippine: Rhizome decoction is used for indigestive and antimalarial treatment. Hot leave as topical patches for rheumatic treatment.	
		Chinese: *sha jiang* or *shan nai*.	**China**: It is used in the food spice and medicinal industry, traditionally treating symptoms ranging from hypertension, pectoral and abdominal pains, toothache, dyspepsia, coughs and inflammatory tumor. It is also used as a remedy for toothache, as a stimulant, carminative to treat cholera, contusions, chest pains, headache and constipation. The essential oils from rhizomes are used for indigestion, cold, pectoral and abdominal pains, headache and toothache. Its alcoholic maceration is used in TCM as a liniment for rheumatism.	23
		Malaysia: Cekur, Indonesia: Kencur	**Malaysia:** Rhizome is used for antihypertensive, ulcer and asthma treatment. In Malaysian traditional medicine, the rhizome is used to treat a variety of disorders, such as inflammation, sprains, ulcers, high blood pressure, asthma, colds, coughs and sore throats.	24 25
			Malaysia and Indonesia: as gargle, chewing materials (rhizome, leaves) to treat coughs, as lotions for external use; as an expectorant and carminative (juice of the rhizome), as children's medicine and tonics, as an embrocation or sudorific to treat swelling and muscular rheumatism, as medicine for abdominal pain and as spice and flavor vegetable.	
		Vietnam: Địa liền	**Vietnam:** treatment of pains like stomach pain, abdominal pain, rheumatism, pain in the joints, headache, tooth pain, chest pain, cold treatment, cough expectorant, also used for poor digestion, and pertussis. Rhizome alcohol infusion is topical use for pain relief of muscle aches, backache. Tubers pounded is used for treatment of nausea and vomiting (antiemetic). Tuber is for pain relief, antipyretic, anti-inflammatory, indigestive, cold abdominal pain, rheumatic, tooth pain, diarrhea and pertussis. Tuber is used as food spices.	
		India: Karcura (Kacholam)	**India**: The rhizome is a constituent of a variety of Ayurvedic preparations like *Daśamūlārişţam*, *Valiya rāsnādi kaşāyam*, *Kaccorādi cūrņa*, *Aśanā elādi tailam*, *Valiya Nārāyaņa tailam*, etc.	3
K. laotica Gagnep.	Laos, Thailand, Vietnam	VN: Địa liền Lào	Rhizomes were used for treatment of stomach pain and digestion simulation or as tincture for external uses (limb aching, insect bites).	16
K. parviflora Wall. ex Baker in J.D.Hooker	Thailand, Myanmar, Cambodia, Bangladesh India, Burma	Thai: Thai black ginger, Thai ginseng, Kra-chai-dam, Krachai Dum	**Thailand:** The rhizomes have been used for treatment of gout, apthous ulcer, peptic ulcer and abscesses. Rhizomes have been traditionally used in Thai folklore medicine for treatment of leucorrhea, oral diseases, stomachache, flatulence, digestive disorders, gastric ulcer as well as diuresis and tonic[12], for treatment of allergy and gastrointestinal disorders, as well as an aphrodisiac agent.	9 12 26
			Traditionally used to improve blood flow	2

Table 1. Ethnobotanical uses of several *Kaempferia* species. (cont.)

Species	Distribution[17]	Local name	Ethnobotanical / Traditional uses	Ref.
			and treat inflammatory, allergic, and gastrointestinal disorders. **Laos:** in Laos folk medicine, it has been used for lowering blood glucose levels, improving blood flow and increasing vitality.	
		Japan: Black ginger	**Japan**: KP extract is commercially available as a food supplement for the treatment of metabolic syndrome.	
K. pulchra	Thailand, Indonesia	Indonesia: temu kunci	traditionally used for food and also medicinal purposes for diarrhea, and for its anti-mutagenic, anti-tumour, anti-inflammatory activities, etc.	29
K. roscoeana Wall.	Myanmar, Thailand	Thai: Pro pa	spice and food in Thai cuisine.	6
K. rotunda L.	China (Guangdong, Guangxi, Hainan, Taiwan, Yunnan), India, Nepal, Assam, Bangladesh, Indochina	VN: Cẩm địa la, Ngải máu (blood Kaempferia) Thai: Waan dokdin, Waan som, Wan How Non	**Vietnam:** ornament plant; used for treatment of abdominal pain, menstrual disorder, less menstruation and dysmenorrhea. **India:** rhizome: topical use, swelling and injury, stomach pain treatment. Rhizomic decoction: phù tay chân, tràn dịch ở khớp, ho đờm. **Indonesia:** rhizome is used for abdominal pain. Crushed whole plant with salt is to reduce fever. **Philippine, Malaysia**: rhizome is used for treatment of stomach pain, skin wound healing, mump and cosmetic preparation.	30 31

CNS: central nervous system; TCM: traditional Chinese medicine

3.2. Morphological study

In general, *Kaempferia* species are perennial rhizomic herbs[9]. Rhizome fragrant, roots often bearing tubers. According to Phokham et. al.[18], the genus *Kaempferia* can be divided into two groups: the *K. galanga* group and the *K. rotunda* group, distinguished from each other by the appearing time of inflorescences. While the "spring-blooming" of *K. rotunda* group is from end of March to early May, the inflorescences of *K. galanga* group appear mostly in August to September[18].

Additionally, several species of *Kaempferia* L. have been also reported as new finding species nowadays including *K. sisaketensis* Picheans. & Koonterm, *K. attapeuensis* Picheans. & Koonterm, *K. grandifolia* Saensouk & Jenjitt, *K. spoliata* Sirirugsa, *K. chayanii* Koonterm[19], *K. udonensis* Picheans. & Phokham, *K. picheansoonthonii* Wongsuwan & Phokham from northeastern Thailand, *K. larsenii* P. Sirirugsa sp. nov, *K. siamensis P. Sirirugsa*[20], *K. noctiflora* Nopporncharoenkul & Jenjitt[21] for Thailand flora, *K. xiengkhouangensis* Picheans. & Phokham from Lao PDR[18]. In 2019, two new more *Kaempferia* species namely *K. phuphanensis* Saensouk & P. Saensouk[22] and *K. mahasarakhamensis* Saensouk & P. Saensouk[23] were discovered by Saensouk & Saensouk for Thailand flora. Two species *K. parviflora* and *K. daklaknensis* were both newly recorded as species for Vietnam flora[24]. These results indicate the biodiversity of Zingiberaceae species in general and *Kaempferia* species in particular is quite abundant and South East Asia is a center of *Kaempferia* biodiversity.

The morphological characteristics of *Kaempferia* species were described in details in several publications. *K. galanga* is differentiated from other galangals by the absence of stem and dark brown, rounded rhizomes, while the other varieties all have stems and pale rose-brown rhizomes. *K. parviflora* is a perennial herb that grows to 90 cm height with dark purple to black rhizomes[13]. *K. pulchra* was diffentiated from *K. elegans* by analysis of molecular phylogenetic and morphological evidences[25]. *Kaempferia pandurata* is a synonym of *Boesenbergia rotunda* (L.) Mansf., no morphological properties but chemical compositions of this species is mentioned in this review. Moreover, the morphological characteristics of several most abundant and important *Kaempferia* species are listed in the Table 2S (Supporting Information) which is useful for professional botanist as well as scientists of

other natural branches for their research.

3.3. Phytochemical study

The *Kaempferia* species of Zingiberaceae family are used as herbal plants for treatment of various ailments so that their chemical compositions are highly interested. Research on chemical composition of *Kaempferia* plants revealed natural compounds classified in monoterpenoids, diterpenoids, flavonoids, phenolic glycosides, cyclohexane oxide derivatives, diarylheptanoids and essential oil with various biological properties.

3.3.1. Monoterpenoids / Diterpenoids

Diterpenoids seem to be the most abundant constituents in *Kaempferia* species with many publications related to these compounds[25].

According to Emerenciano, there are 12 different skeletal structures classified for diterpenoids. At time of writing this review, 74 diterpenoids of skeletal types including labdane, clerodane, pimarane / isopimarane, abietane, and oxygenated isopimaranes-type diterpenoids are found in *Kaempferia* species[26] (Table 2).

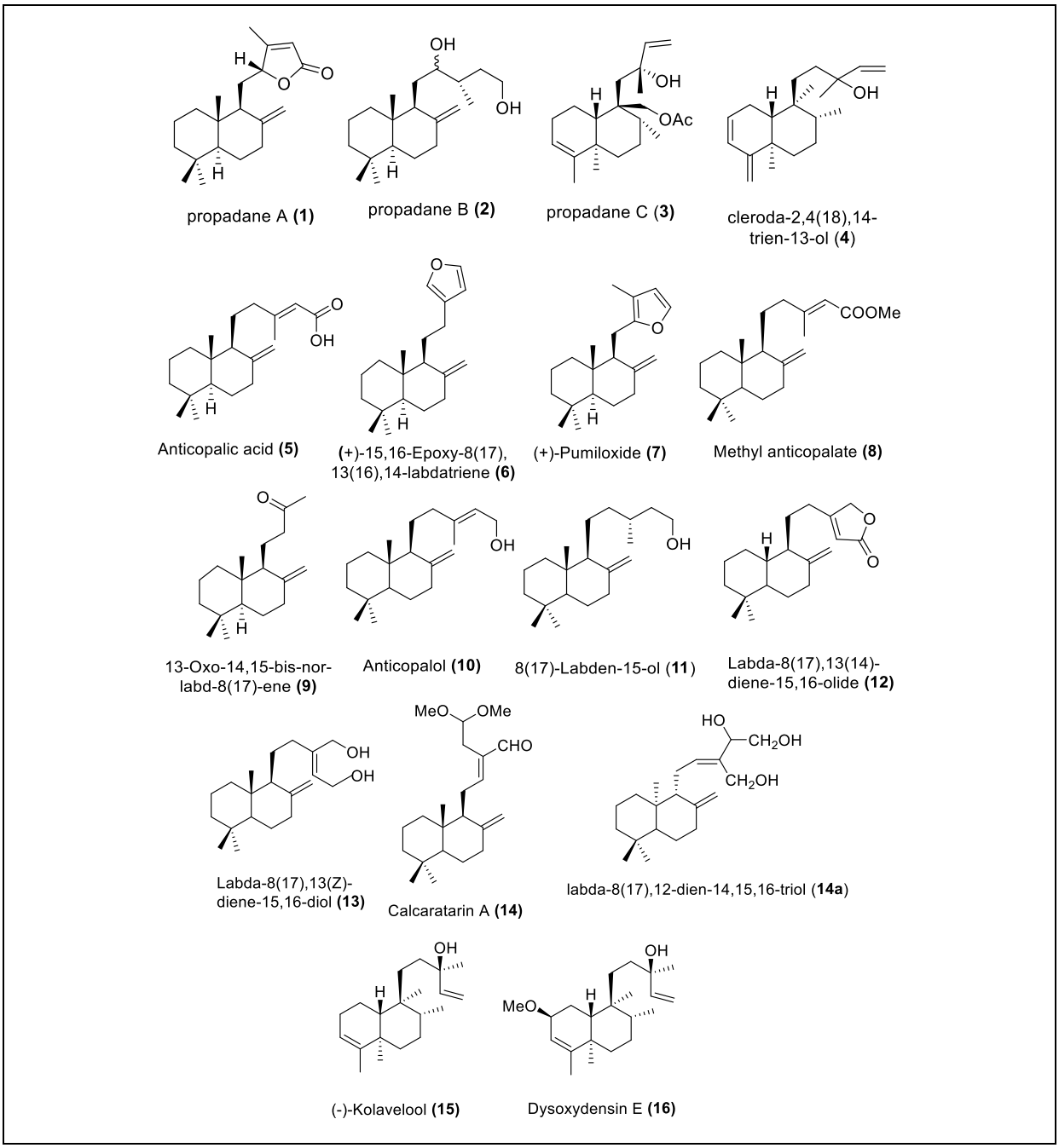


Figure 1. Chemical structures of chemical compositions of *Kaempferia* species.

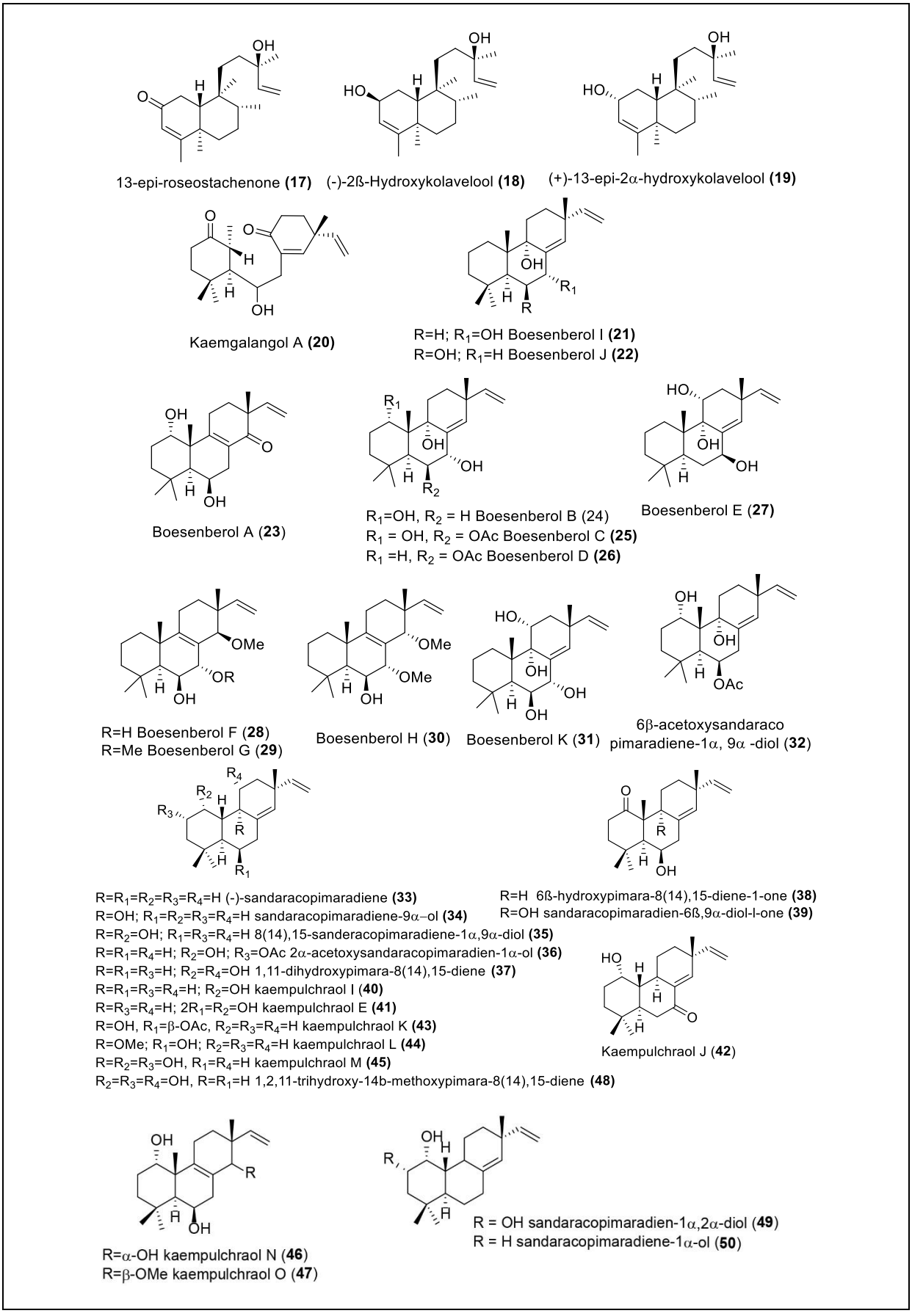
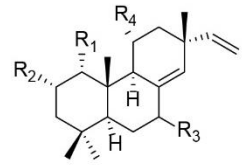
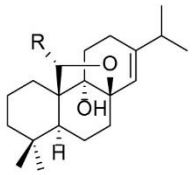


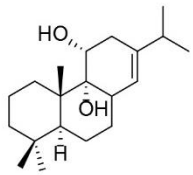
Figure 1. Chemical structures of chemical compositions of *Kaempferia* species. (cont.)



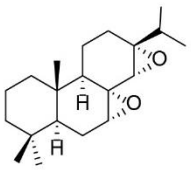
R_1=R_2=OH, R_3=O, R_4=H 1,2-dihydroxypimara-8(14),15diene-7-one (**51**)
R_1=R_2=OH, R_3=β-OH, R_4=H 1,2,7-trihydroxy-pimara-8(14),15-dience (**52**)
R_1=R_2=R_4=OH, R_3=H 1,2,11-trihydroxy-pimara-8(14),15-diene (**53**)
R_1=R_4=OH, R_3=α-OH, R_2=H 1,7,11-trihydroxy-pimara-8(14),15-diene (**54**)
R_1=R_4=OH, R_2=R_3=H -1,11-dihydroxypimara-8(14),15-diene (**55**)



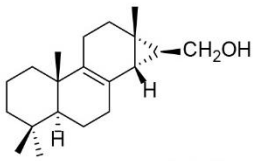
R=OMe roscotane A (**56**)
R=H roscotane B (**57**)



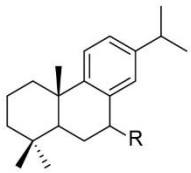
roscotane C (**58**)



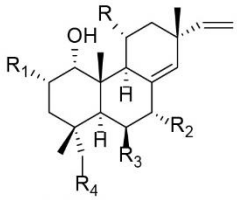
roscotane D (**59**)



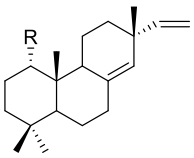
roscorane A (**63**)



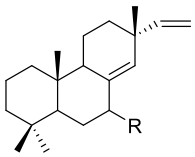
R=H ar-abietatriene (**60**)
R=O 7-dehydroabietanone (**61**)
R=a-OH abieta-8,11,13-trien-7a-ol (**62**)



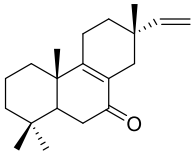
R=OH, R_1=R_2=R_4=H, R_3=OH roscorane B (**64**)
R=R_4=H, R_1=R_2=R_3=OH roscorane C (**65**)
R=R_2=R_3=H, R_1=R_4=OH roscorane D (**66**)



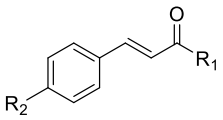
R=H (-)isopimara-8(14),15-diene (**67**)
R=OH 1α-hydroxyisopimara-8(14),15-diene (**68**)



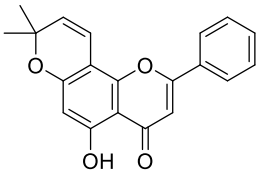
R=O isopimara-8(14),15-diene-7-one (**69**)
R=α-OH 7a-hydroxyisopimara-8(14),15-diene (71)



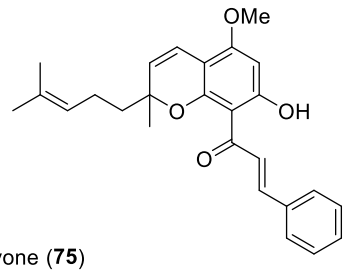
isopimara-8,15-diene-7-one (**71**)



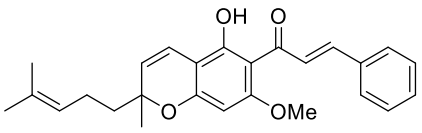
R_1=-OEt, R_2 = H Ethyl trans-p-methoxy cinnamate (**72**)
R_1=-OEt, R_2=H Ethyl cinnamate (**73**)
R_1=-OH, R_2 = OMe p-Methoxycinnamic acid (**74**)



2",2"-Dimethylpyrano-[5",6":8,7]-flavone (**75**)



Boesenbergin A (**76**)



Boesenbergin B (**77**)

Figure 1. Chemical structures of chemical compositions of *Kaempferia* species. (cont.)

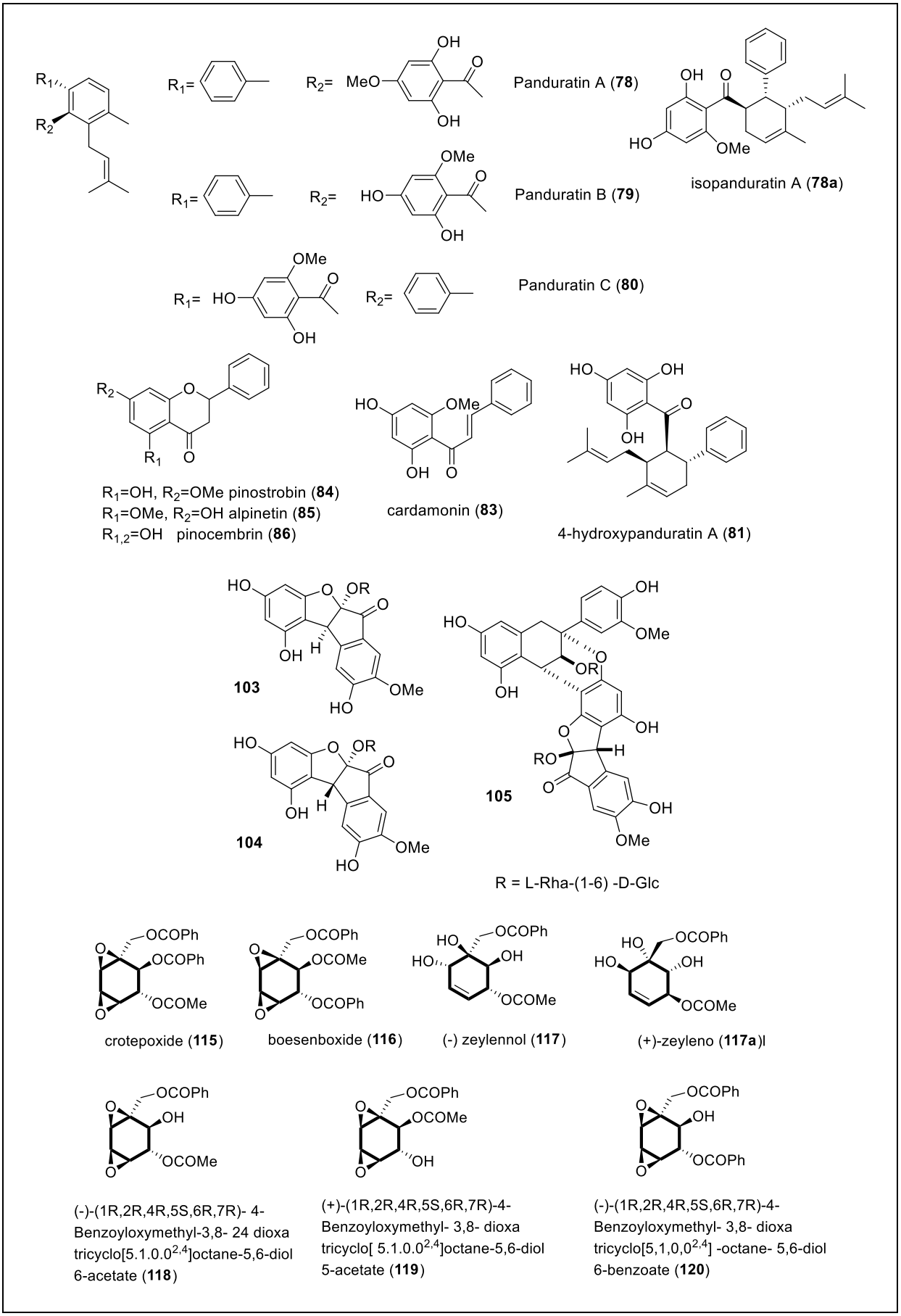


Figure 1. Chemical structures of chemical compositions of *Kaempferia* species. (cont.)

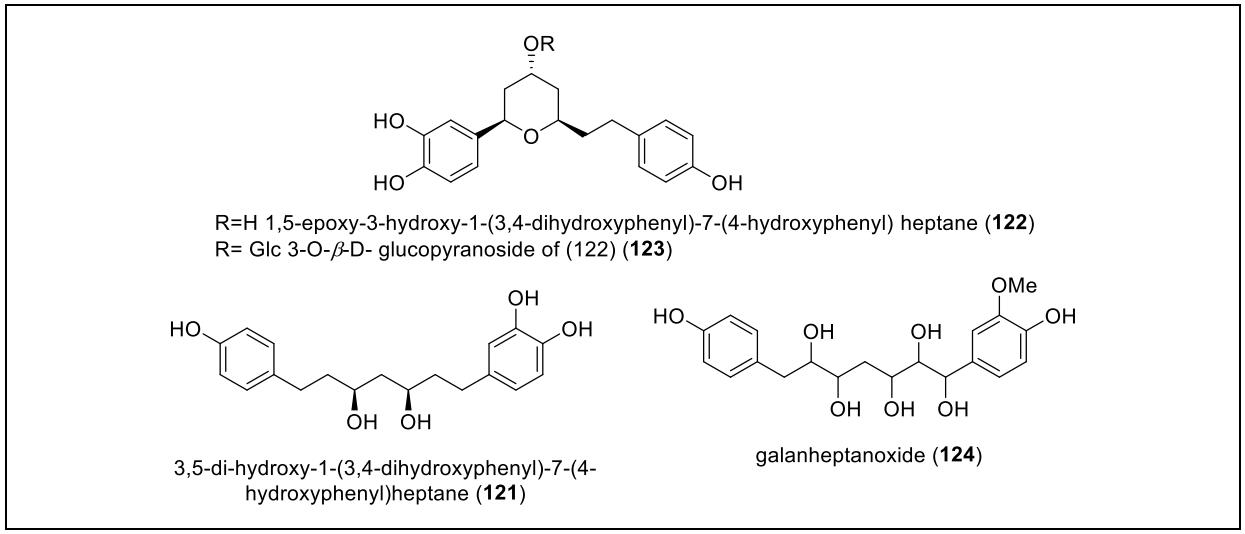


Figure 1. Chemical structures of chemical compositions of *Kaempferia* species. (cont.)

Typically, twenty diterpenoids (abietane-type and isopimarane-type skeleton), including four oxygenated abietanes (roscotanes A-D, (**56-59**)), four oxygenated pimaranes (roscoranes A-D (**63-66**)), along with twelve known diterpenoids (labdanes) were isolated from the whole plants of *K. roscoeana* collected from Phetchaburi Province, Thailand by Boonsombat et al.[6] Swapana et al. isolated a labdane with unusual 9,10-seco-isopimarane skeleton namely kaemgalangol A (**20**) and 12 usual analogs (**2-13**) from the rhizomes of *K. galanga* collected from Imphal West and Senapati district, Manipur, a state in North East India[1]. Isopimarane diterpenes namely boesenberols I-K (**21-31**) were also isolated from *K. pandurata* rhizomes collected from Khon Kaen, Thailand[27], seven new isopimarane diterpenoids namely kaempulchraols I-O (**40-47**), together with one known analog[28] from the $CHCl_3$ soluble extract of *K. pulchra* rhizomes collected

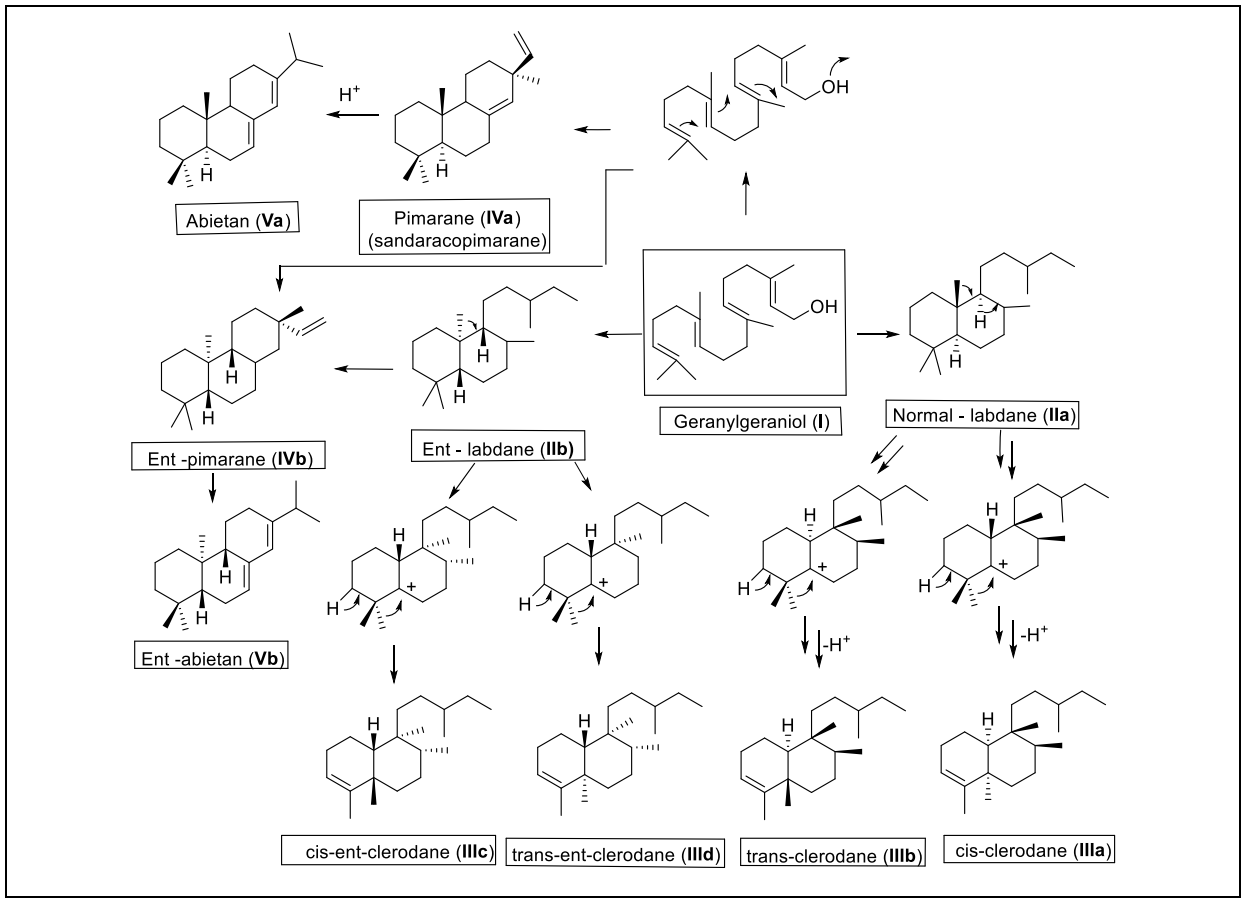


Figure 2. Biogenesis of diterpenoid skeletons from geranylgeraniol (**I**).

Table 2. *Kaempferia* diterpenoids of different skeletal types and their biological properties.

No.	Isolated sources / collected places	Compounds	Biological properties	Ref.
I		**Labdane-type and clerodane-type diterpenoid**		
1.1	*K. elegans* / Kanchanaburi Province, Thailand	Propadane A (labda-8(17),13-dien-12R,15-olide) (**1**)		25
		Propadane B (8(17)-labden-12,15-diol) (**2**)		25
1.2	*K. pulchra* / Kanchanaburi Province, Thailand	Propadane C (20-acetoxy-13R-hydroxy-3,14-clerodadiene) (**3**)		25
		Cleroda-2,4(18),14-trien-13-ol (**4**)	Patented agent for lowering prolactin	25
1.3	*K. elegans* / Kanchanaburi Province, Thailand	Anticopalic acid (**5**)	Antimicrobial activity	25
		(+)-15,16-epoxy-8(17),13(16),14-labdatriene (**6**)		
		(+)-Pumiloxide (**7**)		
		Methyl anticopalate (**8**)		
		13-*oxo*-14,15-bis-nor-labd-8(17)-ene (**9**)		
		Anticopalol (**10**)	Antimicrobial activity	25
		8(17)-Labden-15-ol (**11**)	Antimicrobial activity	25
		Labda-8(17),13(14)-diene-15,16-olide (**12**)		
		(+)-Labda-8(17),13(*Z*)-diene-15,16-diol (**13**)		
		Calcaratarin A (**14**)		
1.4	*K. roscoeana* / Thailand	(12*Z*,14*R*)-labda-8(17),12-dien-14,15,16-triol (**14a**)		6
II		**Clerodane-type diterpenoid**		
2.1	*K. pulchra* / Kanchanaburi Province, Thailand	(−)-Kolavelool (**15**)	Cytotoxic activity against the HL-60 cell line	25
		Dysoxydensin E (**16**)		
		13-epi-roseostachenone (**17**)		
		(−)-2β-hydroxykolavelool (***18***)	Cytotoxic activity against the HL-60 cell line	
		(+)-13-*epi*-2α-hydroxykolavelool (*13-epi*-roseostachenol) (**19**)		
III		**Isopimarane-type diterpenoids**		
3.1	*K. galanga* / India	Kaemgalangol A (**20**)		1
		Boesenberol I (**21**)		1
		Boesenberol J (**22**))		1
3.2	*K. pandurata* / Thailand	Boesenberols A-H (**23**), (**24**), (**25**), (**26**) (**27**) (**28**) (**29**) (**30**)	TRAIL-resistance-overcoming activity in TRAIL-resistant AGS cells.	31
		Boesenberols K (**31**)	TRAIL-resistance-overcoming activity in TRAIL-resistant AGS cells.	27
IV		**Pimarane-type diterpenoids**		
4.1	*K. galanga* / India	6*β*-acetoxysandaraco pimaradiene-1 *α*, 9 *α* -diol (**32**)		1
	K. marginata / Thailand	(-)-Sandaracopimaradiene (**33**)		1
				29
		Sandaracopimaradiene-9*α*-ol (**34**)	Cytotoxic activity	29
			against HSC-2 mouth squamous cell carcinoma (IC_{50} = 69.9 μM),	
			HeLa (IC_{50} = 75.1 μM)	1
4.2	*K. galanga* / India	8(14), 15-Sanderacopimaradiene-1*α*,9α-diol (**35**)		1
	K. pandurata / Thailand			27
4.3	*K. galanga* / India	2*α*-acetoxysandaracopimaradien-1*α*-ol (**36**)	antituberculous activity against *Mycobacterium tuberculosis* H37Ra with MIC = 50 μg/mL	1
				29
		1,11-dihydroxypimara-8(14),15-diene (**37**)		1
		6*β*-hydroxypimara-8(14),15-diene-1-one (**38**)		1
		Sandaracopimaradien-6*β*,9*α*-diol-l-one (**39**)		1

Table 2. *Kaempferia* diterpenoids of different skeletal types and their biological properties. (cont.)

No.	Isolated sources / collected places	Compounds	Biological properties	Ref.
4.4	*K. pulchra* / *Myanamar* *K. galanga*	Kaempulchraol I (**40**)	Antiproliferative activity Cytotoxic activity against HSC-2 mouth squamous cell carcinoma (IC_{50} = 53.3 µM), HeLa (IC_{50} = 74.2 µM)	28 27 1
		Kaempulchraol E (**41**)		
		Kaempulchraol J (**42**)		
4.5	*K. pandurata* / Thailand	Kaempulchraol K (**43**)	Anti-proliferative against lung cancer A549 cells	27 28
4.6	*K. pulchra* /*Myanmar* *K. pandurata* / Thailand	Kaempulchraol L (**44**)	Anti-proliferative against PSN - 1 cells Cytotoxic activity against HSC-2 mouth squamous cell carcinoma (IC_{50} = 58.2µM), HeLa (IC_{50} = 76.5µM)	27 28 1
4.7	*K. galanga* /	Kaempulchraol M (**45**)	Cytotoxic toxicity	27
4.8	*K. pulchra* /*Myanmar*	Kaempulchraol N (**46**)		28
		Kaempulchraol O (**47**)		28
		1,2,11-trihydroxyisopimara-8(14),15-diene (**48**)	Inhibition of *Candida albicans* with IC_{50} = 17.5 µg/ml	29
4.9	*K. marginata* / Ubonratchathani, Thailand	Sandaracopimaradien-1 α,2 α -diol (**49**)	Weak inhibition of *Candida albicans* with IC_{50} = 49.9 µg/ml	29
		Sandaracopimaradiene-1 α -ol (**50**)	Anti-tuberculous activity against *Mycobacterium tuberculosis* H37Ra with MIC = 25 µg/mL	29
		1,2-dihydroxypimara-8(14),15diene-7-one (**51**)		29
		1,2,7-trihydroxypimara-8(14),15-diene (**52**)		29
		1,2,11-trihydroxypimara-8(14),15-diene (**53**)	Antimalarial activity against *Plasmodium falciparum* K-1 strain, with IC_{50} = 8.8 µg/ml	29
		1,7,11-trihydroxypimara-8(14),15-diene (**54**)		29
		1,11-dihydroxypimara-8(14),15-diene (**55**)	Antimalarial activity against *Plasmodium falciparum* K-1 strain, with IC_{50} = 3.2 µg/ml	29
V		**Abietane-type diterpenoids**		
5.1	*Kaempferia roscoeana* / Thailand	roscotanes A-D (**56**) (**57**) (**58**) (**59**)		6
		ar-abietatriene (**60**)	Antimicrobial against Gram-positive bacterial strains *Staph. epidermidis* and *Bacillus cereus*	6
		7-dehydroabietanone (**61**)		6
		Abieta-8,11,13-trien-7α-ol (**62**)		6
VI		**Oxygenated isopimaranes – type diterpenoids**		
6.1	*Kaempferia roscoeana* / Thailand	Roscoranes A-D (**63**) (**64**) (**65**) (**66**)		6
		(-)-Isopimara-8(14),15-diene (**67**)		6
		1α-hydroxyisopimara-8(14),15-diene (**68**)		6
		Isopimara-8(14),15-dien-7-one (**69**)		6
		7α-hydroxyisopimara-8(14),15-diene (**70**)		6
		Isopimara-8,15-dien-7-one (**71**)		6
6.2	*K. galanga*	Ethyl-*p*-methoxycinnamate (**72**)	Anti-inflammatory activity in rats (100 mg/kg)	30
		Ethyl cinnamate (**73**)	Sedative activity	32
		p-methoxycinnamic acid (**74**)		30

from Pindaya Township, Shan State, Myanmar. Thongnest et al. isolated six new pimarane-type diterpenoids along with four known diterpenes from the dichloromethane extract of whole plants of *K. marginata* collected in Ubonratchathani, Thailand[29]. Monoterpenes such as cinnamate derivatives including ethyl-*p*-methoxycinnamate (**72**), ethyl cinnamate (**73**) and *p*-methoxycinnamic acid (**74**) were found in *K. galanga* roots[30]. The *Kaempferia* diterpenoids with their biological properties, which we discussed in following section, were presented in Table 2 and their structures were displayed in Figure 1.

3.3.2. Diterpenoid biogenesis

Diterpene skeleton is produced from geranylgeraniol (**I**) ($C_{20}H_{34}O$) which rearranges along one of two routes, to labdane (normal (**IIa**) or ent - labdane (**IIb**)). Normal-labdane (**IIa**) rearranges multistep in the presence of protone to cis-clerodane (**IIIa**) and trans-clerodane (**IIIb**) while ent-labdane (**IIb**) repositions to cis-ent-clerodane (**IIIc**) and trans-ent-clerodane (**IIId**). The relocation of □-bonds and the rearrangement of proton or methyl group in geranylgeraniol (**I**) also lead to pimarane (**IVa**) (sandaracopimarane (**35**)) and ent-pimarane (**IVb**) (isopimarane), whose rearrangements lead to abietane (**Va**) and ent-abietane (**Vb**) respectively (Figure 2)[33]. Another route, as suggestion from Swapana et. al., the biogenesis pathway of abietane diterpenoids like roscorane A (**5**) could be derived from sandaracopimaradiene (**33**)[1,6], where the double bond in (**33**) was epoxidized and protonated and rearranged to be a primary cyclic alcohol roscorane A (**63**) (Figure 3).

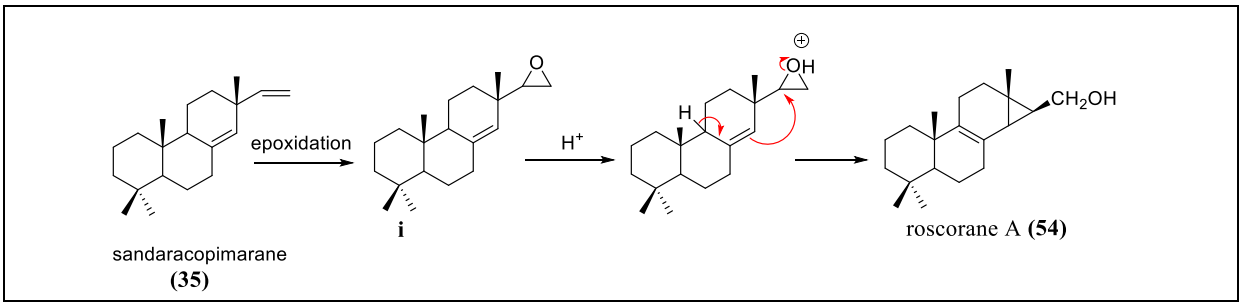


Figure 3. Biogenesis Pathways of an abietane compound - roscorane A (**5**) from pimarane skeleton - sandaracopimarane.

3.3.3. Flavonoids

Several flavones were separated from *K. elegans, K. pandurata and K. rotunda*. Flavonoids like cardamonin (**75**) pinostrobin (**76**) alpinetin (**77**), pinocembrin (**78**) were isolated from *K. pandurata*[34]. 2",2"-dimethylpyrano-[5",6":8,7]-flavone (**79**) was isolated from *K. elegans*[25]. Chalcons and derivatives like panduratin A-C (**80**) (**81**) (**82**), hydropanduratin A(**83**) and boesenbergin A - B (**84**) (**85**) were also isolated from *K. pandurata*[35,36]. Flavonoids especially polymethoxy flavonoid (PMF) are secondly abundant compounds found in *Kaempferia*. PMF were isolated from *Kaempferia* species were listed in Table 3.

Highly-methoxy flavones were isolated mainly from *K. parviflora* and *K. pandurata*. Saewong et. al. by using silica gel column chromatography and HPLC separated and identified 12 known methoxyflavonoids from the chloroform fraction and ethanol extract of *K. parviflora* rhizomes including techtochrysin (**86**, 0.131% yield from the material), 5,7-dimethoxyflavone (**87,** 0.289%), 7,4′-dimethylapigenin (**88**, 0.0453%), trimethylapigenin (**89**, 1.29%), 5-hydroxy-3,7-dimethoxyflavone (**90**, 0.0252%), 3,5,7-trimethoxyflavone (**91**, 0.0101%), 3,7,4′-trimethylkaempferol (**92**, 0.0719%), tetramethylluteolin (**93**, 0.0312%), 3,5,7,4'-tetramethylkaempferol (**94**, 0.0070%), retusine (**95**, 0.0215%), ayanin (**96**, 0.0111%) and pentamethylquercetin (**97**, 0.391%)[43]. The same methoxyflavonoids were also isolated from the black rhizomes of *K. pandurata*[38]. In other publication, they also reported to isolate some other methoxyflavonoids[13] which were listed in Table 3.

Panduratin A (**78**) and its derivatives panduratin B-C (**79**) (**80**) are a chalcone derivative isolated from the rhizome of *K. pandurate* has various biological activities including anti-proliferative and apotosis-induced effect in human colon cancer cells, anti-inflammatory actions by inhibition of NO production in RAW 264.7 cells, anti-human immunodeficiency virus-1 protease activity, protective skin ageing induced by ultraviolet radiation, and anti-bacterial activity[44]. Panduratin A (**78**) and its pharmacological effect is mentioned in several patents described later in this review.

Table 3. Highly-methoxy flavones were isolated mainly from *Kaempferia* species.

		Substitution						
Sources	**Highly-methoxy flavones**	**3**	**5**	**7**	**3'**	**4'**	**Biological activity**	**Ref**
K. parviflora *K. padurata* *K. rotunda*	5-OH, 7-methoxy flavone (Tectochrysin) (**1**)		OH	OMe			Anti-allergic activity	37 38
K. parviflora *K. rotunda* *K. pandurata*	5,7-dimethoxyflavone (**2**)		OMe	OMe			Inhibited NO synthesis, TNF-a production and iNOS mRNA expression Hepatoprotective against cancer Anti-periodontic Inhibition of viral protease PDE-5 inhibitor	13 12 11 39 40 41
K. parviflora *K. pandurata*	5-OH-7,4'-dimethoxyflavone (7,4'-dimethyl apigenin) (**3**)		OH	OMe		OMe	Anti-allergic activity	37
K. parviflora *K. pandurata*	5,7,4'-trimethoxyflavone (trimethylapigenin) (**4**)		OMe	OMe		OMe	Inhibited NO synthesis, TNF-a production and iNOS mRNA expression anti-cholangio-carcinoma action Anti-periodontic activity Anti- allergenicactivity	13 12 11 41 40 12
K. palviflora *K. pandurata*	5-OH-3,7-dimethoxy flavone (**5**)	OMe	OH	OMe				41 12
K. parviflora	3,5,7-trimethoxy flavone (**6**)	OMe	OMe	OMe				41 37 12
K. parviflora *K. pandurata*	5-OH-3,7,4'-trimethoxyflavone (**7**) (3,7,4'-trimethylkaempferol)	OMe	OH	OMe		OMe		41 37 38
	Tetramethylmethyl luteolin (**8**)		OMe	OMe	OMe	OMe	Inhibited NO synthesis, TNF-a production and iNOS mRNA expression	13
K. parviflora	3,5,7,4'-tetramethoxyflavone (Tetramethyl kaempferol) (**9**)	OMe	OMe	OMe		OMe		37 12
K. pandurata	5,7,3′,4′-tetramethoxyflavone		OMe	OMe	OMe	OMe		38
K. parviflora *K. pandurata*	5-OH-3,7,3',4'- tetramethoxy flavone (Retusine) (**10**)	OMe	OH	OMe	OMe	OMe	nitric oxide (NO) inhibition in RAW 264.7 cells Anti-allergic activity	11 12 13 38 37
	Ayanin (**11**)	OMe	OH	OMe	OH	OMe		
	3,5,7,3',4'-pentamethoxyflavone (**12**) (pentamethyl quercetin)	OMe	OMe	OMe	OMe	OMe	Inhibitory activity of multidrug resistance associated-protein PDE-5 inhibitory inhibit P-glycoprotein function Anti-periodontic activity	11-12 41 11 40
K. rotunda	5-OH-7-methoxyflavanone (1) (**13**)		OH	OMe			Inhibition of viral protease Anti-mutagenic activity	39
K. parviflora	5,3'-di-OH-3, 7,4'-tri methoxyflavone (**14**)	OMe	OH	OMe	OH	OMe	Anti-allergic activity	12
	4'-OH-5,7-dimethoxy flavone (**15**)		OMe	OMe		OH		12
K. rotunda	7-OH-5-methoxyflavanone (2) (**16**)		OMe	OH			Anti-mutagenic	
K. rotunda	5,7-dihydroxyflavanone (3) (**17**)		OH	OH				
K. rotunda	Kaempferol (**18**)	OH	OH	OH		OH	Anti cancer Anti-rheumatic	42

3.3.4. Phenolic glycosides

Several flavonol glycosides were isolated from the water soluble fraction of rhizomes of *Kaempferia parviflora* including *rel*-(5a*S*,10b*S*)-5a,10b-dihydro-1,3,5a,9tetrahydroxy-8-methoxy-6*H*-benz[*b*]indeno[1,2-*d*]furan-6-one 5a-*O*-[*α*-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranoside] (**104**), its *rel*-5a*S*,10b*R* isomer (**105**), and (2*R*,3*S*,4*S*)-3-*O*-[*α*-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranosyl]-3′-*O*-methyl-*ent*-epicatechin-(2*α*→*O*→3, 4*α*→4)-(5a*S*,10b*S*)-5a,10b-dihydro-1,3,5a,9-tetrahydroxy-8-methoxy-6*H*-benz[*b*]indeno[1,2-*d*] furan-6-one 5a-*O*-[*α*-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranoside] (**106**)[45].

3.3.5. Fatty acids and derivatives

According to Ali et. al., the rhizome of *K. galanga* L. collected from the hilly areas of Chittagong, Bangladesh were extracted with methanol to obtain methanolic crude extract. GC–MS analysis of this extract showed the presence of fatty acids and derivatives including palmitic acid (35.17%) (**107**), oleic acid (22.15%) (**108**), octadecanoic acid (10.10%) (**109**), phthalic acid (**110**), glycidyl stearate (7.27%) (**111**), 2-Propenoic acid (**112**), 3-(4-methoxyphenyl)-, ethyl ester (10.18%) (**113**), 6-ethyloct-3-yl2-ethylhexyl ester (3.37%) (**114**), sandaracopimaradiene (8.20%) (**33**), and 2-[2-(4-nonylphenoxy)ethoxy]ethanol (3.57%) (**115**)[7].

3.3.6. Cyclohexane diepoxide derivatives

A series of cyclohexane diepoxides and cyclohexane oxide derivatives were isolated from the fresh rhizomes of *K. angustifolia* collected in Thailand including crotepoxide (**116**) and boesenboxide (**117**), (-)-Zeylenol (**118**), (-)-(1R,2R,4R,5S,6R,7R) - 4 - benzoyloxymethyl-3,8- 24 dioxatricyclo[5,1,0,$0^{2,4}$]octane-5,6-diol 6-acetate (**119**), (-)-(1R,2R,4R,5S,6R,7R) -4-benzoyloxymethyl- 3,8- dioxatricyclo [5,1,0,$0^{2,4}$] -octane - 5,6 - diol 6-benzoate (**120**), and (+) -zeylenol (**121**)[46].

3.3.7. Diarylheptanoids

Several diarylheptanoids including (3R,5S)-3,5-di-hydroxy-1-(3,4-dihydroxyphenyl) -7-(4-hydroxyphenyl)heptane (**122**), (1R,3R,5R)-1,5-epoxy-3-hydroxy-1-(3,4-dihydroxyphenyl)-7-(3,4-dihydroxyphenyl) heptane (**123**), with its glycoside (1R,3R,5R)-1,5-epoxy-3-hydroxyl-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)heptane 3-O-β-D-glucopyranoside (**124**), and 1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)heptane-1,2,3,5,6-pentaol (namely galanheptanoxide) (**125**) were isolated from the *K. galanga* rhizome collected in Guangzhou, China[47]. These isolated diarylheptanoids exhibited pronounced inhibitory activities compared with indomethacin on NO production induced by LPS in RAW 264.7 with the most effective IC_{50} = 26.98 ± 1.39 μM of compound (3R,5S)-3,5-di-hydroxy1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl) heptane (**122**).

3.3.8. Essential oils

According to Ridtidid et. al., the major chemical constituents of the essential oil extracted from dried *K. galanga* rhizome were ethyl-*p*-methoxycinnamate (31.77%) (**72**), methyl cinnamate (23.23%) (**126**), carvone (11.13%) (**127**), eucalyptol (9.59%) (**128**) and pentadecane (6.41%) (**129**), respectively[48]. Wong et. al. reported that the hat the composition of the essential oil of rhizomes of *K. galangal* L. contained 54 components[3,49], of which the major constituents are ethyl-trans-*p*-methoxy cinnamate (16.5%) (**72**), pentadecane (9%) (**130**), 1,8-cineole (5.7%) (**131**), γ-carene (3.3%) (**132**), borneole (2.7%) (**133**) and other components in minor amount including camphene (**134**), kaempferol (**102**), kaempferide (**135**), cinnamaldehyde, *p*-methoxycinnamic acid (**136**) and ethyl cinnamate[8]. Other compounds as dicyclohexyl propanedinitrile (**137**), dipentene dioxide (**138**), 9-hydroxy, 2-nonanone (**139**), 2,7-octadiene-1-yl acetate(**140**), ethyl cyclohexyl acetate (**141**), cis-11- tetradecenyl acetate (**142**), 2-heptadecanone (**143**), 4-methyl isopulegone (**144**), camphidine (**145**), trans,trans-octa-2, 4-dieny acetate (**146**), 10 undecyn-1ol (**147**), 3,7-dimethoxycoumarin (**148**), δ-3-carene (**149**), alpha pinene (**150**), camphene (**151**), borneol (**152**), cymene (**153**), α-terpineol (**154**), α-gurjunene (**155**), germacrene (**156**), cadinene (**157**), caryophyllene (**158**), luteolin (**159**) and apigenin (**160**) were also present in the essential oil of this plant[8,50]. Terpene oil constituents made up to 16.4%[49].

3.4. Biological properties

The *Kaempferia* rhizome have also been reported to possess various biological activities including anti-microbial activities[7], sedative and anti-nociceptive; cytotoxic; cancer-preventive, anti-tumor, anti-mutagenic, anti-proliferative; anti-rheumatic; anti-oxidant; anti-inflammatory; hepatoprotective; anti-allergic; antihypertensive, hypolipidemic[30]; anti-helmintic, anti-amoebic, mosquito repellent and larvicidal activities; vasorelaxant active and smooth muscle relaxant

effects; aphrodisiac effects and wound healing activity, which are described in detail as following. Not only the rhizome extract, but also the constituents of *Kaempferia* species also possess various pharmacological activities. For instance, kaempferol (**102**) is a flavonoid commonly occurring in plants such as tea, beans and occurring widely in *K. rotunda*. Kaempferol was known to possess numerous biological activities including anticancer activity by inhibition of migration and invasion of several cancer cell lines[42]. PMFs with their multiplicity biological effects are reserved in various patents for their uses in life.

3.4.1. Anti-microbial properties anti-fungal, anti-virus

Boonsombat et. al. reported that, compound *ar*-abietatriene (**60**) isolated from the whole plants of *K. roscoeana* collected from Phetchaburi Province, Thailand, had a specific antimicrobial activity with the most activity against Gram-positive bacteria strains *Staphylococcus epidermidis* and *Bacillus cereus* with MIC (MBC) values of 25 (75) and 25 (50) µg/ml, respectively[6]. Other compounds as anticopalic acid (**5**), anticopalol (**10**), and 8(17)-labden-15-ol (**11**) from *K. elegans* showed antimicrobial activity against the Gram-positive bacterium, *Bacillus cereus*, with MIC values of 3.13, 6.25, and 6.25 µg/mL, respectively[25].

Ethanol extract of *K. pandurata* showed powerful antibacterial activity against all the tested bacteria and was the most potent against MRCNS (methicillin-resistant coagulase negative *Staphylococci*) with MIC 4 ppm, *Bacillus subtilis* and MRSA (methicillin-resistant *Staphylococcus aureus*) with MIC 16 ppm, MSSA (methicillin-sensitive *Staphylococcus aureus*) and *Salmonella typhi* with MIC 8 ppm[51]. The chloroform extract, panduratin A (**78**) and isopanduratin A (**78a**) - isolated from this plant extract also showed a good antibacterial activity by damage of bacterial cell wall and effects on bacterial virulence factors including protease enzyme and haemolysin against haemolysin against *Streptococcus pyogenes*[52,35]. Essential oils of Zingiberaceae members in general and *Kaempferia* species in particular were known antimicrobial agents. The mode of antibacterial action of *K. pandurata* essential oil was its ability to change permeability of the cell, leakage the endocellular materials including inorganic compounds (potassium, calcium ion) and organic compounds (nucleic acid, protein) from cytoplasmic membrane and leading to death of *E. coli* K1.1 cell[53].

3.4.2. Sedative and anti-nociceptive activity

As mentioned in the Traditional Use session, *Kaempferia* species is special used in almost all folk medicines as pain killer on the whole body (abdominal, chest, headache, toothache, rheumatism, limb pains). Ridtitid et. al. investigated the biological activities of *K. galanga* and found that the methanol extract of this species exhibited anti-nociceptive activity. The mechanism of action is likely to be mediated peripherally and centrally (spinally and supraspinally), on opioid receptors on the nervous system[48]. Huang et. al. have found that, compounds ethyl *trans-p*-methoxycinnamate (**72**) and ethyl cinnamate (**73**) mainly active aromatic compounds of hexane extract of *K. galanga* collected in Japan caused sedative effects at dose of 0.0014 mg and 0.0012 mg by means on inhalation in mice[32]. This finding might be scientific evidence for the use of *K. galanga* in aromatherapy in treatment of some anxiety and psychological disorders in human[32].

3.4.3. Cytotoxic activity

Compounds (-)-kolavelool (**15**) and (-)-2*β*-hydroxykolavelool (**18**) from *K. elegans* showed selective cytotoxic activity against the HL-60 cell line with IC_{50} values of 8.97 ± 0.66 and 9.58 ± 0.88 µg/mL, respectively[25]. Swapana et. al. also reported that, diterpenoids, sandaracopimaradiene-9α-ol (**34**), kaempulchraol I (**40**) and kaempulchraol L (**44**) exhibited moderate activity against HSC-2 mouth squamous cell carcinoma with IC_{50} 69.9, 53.3 and 58.2µM, respectively, more effective than against HeLa cells cervical cancer with IC_{50} 75.1, 74.2 and 76.5µM, respectively[1].

3.4.4. Cancer-preventive, anti-tumor, anti-mutagenic and anti-proliferative activities

The methanolic extract of *K. galanga* rhizome contained fatty acid like oleic acid (**108**), octadecanoic acid (**109**) and phthalic acid (**110**) found to induce apoptosis and also inhibited the cancer cell growth of Ehrlich ascites carcinoma (EAC) with IC_{50} 17.10 µg/ml[7]. Ethyl-p-methoxycinnamate markedly induced cytotoxicity on human oral squamous carcinoma HSC-3 (IC_{50} 0.075 mg/mL) and Ca922 (IC_{50} 0.085 mg/mL) cell lines[54].

K. parviflora extract with PMF constituents like 3,5,7,3',4'-pentamethoxyflavone (**97**) and 5,7,3',4'-tetramethoxyflavone (**94a**) suppressed the weights of prostates and seminal vesicles in benign prostate hyperplasia (BPH) in rat model and can be applied as a promising natural medicine for the treatment of BPH[55].

One of the causing cancer factors is the DNA mutation[39]. This type of cancer is not only difficult to cure but also being general incidents leading to numerous deaths in the human population. Atun et. al. was evaluating the mutagenic inhibitory activity of natural compounds isolated from the methanol extract of *K. rotunda*[39]. The anti-mutagenic activity test of three known flavanons was observed *in vivo* based on the number of micro-nucleated polychromatic cell erythrocytes (MNPCE) from male Balb-c mice (8-12 week) induced by a known immune system suppressor - cyclophosphamide. The results showed that % anti-mutagenic activity of 7-hydroxy-5-methoxyflavanone (**101**) dose 60 mg/kg BW and 5,7-dihydroxyflavanone (**102**) dose 60 mg/kg BW (both followed cyclophosphamide 50 mg/kg body weight) reached 100%. While 5-hydroxy-7-methoxyflavanone (**98**) dose 60 mg/kg body weight followed cyclophosphamide 50 mg/kg body weight demonstrated a % anti-mutagenic activity of 96.5%. Meanwhile, at a dose of 60 mg/kg body weight, three compounds showed a very high activity. Methanol extract of *K. rotunda* which is a crude extract contain a mixture of some flavanone compounds showed significant activity but lower than pure compounds[39].

Win et. al. also reported that several diterpenoids kaempulchraol I-O (**40**-**47**) isolated from *K. pulchra* rhizomes (collected in Myanmar) were evaluated for their antiproliferative activity against human cancer cell lines[28]. Kaempulchraol I (**40**) exhibited mild antiproliferative activity against all of the cell lines including human lung cancer (A549); human cervix cancer (HeLa); human pancreatic cancer (PANC-1, PSN-1); human breast cancer (MDA-MB-231); and normal human primary fibroblast cell (TIG-3), with IC_{50} values ranging from 39.9 to 87.5 μM. Kaempulchraol *K* (**43**) inhibited against lung cancer cell line A549 with IC_{50} 33.1 μM (the anticancer drug 5-fluorouracil was used as a positive control with IC_{50} 2.8 μM). Kaempulchraol L (**44**) found in many *Kaempferia* species with the presence of the methoxy group at C-9, had a good antiproliferative activity against pancreatic cancer cell lines (PANC-1 and PSN-1) with IC_{50} 39.9 and 22.6 μM respectively.

In cancer chemotherapy, it is recognized that several cancer cell lines like lung, breast, prostate and gastric cancer have developed resistance to necrosis or apoptosis, which was induced by TNF-related ligand (Tumor necrosis factor-related apoptosis inducing ligand - TRAIL). The search of new anti-cancer agent from natural products sources based on the finding bioactive compounds with anti-TRAIL resistance activity is one of the research trend nowadays on anticancer drug discovery. Karmakar et. al. have found that MeOH extract of *K. pandurate* rhizomes and its all isolated compounds showed the TRAIL resistance overcoming activity against the human gastric adenocarcinoma (AGS) cells. Compound 6β-acetoxysandaracopimaradiene-1α, 9α-diol (**32**) sensitized AGS cells to TRAIL-induced apoptosis by controlling the levels of cellular proteins for example it up-regulated the levels of "good proteins" such as apoptosis - inducing proteins DR4, DR5, p53, and cleaved caspases-3, -8, and -9, and down-regulated the levels of "bad proteins" like cell survival proteins Bcl-2, cFLIP, and GSK-3β, in TRAIL-resistant AGS cells. Furthermore, this compound did not affect the viability of noncancerous (HEK293) cells at concentrations up to 30 μM[27,31].

3.4.5. Anti-platelet activity

Platelet-activating factor (PAF) involved in both physiological process like platelet aggregation, vascular permeability changes and pathological conditions like thrombosis, inflammation, cardiac anaphylaxis. The extract of *K. pandurata* was reported to be a potential new PAF antagonist with significant inhibitory effect binding to the PAF-receptor (IC_{50} = 8.6 μg/ml) and therefore can potentially reduce pathophysiological responses and be applied as therapeutic agents for the treatment of immunological and inflammatory disorders[56].

3.4.6. Anti-rheumatic, anti-osteoporosis activity

Pan et. al. reported that kaempferol (**103**), flavonoid occurring widely in *K. rotunda*, reduced migration, invasion and matrix metalloproteinases (MMPs) expression in rheumatoid arthritis - fibroblast-like synoviocytes (RA-FLSs), dramatically suppressed tumor necrosis factor (TNF)-α- by blocking activation of the MAPK pathway. Kaempferol (**103**) therefore inhibited cartilage destruction and attenuated the rheumatic artitis progression[42]. 5,7-dimethoxyflavone (**87**) and 5,7,4'-trimethoxyflavone (**89**), constituents of *K. parviflora* extract also reduced the expression of extracellular MMPs, reduced degradation of collagen within cartilage and thus reduced the pain threshold and severity of osteoarthritic cartilage lesions[57].

3.4.7. Anti-oxidant activity

Studies on biological activities of *Kaempferia* species showed that both the plant extracts and their

chemical compositions especially flavonoids possessed anti-oxidant activity. The methanolic extract of *K. galanga* rhizome on DPPH, ABTS and nitric oxide radical scavenging assays showed that its radical scavenging activity increased in concentration-dependent manner and with IC_{50} values of 16.58, 8.24 and 38.16 µg/ml, respectively (IC_{50} values of positive control catechin were 2.67, 4.53 and 3.18 µg/ml, respectively)[7]. Two flavanones, pinostrobin (**84**) and pinocembrin (**86**) from the rhizomes of *K. pandurata* showed their antioxidant activities against 2,2-diphenyl-1-picrylhydrazyl (DPPH) with IC_{50} 6 268 and 5 816 µmol/L[58].

3.4.8. Anti-inflammatory activity

The nitric oxide (NO) radical is known to play a central role in inflammatory and immune reactions. Under pathological conditions, it is synthesized in large amount through L-arginine pathway by the catalysis of inducible nitric oxide synthase (iNOS). In the study of Sae-wong et. al., the crude ethanol extract of *K. parviflora* and its constituent (5-hydroxy-3,7,3′,4′-tetramethoxyflavone (**95**)) were investigated for the anti-inflammatory mechanism against (iNOS) and cyclooxygenase-2 (COX-2) mRNA expressions. The results revealed that the ethanol extract of *K. parviflora* markedly inhibited PGE_2 release with an IC_{50} value of 9.2 µg/ml. This plant extract and compound (**95**) also suppressed mRNA expression of iNOS in dose-dependent manners, whereas COX-2 mRNA expression was partly affected. According to the *in vivo* study, chloroform and hexane fractions greater decreased rat paw edema than the other fractions[13]. Compounds 5-OH-3,7,3',4'-tetramethoxyflavone (**95**), 5-OH-7,4'-dimethoxyflavone (**88**) and 5-OH-3,7,4'-trimethoxyflavone (**92**) isolated from *K. parviflora* showed moderated to mild NO production inhibitory effect with IC_{50} = 16.1 µM, 24.5 µM and 30.6 µM, respectively[59].

Other flavonoids like 5,7-dimethoxyflavone (**87**), trimethylapigenin (**89**), and tetramethylluteolin (**93**), markedly inhibited the production of NO in lipopolysaccharide (LPS)-activated RAW264.7 cells, moderately inhibited production of TNF-α and strongly inhibited expression of iNOS mRNA and iNOS protein in a dose-dependent manner[43]. Trimethylapigenin (**89**) appeared to be the most abundant compound (1.29%) and it also showed interesting biological activity by inhibition of spleen tyrosine kinase (SYK) which plays important role in intracellular signaling cascades like activation of NF-κB in inflammatory process[43].

Tewtrakul et. al. also found that panduratin A (**78**) isolated from *K. pandurata* rhizome displayed the most potent effect against NO production, with an IC_{50} value of 5.3 µM, in comparable to that of caffeic acid phenethylester (CAPE) (IC_{50} = 5.6 πM). Other compounds such as 4-hydroxypanduratin A (**81**) and cardamonin (**83**) showed lower effect with IC_{50} values 13.3 µM and 24.7 µM, respectively[59].

In addition, the isolated diarylheptanoids from *K. galanga* rhizome exhibited pronounced inhibitory activities compared with indomethacin on NO production induced by LPS in RAW 264.7 with the most effective IC_{50} = 26.98 ± 1.39 µM of compound (3R,5S)-3,5-di-hydroxy-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)heptane (**121**).

These all results support the use of *K. parviflora* and *K. pandurata* rhizomes in traditional medicine for the treatment of inflammatory - related diseases[59]. Jagadish et al. conducted the study to explore the effect of *K. galangal* obtained from Abirami Botanicals, Tuticorin, Tamilnadu, India and found its effects against acute and chronic inflammation in rats. However the active constituents of the extract and their mechanism of action for the treatment of chronic inflammatory conditions were still unclear[30].

3.4.9. Vasorelaxant active and smooth muscle relaxant effects

Mustafa et al. (1996) reported that the chloroform extract of *K. galanga* inhibits vascular smooth muscle contraction on the precontracted rat thoracic aorta by inhibiting Ca^{2+} influx through both voltage and receptor-operated non-selective cation channels[60]. Ethyl *p*-methoxycinnamic acid (**72**), one of major compounds in a crude dichloromethane extract of *Kaempferia galanga* (24%, GCMS), also isolated as white needles but did not exhibit any relaxant effect on the precontracted thoracic rat aorta[61].

3.4.10. Hepatoprotective activity

According to Mekjaruskul et. al. *K. parviflora* possessed modulatory effects on hepatic cytochrome P450 enzymes. In his publication, *K. parviflora* extract significantly induced several CYP450 enzyme activities like CYP1A1, CYP1A2 CYP2B, and CYP2E1 activities. CYP1A2 was affected by *Kaempferia parviflora* with the highest value of V_{max} (15.276 ± 0.206 nmol/min) and lowest of K_i value (0.008 ± 0.002 µg/ml). Thus, its utilization with drugs or other herbs should raise concern for potential drug–herb interactions[11].

In another paper, Tsai et. al reported that kaempferol (**102**) - a flavonoid isolated from

K. rotunda showed protective effect on acute liver injury induced by propacetamol overdose (a prodrug of paracetamol). Kaempferol administration also reduced propacetamol-induced oxidative stress, and changed the level of liver enzymes like downregulating cytochrome P450 2E1 (CYP2E1) expression but upregulation of UDP glucuronosyltransferase family 1 member A1 (UGT1A1) expression. These enzymes play important role in metabolized process (phase I and II) in the liver. This result supposed for an new therapeutic option for treatment of paracetamol-induced hepatotoxicity and protection of acute liver injury[62].

3.4.11. Aphrodisiac effects

Erectile dysfunction (ED) is sexual dysfunction characterized by the inability to develop or maintain an erection off the penis during sexual activity in humans. In order to treat this disorder, many molecular targets are under investigation. Phosphodiesterase 5 (PDE-5) is one of the most protein targeted for this purpose. By inhibition of PDE-5 enzyme, the concentration of intracellular second messenger cGMP (cyclic guanosin 3,5-monophosphatase) will be increased, leading to the relaxation of smooth muscles, improving the blood supply to the corpus cavernosum and consequently improving ED[63]. Temkitthawon et. al. reported that *Kaempferia parviflora* rhizome extract and its 7-methoxyflavone (**86**) constituents had moderate inhibitory activity against PDE-5[41]. Among the tested flavones, 5,7-dimethylflavone (**87**) seemed to be the most potent PDE-5 inhibitor with IC_{50} = 10.64 μM and 3,5,7,3',4'-pentamethoxyflavone (**97**) also remarkably inhibited PDE-5 with IC_{50} = 30.41 μM. Sildenafil was used as positive control with IC_{50} = 0.0068 μM. This finding supports that *K. parviflora* can be used in traditional medicine for enhancing sexual performance. Moreover, 5,7-dimethoxyflavones (**87**) should make a useful lead compound to further develop clinically efficacious PDE5 inhibitors[41]. The components, 5,7-dimethoxyflavone (**87**) and retusine (**95**) from *K. parviflora* extract also enhanced testosterone production in mouse testis-derived tumour cells I-10via cyclic AMP (cAMP)/cAMP response element binding protein signaling[64].

3.4.12. Anti-allergic activity

PMFs isolated from *K. parviflora* were found to be capable of inhibiting antigen-stimulated degranulation in rat basophile leukemia RBL-2H3 cells. 5-hydroxy-3,7,4′,-trimethoxyflavone (**92**) and 5,3′-dihydroxy-3,7,4′,-trimethoxyflavone (**99**) showed potent inhibitory activities and these effects were related to the suppression of degranulation due to Ca^{2+} influx, and translocation of IgE receptor FcεRI to the cell surface. The cross-linking of the cell-bound IgE–FcεRI complex with a specific antigen causes the aggregation of FcεRI, which induces a variety of cellular responses, including the release of chemical mediators such as histamine, arachidonic acid metabolites, and cytokines. *K. parviflora* and PMFs may be beneficial for ameliorating the symptoms of type I allergic responses, which is the most common allergic reaction associated with asthma, hives, hay fever, and allergic dermatitis[12].

Tewrakul et. al. also reported that among the compounds isolated from *K. parviflora*, retusine (**95**) possessed the highest anti-allergic activity against antigen-induced β-hexosaminidase release as a marker of degranulation in RBL-2H3 cells with an IC_{50} value of 8.0 μM. Two other PMF compounds, 5-hydroxy-7-methoxyflavone (**98**), and 5-hydroxy-7,4′-dimethoxyflavone (**88**) also inhibited β-hexosaminidase release with IC_{50} = 20.6 μM and 26.0 μM, respectively. The findings support the traditional use of *K. parviflora* rhizomes for treatment of allergy and allergy-related diseases[37].

3.4.13. Anti-helminthic, anti-amoebic, mosquito repellent and larvicidal activities

The methanolic extract of *K. galanga* containing cinnamate group as ethyl cinnamate (**73**), ethyl *p*-methoxycinnamate (**72**) and *p*-methoxycinnamic acid (**74**), was reported to possess larvicidal activity against the second stage larva of dog roundworm, *Toxocara canis*[65], against neonate larvae of *Spodoptera littoralis*[34], amoebicidal activity against three species of *Acanthamoeba* including *Acanthamoeba culbertsoni, Acanthamoeba castellanii, and Acanthamoeba polyphaga* that cause granulomatous amebic encephalitis and amebic keratitis in human[65]. The *K. galanga* extract and fractions also showed repellent activity and larvicidal potency against mosquitos species like *Culex quinquefasciatus, Culex gelidus, Culex tritaeniorhynchus Anopheles barbirostris, Anopheles aconitus, Mansonia uniformis, and Aedes aegypt*[65]. The working results encourage the use of *K. galanga* as an additional manner in order to control vector-borne diseases by mosquitos like malaria, Dengue fever and Zika disease.

3.4.14. Skin effect and wound-healing activity

Ethanolic extract of *K. galanga* rhizomes

are used to treat wounds with increase of collagen level[66]. The ethanolic extract of *K. parviflora* rhizomic powder showed an anti-gastric ulcer activity in mice by preservation of gastric mucus secretion and unrelated to the inhibition of gastric acid secretion[67].

Exposure of ultraviolet (UV) light on the skin induces photoaging associated with up-regulation of matrix metalloproteinases (MMP-1) expression through activation of mitogen-activated protein kinases (MAPKs) signal pathways. Hwang et.al. investigated that 4-hydroxypanduratin A (**81**), isolated from *K. pandurata*, in the range of 0.001-0.1 μM significantly reduced the expression of MMP-1 levels, prevented and treated UV-associated skin irritation and aging[68]. He also reserved a patent for this activity of *K. pandurata* and its compounds.

3.5. Potential application in life of *Kaempferia* species - derived products: Patents in relation to *Kaempferia* species

Patents in relation to the application of *Kaempferia* species in life have been issued and reserved regionally or globally. Most of these patents are highly practical, applicable and significant in life, which are described as following.

3.5.1. A composition of Kaempferia parviflora extract or flavone compounds for preventing, treating muscle diseases and/or improving muscle function

K. parviflora has been commonly used as folk medicine to prevent fatigue and improve physical fitness by some athletes in Asia. In fact, scientific evidences show that application of *K. parviflora* supplements (180 mg of *K. parviflora* extract in capsules) for 12 weeks increased cardiorespiratory fitness, as indicated by increasing V_{O2} max values, increased blood flow to the organs, especially to the muscles, therefore significantly enhance some physical fitness components in soccer players[69]. Hwang et al. in his patent had announced the use of *K. parviflora* Wall. ex. Baker extracts containing active flavone components for improving muscle function, reducing protein catabolism in the muscles and increasing muscle cell differentiation and anabolism. This pharmaceutical composition is thus effective for treating muscle diseases like atony, muscular atrophy/dystrophy, muscle degeneration, myasthenia and sarcopenia, increasing muscle mass and improving muscle function[70]. A herbal formulation containing in *K. parviflora* powder and its active constituent 5,7-dimethoxy flavone in capable of increasing the nitrate and nitrite levels in serum and saliva in human has been invented to improve the general health and enhance the physical endurance or strength of the athletes[71].

Based on these results, the *K. parviflora* might be useful in order to recover muscle cell destruction or rhabdomyolysis and compartment syndrome as a serious side effect of lipid - lowering drug statins (simvastatin), resulting from drug-drug interactions by co-administration with other drugs like anti-psychotic drug (risperidone)[72], the platelet inhibitory drug (ticagrelor)[73], antifungal agent (itraconazole)[74].

3.5.2. The use of Kaempferia extract as pesticide, herbicide compositions

K. galanga extract containing active flavones components ethyl trans-cinnamate (**73**) and ethyl p-methoxycinnamate (**72**) in composition with other medicinal plants like slender (*Asarum sieboldii*), octagonal anise (*Illicium verum*) and seokchangpo (*Acours gramineus*) found to have a insecticidal activity against *Bursaphelenchus xylophilus*, a species of nematode greatly damage to pine trees (*Pinus* sp.) (pine wood nematode). This invention might provide an environmentally-friendly nematode control agent for pine forest[75]. *K. galanga* powder in composition with other components like thiophanate-methyl, chlorothalonil, atrazine are effective herbicide with high safety, long efficiency duration, wide weeding range and low cost for protecting crops[76].

3.5.3. Using Kaempferia extract and its components as photo-stable sunscreen, anti-wrinkle, anti-aged cosmetic, skin food and external medical compositions

Gonzalez et. al. in his patent described the extract of *K. galanga* rhizome containing isoamyl p-methoxycinnamate and other compositions as useful as an active photostablized agent and UV absorbency for sunscreen product[77]. This formulation is potential as a photostable, enhanced-degree sunscreen protective and extended for period of time product. Another invention of Chinese authors related to formulations of *K. galanga* extract with sun cream ingredients like glycerin, stearic acid, stearyl alcohol, etc. has been issued to effectively resist the ultraviolet ray and prevent the skin from sunburn[78]. Isoamyl p-methoxycinnamate which is considered to be one of the few compounds which are capable to absorb UV UV-B range (280 to 320 nm wavelength) and are is produced from *K. galanga* organic solvent extract rich of its precursor p-methoxycinnamate in order by transesterase

like lipases and esterases to use in cosmetic and pharmaceutical sunscreen preparations[79].

A patent related to a composition comprising an extract of *K. parviflora* as an active ingredient for skin cosmetic products has been issued by Korean authors. In addition, the extract also exhibits remarkable anti-inflammatory activities by inhibition of tyrosinase activities and NO production. According to the authors, the extract can be usefully used as a pharmaceutical and cosmetic composition for external application with effects in preventing skin-aging and improving skin-whitening[80,81], used as wrinkle improvement, anti-aging, skin elasticity enhancement, and skin moisturization via the inhibition of moisture loss from the skin[82]. The rhizomic *K. galanga* extract is also used as personal care compositions[83].

A composition containing *K. pandurata* extract is also used for preventing or treating dermatitis by the expression of cytokines such as IL-1alpha, IL-6, IL-8 and MCP-1 (monocyte chemotactic protein). The *K. pandurata* extract inhibits the sebum secretion by decreasing the activation of PPAR-gamma so that in the form of lotion, astringent, massage cream, pack, powder, body lotion, body cream, rinse and shampoo, the formulation containing *K. pandurate* extract can be used as skin adhesive cosmetic products to control inflammatory skin disease in relation to sebum production disorders[84].

Composition containing *K. angustifolia* extract is obtained as beautifying and whitening dermal preparation for preventing and reducing pigmentation, dermal stains, ephelides, chloasma[85].

K. galanga rhizome extract is used as ingredients for production of transdermal patches or drug-in-adhesive tape to deliver pain-relief drug through skin[86.] This extract is also used to treat skin irritation or inflammation[87].

3.5.4. Using K. parviflora as an effective component for prevention or treatment of thrombosis and health functional food

The black ginger (*Kaempferia parviflora*) ethanol extracts and fractions (*n*-hexane fraction of the hot water extract or ethyl acetate fraction of the ethanol extract) was reserved as an effective component for the prevention and treatment / improved pharmaceutical composition for the thrombosis. The formulation prevented thrombosis through a strong platelet aggregation inhibition, inhibition of thrombosis related enzymes and blood clotting factors[88]. According to the Korean inventors, the formulation from *K. parviflora* improves the blood circulation, treats thrombosis and is useful for disorders such as ischemic stroke and hemorrhagic stroke[88]. A food or drink containing ginger extracts of Zingiberaceae including *K. parviflora*, *K. galanga*, and and several *Curcuma* sp. with platelet aggregation inhibitory activity has been pronounced in patent of Goto et. al.[89]

3.5.5. The use of flavone compounds or K. parviflora extract as anti-periodontitis and anti-Alzheimer's compositions

Flavone compounds from *K. parviflora* extract including 5,7-dimethoxyflavone (**87**), 5,7,4'-trimethoxyflavone (**89**) và 3,5,7,3',4'-pentamethoxyflavone (**97**) are worthy for the prevention and treatment of periodontal disease by inhibition of the production of collagen-decomposing enzyme, and bone resorption enzyme[40]. These compounds are reserved to be active compositions for produce flavone-based or a pharmaceutical formulation or a therapeutic composition for treating periodontal diseases[40].

Three flavones are also active components in used as anti-aging, skin elasticity enhancement, and skin moisturization compositions[82]. These flavones also pronounced to be potential therapeutic agent / compositions for preventing or treating Alzheimer′s dementia by preventing the accumulation of beta-amyloid (Aβ) in brain cells. These natural compounds have no cytotoxicity, and thus have an advantage of least side effects to human in long-term dosage in compare to that synthetic chemical drugs. These flavones according to inventors can be used as medicines and functional health foods for preventing, alleviating, or treating Alzheimer′s dementia[90].

Poly-methoxy flavonoid compound from *K. parviflora* like apigenin -5,7,4'- trimethyl ether, 3,5,7,3',4'-pentamethylflavone (**97**), chrysin dimethyl ether; 3,5,7,4' tetramethoxy flavone (**89**), and 3,5,7, trimethoxyflavon (**9**1) are reserved as sirtuin-activating agent according to patent of Shimada et. al.[91]

3.5.6. Using Kaempferia extract as drink products

Chinese inventors in their patents announced to applied *K. galanga* extract with other valuable traditional medicinal plants like angelica (*Angelica sinensis*, Apiaceae), mulberry (*Morus alba*, Moraceae), astragalus (*Astragalus membranaceous*, Fabaceae), poria (*Poria cocos*, Polyporaceae) etc. to produce oral products to enhance immune function in women[92]. *K. parviflora*

extract might be also useful in food processing to provide ginger bitterness, astringency, sweetness and aftertaste for good overall taste to beverage and drink products[93]. *K. galanga* extract in combination with other fruits, herbs, medicinal plants, vegetable and/or spices is used for making a tea beverage and vegetable broths[94].

3.5.7. The use of Kaempferia extract as health food, anti-cold, anti-obesity product

K. parviflora extract in composition with medicinal plant extracts of *Zingiber officinale*, *Cinnamomum cassia*, medicinal ginseng, and vitamin B was pronounced to exhibit PPARγ expression, inhibit excessive accumulation of subcutaneous fat and prevent cellulite generation[95]. Another composition of *K. parviflora* extract consisting hops (*Humulus lupulus*, Cannabaceae), sicklepod (*Cassia obtusifolia*, Fabaceae), sweet clover *(Melilotus officinalis*, Fabaceae), ginger (*Zingiber officinale*, Zingiberaceae) with elastin, gallic acid, caffeine, oligosaccharide, and amino acid was found to exhibit UCP1 (Uncoupling proteins UCPs) expression-promoting effect and/or brown adipocyte differentiation-promoting effect. UCP1 causes the uncoupling of oxidative phosphorylation in the inner mitochondrial membrane of brown adipose cells, which are responsible to provide energy as heat to the body. UCP1 is specifically expressed in brown adipose cells to promote differentiation of precursor cells into brown adipose cells and promote consumption of the neutral lipid into the heat and therefore eliminate obesity[96]. Composition containing extract of black ginger *K. parviflora* can provide heat, promote blood circulation and eliminate coldness for the body[97].

An extract and/or dried powder of *K. parviflora* has also inhibitory effect against xanthine oxidase is an enzyme that produces uric acid causing gout or hyperuricemia. It also inhibits 5α-reductase that causes male pattern baldness and benign prostatic hyperplasia[98]. So, compositions containing *K. parviflora* extract might be a good health product for prevention of diseases associated with obesity and adipose, such as type-2 diabetes mellitus, hypertension, hyperuricemia and hyperlipidemia.

Additionally, several patents related to the cultivation of *Kaempferia* species in order to obtain *Kaempferia* plants normally or by tissue culture[99] with extremely high ornamental value[100], beautiful plant type and suitable as potted foliage plants[101], with highly yield of *K. parviflora* black ginger in a shortest time[102].

The alcohol extract (instead of dichloromethane) of *K. parviflora*, which caused a decrease in visceral and subcutaneous fat, fasting serum glucose and triglyceride levels and liver lipid accumulation, with no changes to liver and kidney functions or to total blood cell counts, can be potentially developed as a health product for mid-aged humans to reduce obesity, diabetes type II and cardiovascular disease[103].

4. CONCLUSIONS

The potential for use of *Kaempferia* species in everyday life is very large. *Kaempferia* species like *K. galanga*, *K. parviflora*, *K. rotunda*, etc. are among the most important herbs and widely used in traditional medicines in Asian countries. The *Kaempferia* in the different formulations like powder, alcohol extracts, maceration, tincture, or water decoctions can be potentially used as food supplements, alternative medicines, and healthcare foods. The water decoctions of *K. pandurata*, *K. parviflora* were used as tonic. *K. galanga* products were used for osteoporosis treatment. These species are also easily cultivated in tropical, sub-tropical but high humidity climate in Asian countries, where many poor people are living. Using the medical products derived from *Kaempferia* plants will raise economic level and also enhance the life quality of developing countries.

5. ACKNOWLEDGEMENTS

Authors acknowledge Prof. Dr. Nguyen Manh Cuong, Institute of Natural Products Chemistry, Vietnam Academy of Science and Technology for his support in preparation this review.

Conflict of interest (If any)

We authors declare that no conflict of interest in publication of this review.

Funding

This work was supported by the Institute of Natural Products Chemistry, Vietnam Academy of Science and Technology through Project No. QTSK01.01/21-22 (PI Pham Ngoc Khanh).

Ethical approval

None to declare.

Article info:
Received August 6, 2019
Received in revised form November 13, 2019
Accepted March 30, 2020

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