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Review

Exploring the Phytochemical Profile and Therapeutic Potential of *Kaempferia galanga L.*

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***Kaempferia galanga* L. (KG), commonly known as cekor is one of those precious medicinal herbs of Zingiberaceas that are still included in un-utilized herbs inspite of the variety of useful pharmacological properties it possesses. Extracts of KG have anti-inflammatory, analgesic, nematicidal, mosquito repellent, larvicidal, vasorelaxant, sedative, antineoplastic, antimicrobial, anti-oxidant, antiallergic and wound healing properties. Here, we have reviewed all the reported pharmacological properties of this valuable herb with an intention to highlight the effectiveness and potentials of this herb. Ethyl-*p*-methoxycinnamate and ethyl-cinnamate are found to be the most vital constituents responsible for most of these pharmacological properties. Antinociceptive effect of KG extracts is comparable with that of aspirin whereas its nematicidal effect is even more potent than Carbofuran and metham sodium.**

Key words: Antinociceptive, nematicidal, cekor.

INTRODUCTION

Kaempferia galanga L. (KG) is a small monocotyledonous herb from Zingiberaceae that is well known for its medicinal properties since decades. The plant is native to tropical Asia including southern China, Indochina, Thailand, Taiwan, Malaysia and India (Koh, 2009; Mitra et al., 2007; Techaprasan et al., 2010). Being a source of valuable bioactive compounds, KG is famous for its medicinal as well as edible use (Techaprasan et al., 2010). Although included in the list of 112 medicinal herbs and spices issued by the international organization for standardization, KG is one of those medicinal herbs which are still comparatively less known and are underutilized (Peter, 2004). Owing to the threat of extinction that this important medicinal herb is facing today, the plant is also propagated by using *in vitro* multiplication methods (Chithra et al., 2005; Swapna et al., 2004). Inspite of the finding that the intraspecific genetic variations are not observed in many Kaempferia species including KG, taxonomic identification of Kaempferia species is quite difficult due to the morphological similarities in the vegetative parts of Zingiberaceae (Techaprasan et al., 2010). That is why misuse of other species, for instance *Kaempferia marginata* as KG is quite common (Yu et al., 2000). The herb was reported for the first time in 1983 for its capacity to inhibit monoamine oxidase enzyme (Noro et al., 1983). Since then, KG extracts have been studied for a number of pharmacological activities. The following is a comprehensive and up-to-date review about the chemistry, toxicity and medicinal properties of KG with an urge of further advancements in the medicinal uses of the herb worldwide.

CHEMISTRY

A considerable work has already been done to identify and isolate the chemical constituents from different polar and non polar extracts of KG. Ethyl-cinnamate and

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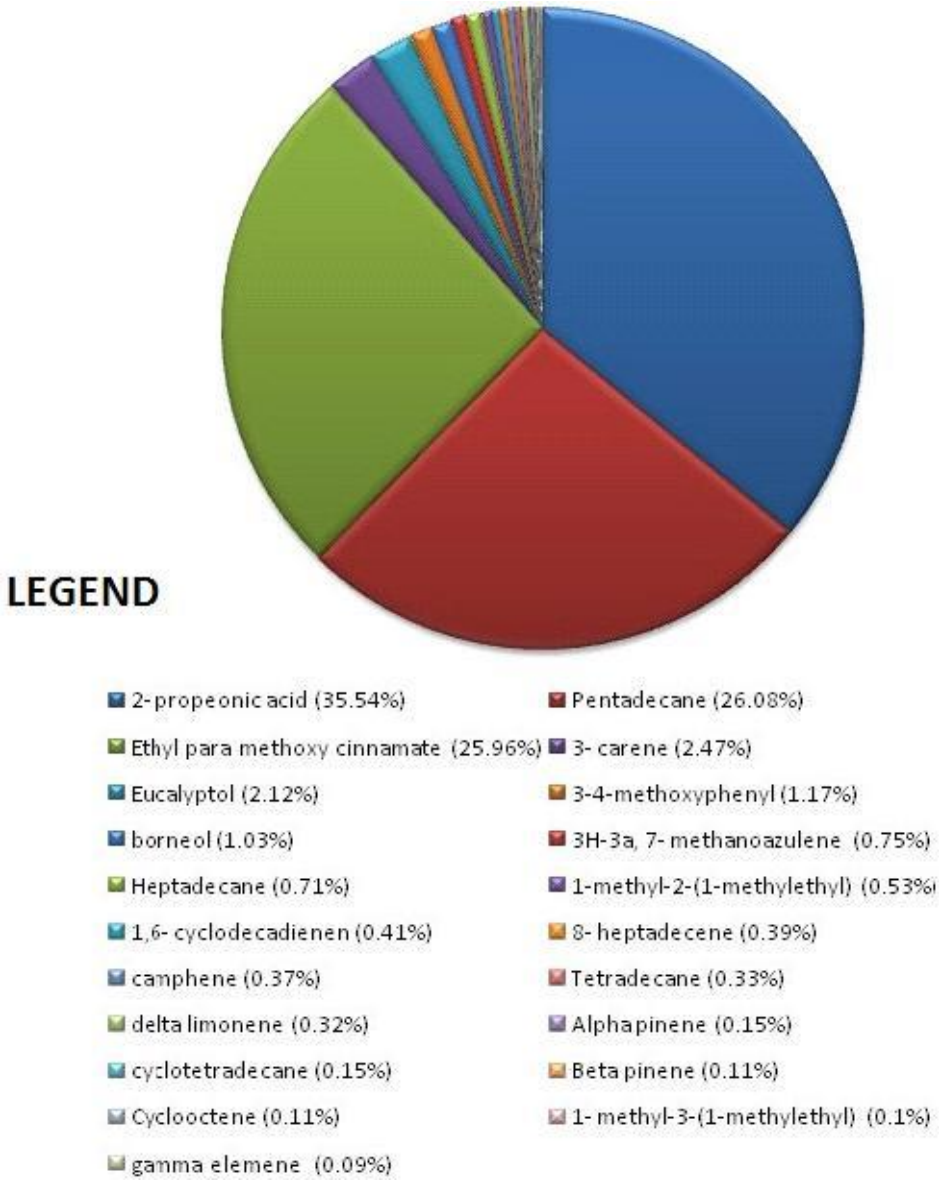


Figure 1. Percent composition of essential oil content of KG extracts (Sutthanont et al., 2010).

ethyl–*para*-methoxycinnamate are found to be the most vital constituents in the dichloromethane (Othman et al., 2006), hexane (Yu et al., 2000) and methanol extracts (Huang et al., 2008). About 98.98% of essential oil constituents have been isolated and identified with only 1.11% constituents that are still unknown (Sutthanont et al., 2010). The most abundant essential oil constituents include propanoic acid, pentadecane, ethyl-*p*-methoxycinnamate. Other constituents include 1,8-cineol, undecanone, isopropyl cinnamate, dicyclohexylpropane-dinitrile, dipentene dioxide, 9-hydroxy, 2-nonanone, 2,7-octadiene-1- yl acetate, ethyl cyclohexyl acetate, cis-11-tetradecenyl acetate, 2-heptadecanone, 4-methyl isopulegone, camphidine, trans,trans-octa-2, 4-dienyl acetate, 10-undecyn-1-ol, 3,7-dimethoxycoumarin, delta-3-carene, alpha pinene, camphene, borneol, cymene, alpha terpineol, alpha gurjunene, germacrenes, cadinenes, caryophyllenes, luteolin and apigenin (Koh, 2009; Mustafa et al., 2010; Othman et al., 2006; Sutthanont et al., 2010).

The percent concentrations of essential oil constituents are shown in Figure 1. There is a remarkable difference between the higher ethyl- *p*-methoxycinnamate content (25.96 to 87.4%) of KG and contents of the same constituents *in K. marginata* (4.46%) which strongly discourages the misuse of *K. marginata* as KG in many areas of the World (Yu et al., 2000). The chemistry of important constituents of KG is given in Table 1.

Table 1. Important phytoconstituents isolated from KG extracts (Koh, 2009; Othman et al., 2006; Sutthanont et al., 2010).

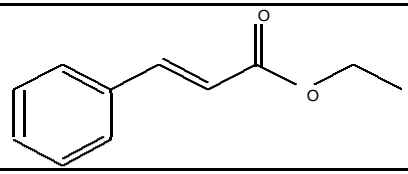
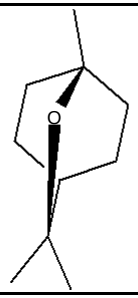
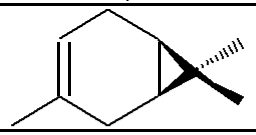
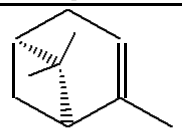
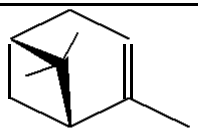
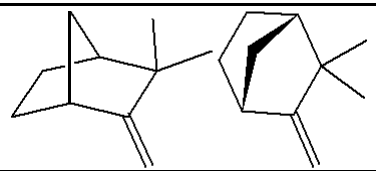
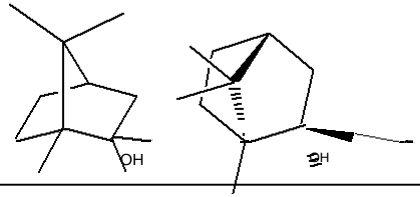
S/N	Common name	IUPAC name	Structure
1	Ethyl-cinnamate	Ethyl 3-phenylprop-2-enoate	
2	1, 8 – cineole	1,3,3- trimethyl-2-oxabicyclo[2.2.2]octane	
3	Delta 3 Carene	(1*S*, 6*R*)-3,7,7- trimethylbicyclo[4.1.0]hept-3-ene	
4	(+)Alpha Pinene	(1 *S*, 5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene	
5	(-)Alpha Pinene	(1*S*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]hept-2-ene	
6	Camphene	(1*S*,4*R*)-2,2-dimethyl-3-methylenebicyclo[2.2.1]heptane	
7	Borneol	(1*S*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol	

Table 1. Contd.

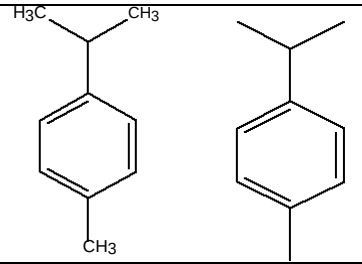
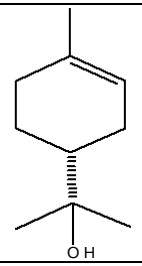
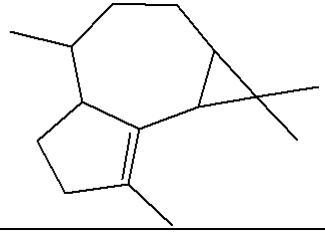
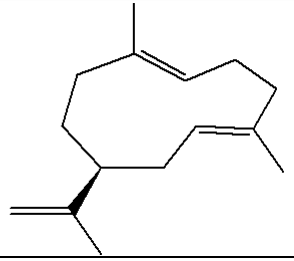
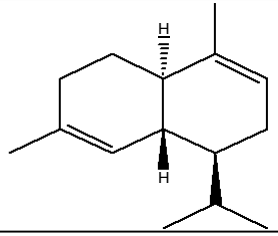
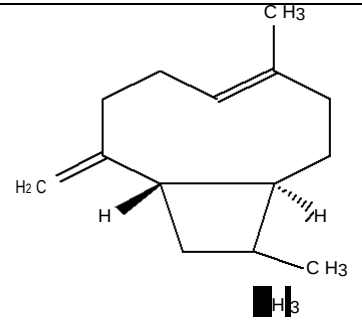
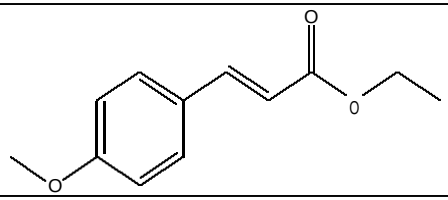
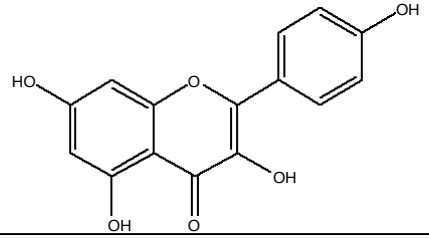
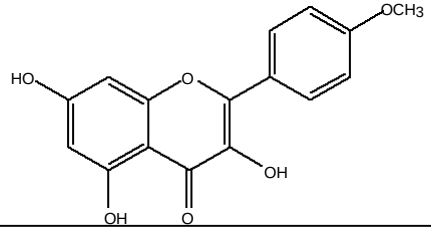
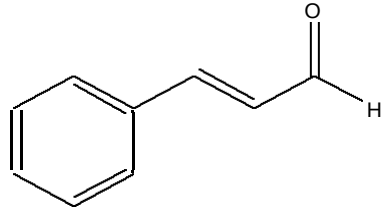
8	Cymene	1-Methyl-4-(1-methylethyl)benzene	
9	Alpha Terpineol	(*R*)-2-(4-methylcyclohex-3-en-1-yl)propan-2-ol	
10	Alpha Gurjunene	1,1,4,7-tetramethyl-1 a,2,3,4,4a,5,6,7b-octahydro-1 *H*-cyclopropa[e]azulene	
11	Germacrene	(*S*,1*E*,5*E)*-1, 5-dimethyl-8-(prop-1-en-2-yl)cyclodeca-1,5-diene	
12	Cadinenes	(1S,4aR,8aR)-1-isopropyl-4,7-dimethyl-1,2,4a,5,6,8a-hexahydronaphthalene	

Table 1. Contd.

13	Beta-Caryophyllen	(1*R*, 9*S*,*E*)-4,11,11-trimethyl-8-methylenebicyclo[7.2.0]undec-4-ene	
14	Ethyl-*p*-methoxycinnamate	(*E*)-ethyl 3-(4-methoxyphenyl)acrylate	
15	Kaempferol	3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one	
16	Kaempferide	3,5,7-trihydroxy-2-(4-methoxyphenyl)-4H-chromen-4-one	
17	Cinnamaldehyde	(2*E*)-3-phenylprop-2-enal	

The structural drawings and nomenclature is based on ChemBioDraw verion 12.0.

TOXICITY

Ethanolic extracts of KG cause central nervous system depression, decreased motor activity and respiratory rate, loss of screen grip and analgesia in rats at doses of 25, 50, 100 and 800 mg/kg (Kanjanapothi et al., 2004; Koh, 2009). An administration of ethanolic extracts to rats up to 5 g/kg neither resulted into mortality, nor any significant difference in body and organ weights between control and test animals. However, an administration of 25, 50 and 100 mg/kg for 28 days resulted into a slight, but significant decrease in the lymphocyte count in male rats, with all the other parameters normal. Hexane fraction of KG, when applied on skin of rabbits, showed no sign of dermal irritation (Kanjanapothi et al., 2004).

MEDICINAL PROPERTIES Anti-

inflammatory and analgesic activity

Leaves and rhizomes of KG are used in traditional medicine to treat swelling, headache, stomach ache, toothache and rheumatism (Mitra et al., 2007). When given subcutaneously in doses of 30, 100 and 300 mg/kg, the aqueous extracts of KG leaves show significant anti-nociceptive and anti-inflammatory effect in rats in a dose-dependent manner (Sulaiman et al., 2008). When it is given orally at a dose of 200 mg/kg, the anti-nociceptive effect of KG rhizome extracts is more potent than aspirin using 100 mg/kg, but lesser than morphine using 5 mg/kg subcutaneously (Ridtitid et al., 2008). This anti-nociceptive effect is reversed by naloxone in a dose of 10 mg/kg (Sulaiman et al., 2008). The capacity of the extracts to block abdominal constriction, hot plate and formaline test indicates that analgesic activity has both central mechanism, involving opioid receptors, and peripheral mechanism that involves cyclooxygenase pathway (Ridtitid et al., 2008; Sulaiman et al., 2008).

Nematicidal activity

KG extracts have potent nematicidal effect. Crude extracts have shown 100% mortility in male, female and juvenile pine wood nematodes, *Bursaphelenchus xylophillus* at a dose of 1000 µg/ml (In-Ho et al., 2006). In-Ho et al. (2006) have further isolated ethyl- *trans*-cinnamate and ethyl-*p*-methoxycinnamate from the crude extracts and have demonstrated that these constituents have 100% mortality in pine wood nematodes even at dose of 60 µg/ml. Crude methanolic extract of rhizomes has shown considerable nematicidal activity against *Meloidogyne incognita* juveniles and eggs that is greater than that of carbofuran and metham sodium but lesser than fosthiazate (Tae-Kyun et al., 2010). Ethyl-cinnamate and ethyl-*p*-methoxycinnamate isolated from KG rhizome extracts are proven to be responsible for this killing effect on *M. incognita* juveniles and eggs. median lethal dose (LC_{50}) value (48 h) of ethyl-cinnamate and ethyl-*p*-methoxycinnamate against Phase 2 juveniles of *M. incognita* is 37 and 41 µg/ml, respectively that is greater than Carbofuran (92 µg/ml) but lesser than fosthiazate (2 µg/ml) (Hong et al., 2011). At a dose of 62 µg/ml, ethyl-cinnamate shows 100% hatch inhibition; however ethyl-*p*-methoxycinnamate shows 81% hatch inhibition that rises to a maximum of 93% at a dose of 125 µg/ml. This hatch inhibition dose is lesser (more efficient) than carbofuran and metham sodium (Hong et al., 2011). Hong et al. (2011) have further demonstrated that the efficiency of ethyl-cinnamate and ethyl-*p*- methoxycinnamate in steam phase mortality bioassay is greater in closed container than in open container which suggests that mode of delivery of these constituents is partly through vapour phase.

Mosquito repellent and larvicidal activity

Essential oils extracted from the rhizomes of KG have shown considerable repellent and larvicidal activity against a number of mosquito species including *Aedes aegypti* (Choochote et al., 1999; Choochote et al., 2007; Yang et al., 2004), *Aedes togoi* (Yang et al., 2004) *Armigeres subalbatus*, *Anopheles barbirostris*, *Anopheles aconitus*, *Mansonia uniformis*, *Culex quinquefasciatus*, *Culex gelidus*, *Culex tritaeniorhynchus* (Choochote et al., 1999) and *Culex pipens pallens* (Yang et al., 2004). These essential oils exert repellent effect against *A. aegypti* (effective dose (ED 50) = 30.73 µg/cm ^{2}) with a complete protection time of about 3 h without irritating human skin (Choochote et al., 1999). This protection time increases further by the addition of 10% vanillin (Choochote et al., 2007). The extracts have shown remarkable larvicidal activity even against pyrethroid resistant strains of *A. aegypti* (Sutthanont et al., 2010). Methanolic extracts of KG showed 100% mortality against *A. aegypti*, *A. togoi* and *C. pipens pallens* at a concentration of 100 ppm that reduced up to 78% at the concentration of 50 ppm (Yang et al., 2004).

The larvicidal activity is mainly due to ethyl-*p*-methoxycinnamate, ethyl-cinnamate, 3-carene, 2-propionic acid and pentadecane (Kim et al., 2008; Sutthanont et al., 2010). Ethyl-*p*- methoxycinnamate has shown more larvicidal activity (LC 50 = 12.3 to 20.7 mg/L) against *A. aegypti*, *O. togoi* and *C. pipens pallens*, however, ethyl-cinnamate and 3-carene have more larvicidal activity (LC 50 = 24.1 and 21.6 mg/L respectively) against *C. pipens pallens* but less activity (LC50 = 40 to 60 mg/L) against *A. aegypti* and *O. togio* (Kim et al., 2008).

A study on the possible mechanism of toxicity of ethanolic extracts of KG against *C. quinquefasciatus* larvae has revealed that the possible site of action is the

anal gills of *C. quinquefasciatus* where it causes the destruction of ionic regulation (Insun et al., 1999).

Vasorelaxant activity

Extracts of KG exhibit significant anti-hypertensive activity (Zakaria, 1994). Intravenous administration of KG extracts to rats has shown dose related reduction of basal mean arterial pressure with maximum effect seen 5 to 10 min after injection (Othman et al., 2006). Ethyl-cinnamate, isolated from the extracts of rhizomes as a colourless oil (Othman et al., 2006) inhibits tonic contractions induced by increased potassium influx and phenylephrine in a concentration dependent manner (Othman et al., 2002). However, this vasorelaxant effect is reversed by pretreatment of aorta with methylene blue and indomethacin which indicates that the mechanism of this vasorelaxation may involve inhibition of calcium influx into vascular cells and release of nitric oxide and prostaglandins from endothelial cells (Othman et al., 2002). Ethyl-*p*-methoxycinnamate is also isolated from KG rhizomes as white needles, but it does not exhibit relaxant activity on precontracted thoracic rat aorta (Othman et al., 2006).

Sedative activity

Inhalation of hexane extract of KG at doses ranging from 1.5 to 10 g has shown considerable decrease in locomotor activity in rats (Huang et al., 2008). This sedative activity is due to ethyl trans-*p*-methoxycinamate and ethyl-cinnamate that inhibits locomotor activity in doses of 0.0014 and 0.0012 mg, respectively.

Antineoplastic and apoptotic activity

Extracts of KG have already been reported as antineoplastic (Koh, 2009; Kosuge et al., 1985; Vimala et al., 1999). It is one of those herbs that have inhibitory effects on the tumor-promoting stage of neoplasia. When assessed by indirect immunofluorescent assay and western blot, it is proven that the methanolic extracts of KG inhibit TPA (12-O tetradecanoyl-phorbol-13-acetate) - induced activation of epstein barr virus early antigen in Raji cells and thus, it inhibits tumor promoting stage (Vimala et al., 1999).

However, this inhibitory effect on tumor -promoting stage is partial and not complete. At a dose of 320 µg/ml, 80% inhibition is seen which is increased up to a maximum of 90% at 640 µg/ml (Vimala et al., 1999). Methanolic extracts of KG Linn have also shown inhibitory effect on human cardiac fibroblast (cell line HCF-7) and human T cell leukemia (HT-29 cell line) only at doses more than 250 µg/ml by colorimetric tetrazolium salt assay (Kirana et al., 2003). Recently, it is reported that this inhibitory effect of the plant is due to ethyl-*p*-methoxycinnamate. This chemical constituent of galanga extracts inhibits proliferation of human hepatocellular liver carcinoma (Hep G2 cell line) in a dose dependent manner (Liu et al., 2010). Annexin- fluorescein isothiocyanate and propidium iodide staining shows an increased early apoptotic population in human hepatocellular carcinoma cells. It is believed that ethyl-*p*-methoxycinnamate induces translocation of phosphatidylserine of Hep G2 cells to cell surface, resulting in an increase in sub-G cell population (Liu et al., 2010).

Anti-oxidant activity

KG extracts have weak anti-oxidant activity (Chan et al., 2008; Mekseepralard et al., 2010). Total phenolic content (TPC) of ethanolic extracts of leaves and rhizomes is found to be 146 mg galic acid equivalent (GAE)/100 g and 57 mg GAE/100 g, respectively whereas the anti-oxidant activity of leaves and rhizome extracts is 77 mg ascorbic acid (AA)/100 g and 17 mg AA/100 g (Chan et al., 2008). This anti-oxidant activity is further reduced by drying using different thermal and non-thermal drying methods, however, this decrease is prevented if the plant is subjected to freez-drying (Chan et al., 2009). This anti-oxidant activity is mainly due to the total phenolic content and flavonoids, including luteolin and apigenin (Mustafa et al., 2010).

Antimicrobial activity

Ethyl-*p*-methoxycinnamate isolated from extracts of KG has considerable activity against *Mycobactrium tuberculosis* and *Candida albicans* (Kanjanapothi et al., 2004, Techaprasan et al., 2010). More recently, this ethyl-*p*-methoxycinnamate by resazurin microtitre assay has shown to inhibit drug susceptible and multidrug resistant clinical isolates of *M. tuberculosi*s with minimum inhibitory concentration (MIC) of 0.242 to 0.485 mM (Lakshmanan et al., 2011). KG extracts have also been found to exhibit antimicrobial activity against a number of organisms including *Staphylococcus aureus*, *Streptococcus pyogenes*, *Candida albicans*, *Escheriachia coli*, *Klebsiella pneumonia*, *Salmonella typhi*, *Seratia marcescens*, *Vibrios cholera*, *Vibrios parahaemolyticus*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa* with MIC of 0.81, 3.25, 25, >6.5, > 6.5, >6.5, >6.5, >6.5, >6.5,1.625 and >6.5 µg/ml, respectively (Mekseepralard et al., 2010).

Miscellaneous activities

Water extract of KG have shown weak inhibitory effect on

Table 2. Pharmacological activities of KG extracts with possible mechanism of action.

Pharmacological activity	Responsible active constituent	Possible mechanism of action
Analgesic and anti-inflammatory	-	Central mechanism involving opioid receptors and peripheral mechanism involving cyclooxygenase pathway (Ridtitid et al., 2008; Sulaiman et al., 2008)
Nematicidal activity	Ethyl-*trans*-cinnamate, ethyl-*p*-methoxycinnamate (Hong et al., 2011)	Mode of delivery of constituents is partly through steam phase. Mechanism is still unclear (Hong et al., 2011)
Mosquito repellent and larvicidal activity	Ethyl p-methoxycinnamate, ethyl-cinnamate, 3 carene, 2-propionic acid (Kim et al., 2008; Sutthanont et al., 2010)	Destruction of ionic regulation in the anal gills (Insun et al., 1999)
Vasorelaxant activity	Ethyl-cinnamate (Othman et al., 2006)	Inhibition of calcium influx into vascular cells, release of nitric oxide and prostaglandins from endothelial cells (Othman et al., 2002)
Antineoplastic activity	Ethyl-*p*-methoxycinnamate (Liu et al., 2010)	Translocation of phosphatidylserine of Hep G2 cells to cell surface, resulting in an increase in sub-G cell population (Liu et al., 2010)
Anti-oxidant activity	Total phenolic content and flavovoids including luteolin and apigenin (Mustafa et al., 2010)	-
Anti microbial activity	Ethyl-*p*-methoxycinnamat (Kanjanapothi et al., 2004a)	-

the antigen-induced release of -hexosaminidase in RHB-2H3 cell line (Tewtrakul et al., 2007). Tewtrakul et al. (2007) have further investigated that this anti-allergic effect of KG (water extract half maximal inhibitory concentration (IC_{50}) = 49.5 µg/ml) is lesser than that of *Kaempferia parviflora* (ethanolic extract IC_{50}=10.9 µg/ml), *Zingiber cassumunar* (ethanolic extract IC_{50} = 12.9 µg/ml), *Curcuma mangga* (water extract IC50 = 36.1 µg/ml) and *Zingiber officinale* (Ethanolic extracts IC_{50} = 40.3 µg/mL) but greater than that of *Zingiber zerumbet* (Water extracts IC_{50} = 68.2 µg/ml). Alcoholic extracts of KG have considerable wound healing effect on incision, excision and dead space wounds with a remarkable reversal of dexamethasone induced delay in epithelialization and wound breaking strength (Tara et al., 2006). The plant also have weak monoamine oxidase inhibitory effect (Noro et al., 1983) and antiprotozoal activity (Koh, 2009).

CONCLUSION

KG is an important herb with many valuable medicinal properties. Table 2 briefly summarizes the previous discussion. A considerable work has already been done for the isolation and pharmacological evaluation of different constituents from KG extracts. For instance, larvicidal, nematicidal, vasorelaxant and anti neoplastic effects of the herb are mainly due to ethyl-cinnamate and ethyl-*p*-methoxycinnamate (Choochote et al., 2007; Hong et al., 2011; Kim et al., 2008; Liu et al., 2010; Othman et al., 2006, 2002).

Ethyl trans -*p*-methoxycinnamate and ethyl-cinnamate are found to be the reason of sedative properties of the herb (Huang et al., 2008). Although the plant has a weak anti-oxidant effect, this is mainly due to its total phenolic content and

flavonoids including luteolin and apigenin (Mustafa et al., 2010). A few of the medicinal properties are comparable with conventionally available medicines. For instance, analgesic effect of the herb is comparablewith the aspirin (Ridtitid et al., 2008) and the nematicidal activity is even greater than carbofuran (Tae-Kyun et al., 2010). Although this herb has been used for long time to treat swellings and arthritis (Mitra et al., 2007), the herb is not yet patented for its anti-inflammatory properties (Doreswamy, 2004). Increasing resistance in infectious organisms against conventional antibiotics is a major reason that prominates the use of herbs with immunomodulatory and antimicrobial potentials (Vinothapooshan et al., 2011).

Ethyl-*p*-methoxycinnamate isolated from KG extracts has onsiderable antimicrobial capacity. However its immunomodulatory effect is yet to be investigated. A considerable work is still needed to evaluate the *in vitro* mechanism of the anti-inflammation capacity of KG extracts as it has already been done for other known anti-inflammatory plants such as devil's claw and willow (Gyurkovska et al., 2011; Khayyal et al., 2005). Preclinical and clinical research is required to investigate the effectiveness and safety of KG preparations in the same way as done for other anti-inflammatory herbs (Grant et al., 2007).

It is recently reported that angiotensin converting enzyme inhibitors (ACEI) like losartan, irbesartan and valsartan have profound analgesic activity that is reversed by naloxone (Sekar et al., 2011). KG extracts have profound vasorelaxant and analgesic activity and their analgesic activity is reversed by naloxone too. This may suggest a further work to investigate the capacity of KG extracts to block angiotensin converting enzyme. There is an utmost need to diverse the cultivation of this precious herb and to expand its utilization in cure of those human ailments for which the nature has designed this herb.

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