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Review Article

# THERAPEUTIC POTENTIAL OF *LEEA INDICA* (VITACEAE)

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## ABSTRACT

### *Background*

*Leea indica* (Burm. f.) Merr. (fam. Vitaceae), commonly known as 'bandicoot berry', is a Thai medicinal plant, and distributed widely in the far-east and south-east Asian countries, and in some parts of northern Australia. In Thailand, this plant has traditionally been used for the treatment of diarrhoea, pain, gastric ulcer, viral infections and some forms of cancers.

### *Aims*

To review published findings on medicinal properties of *L. indica* and to critically appraise its therapeutic potential.

### *Methods*

A comprehensive literature search was performed utilizing several databases, notably, Web of Science, PubMed and Google Scholar, and other relevant published materials. The keywords used in the search, individually as well as in combinations, were *Leea indica*, Vitaceae and traditional medicine.

### *Results*

*In vitro* assays and *in vivo* animal studies displayed efficacy of the extracts and fractions of *L. indica* as an analgesic, antidiabetic, anti-inflammatory, antimicrobial, antioxidant and antiproliferative agent and indicated their therapeutic potential. Phytochemical studies revealed the presence of alkaloids, flavonoids, polyphenolics and terpenoids as major bioactive components in *L. indica*.

### *Conclusion*

Preliminary bioactivity studies on *L. indica* provided some scientific basis for its traditional therapeutic applications. The presence of certain bioactive compounds in this plant could further support its therapeutic potential and traditional medicinal uses.

**Keywords:** *Leea indica*, Vitaceae, antitumour, antioxidant, traditional medicine.

## INTRODUCTION

*Leea indica* (Burm. f.) Merr., commonly known as 'bandicoot berry', is a Thai medicinal plant from the family Vitaceae, and distributed widely in the far-east and south-east Asian countries, *e.g.,* Bangladesh, China, India, Malaysia, Nepal, Sri Lanka and Vietnam, and in some parts of northern Australia (Wong and Kadir, 2011; Singh et al., 2019a,b). This species is an evergreen perennial shrub or a small tree growing up to 2-16 m tall (Figure 1).

a.  b.  c. 

**Figure 1.** Stipule (a), flowers (b) and unripe fruits (c) of *Leea indica*

In Thailand, this plant has traditionally been used for the treatment of diarrhoea, gastric ulcers, leucorrhoea, pain, viral infections and some forms of cancers (Mollik et al., 2009; Wong et al., 2012; Mishra et al, 2016; Kekuda et al., 2018; Singh et al., 2019b). The roots are used for treating diarrhoea, dysmenorrhoea fever and muscular pain; roots and stem are consumed for the treatment of diarrhoea, gastric ulcers and haemorrhoid; young shoots are applied externally to reduce swelling; stipules are used to treat *Herpes* infections (Kekuda et al., 2018; Singh et al., 2019b). Furthermore, this plant is used as an ingredient in traditional medicinal preparations to treat leucorrhoea, intestinal and uterus cancers (Wong et al., 2012), and the roots are used as an aphrodisiac and neurotonic remedy in Thai traditional medicines (Temkitthawon et al., 2011). Because of its long-standing contributions to Thai traditional medicinal practice as well as in traditional medicines from various other countries, this plant has been the subject of phytochemical and pharmacological studies providing some scientific evidence for its applications. This review article explores published findings on medicinal properties of *L. indica*, and critically appraises its therapeutic potential.

## PHYTOCHEMISTRY

Previous phytochemical analyses of *L. indica* furnished the presence of various plant secondary metabolites belonging to the phytochemical classes of alkaloids, flavonoids, glycosides, phenolics, saponins, steroids, tannins and terpenoids (Table 1). However, many of these studies were merely qualitative phytochemical screening without isolation and identification of phytochemicals.

### Alkaloids

Alkaloids are nitrogenous compounds where the nitrogen is usually an integral part of the ring, and they form one of the largest groups of plant secondary compounds with a variety of pharmacological activities (Nahar and Sarker, 2029). In fact, several modern natural products derived drugs belong to this class of natural products, *e.g.,* anticancer drugs vincristine and vinblastine from *Catharanthus roseus*, narcotic analgesic morphine from *Papaver somniferum*, and so on. Previous phytochemical studies revealed the presence of alkaloids in the leaves and stem bark of on *L. indica* (Emran et al., 2012a,b; Rahman et al., 2013a,b; Dalu et al., 2014; Mishra et al., 2014; Harun et al., 2016, 2018; Chander and Vijayachari, 2016; Tareq et al., 2017; Ghagane et al., 2017). Emran et al. (2012a,b) established the presence of alkaloids in the leaves of this plant based on qualitative tests for alkaloids, but no isolation of specific alkaloids was attempted. Several other authors also reported the presence of alkaloid in this plant merely on the basis of preliminary qualitative tests (Rahman et al., 2013a,b; Dalu et al., 2014; Mishra et al., 2014; Chander and Vijayachari, 2016; Harun et al., 2016; Tareq et al., 2017). The qualitative test conducted by Harun et al. (2016) identified alkaloids in the leaves extract, but not in the extracts obtained from the stem and roots. However, later this group tentatively identified the alkaloid 3,8,8-trimethoxy-3-piperidyl-2,2-binaphthalene1,1,4,4-tetrone (Figure 2) in the leaves and stem, based on GC-MS analysis (Harun et al., 2018), but this alkaloid was not isolated. Notably, Ghagane et al. (2017) did not find the presence of alkaloids in *L. indica* from the qualitative tests for alkaloids that they performed. Discrepancies in the outcomes of qualitative tests conducted by various groups could certainly raise the questions about their reliability and precision, and points to the need for proper separation, isolation and identification of individual phytochemicals present in various extracts.

**Table 1**| A summary of phytochemistry of *L. indica*

| Phytochemical classes | Plant parts | References |
|---|---|---|
| **Alkaloids** | Leaves and stem bark | Emran et al., 2012a,b; Rahman et al., 2013a,b; Dalu et al., 2014; Mishra et al., 2014; Harun et al., 2016, 2018; Chander and Vijayachari, 2016; Tareq et al., 2017; Ghagane et al., 2017 |
| **Alkanes** | Leaves | Srinivasan et al., 2008 |
| **Alkenes** | Leaves and stem | Srinivasan et al., 2008; Harun et al., 2018 |
| **Cardiac glycosides** | Leaves, roots and stem | Rahman et al., 2013a,b; Dalu et al., 2014 |
| **Carotenoids** | Leaves | Singh et al., 2019a,b |
| **Coumarin** | Leaves | Singh et al., 2019a,b |
| **Dihydrochalcones** | Leaves | Singh et al., 2019a |
| **Fatty acids** | Leaves and stem | Harun et al., 2018; Singh et al., 2019a,b; Baharom et al., 2020 |
| **Fatty alcohols** | Leaves | Srinivasan et al., 2008; Baharom et al., 2020 |
| **Flavonoids** | Leaves | Emran et al., 2012a,b; Joshi et al., 2013; Rahman et al., 2013a,b; Mishra et al., 2014; Chander and Vijaychari, 2016; Harun et al., 2016; Ghagane et al., 2017; Patel et al., 2017; Tareq et al., 2017; Singh et al., 2019a,b |
| **Glycosides** | Leaves and stem | Rahman et al., 2013a,b; Ghagane et al., 2017; Tareq et al., 2017 |
| **Megastigmane** | Leaves | Singh et al., 2019a |
| **Phthalic acid esters** | Flowers, leaves and roots | Joshi et al., 2013, Srinivasan et al., 2008, 2009 |
| **Polyphenolic compounds** | Leaves, roots, stem bark and whole plant | Srinivasan et al., 2008; Emran et al., 2012a,b; Joshi et al., 2013; Rahman et al., 2013a,b; Dalu et al., 2014; Mishra et al., 2014; Harun et al., 2016; Ghagane et al., 2017; Patel et al., 2017; Tareq et al., 2017; Singh et al., 2019a |
| **Saponins** | Leaves, roots and stem | Dalue at al., 2014; Harun et al., 2016; Ghagane et al., 2017 |
| **Steroids** | Leaves, roots and stem | Srinivasan et al., 2008; Emran et al., 2012a,b; Joshi et al., 2013; Rahman et al., 2013a,b; Dalu et al., 2014; Harun et al., 2016; Tareq et al., 2017; Singh et al., 2019a |
| **Terpenoids** | Leaves | Srinivasan et al., 2008; Emran et al., 2012a,b; Wong et al., 2012; Joshi et al., 2013; Dalu et al., 2014; Chander and Vijaychari, 2016; Harun et al., 2016, 2018; Singh et al., 2019a |
| **Various** | Leaves and stem | Harun et al., 2018 |

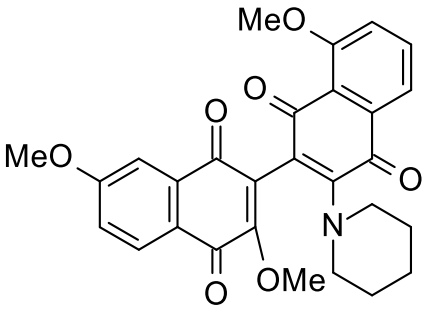



**Figure 2.** 3,8,8-Trimethoxy-3-piperidyl-2,2-binaphthalene1,1,4,4-tetrone in *L. indica*, identified by GC-MS

## Alkanes

Alkanes occur ubiquitously in various plants and are often ignored or discarded by phytochemists when it comes to isolation of bioactive compounds from plant extracts. Srinivasan et al. (2008) identified a series of alkanes in a nonpolar extract of the leaves of *L. indica*, including *n*-eicosane, *n*-heptacosane, *n*-heptadecane, *n*-octadecane, *n*-tetracosane, *n*-tetratetracontane, *n*-tetratriacontane, *n*-tricosane and *n*-tritetracontance.

## Alkenes

Like alkanes, long-chain alkenes are not normally the target compounds in any standard phytochemical isolation protocols. However, they are often identified by GC-MS analysis, usually from nonpolar extracts of plant materials. Srinivasan et al. (2008), and later, Harun et al. (2018) identified a couple of alkenes, *e.g.,* 17-pentatriacontene and 9-octadecene, from the extracts of the leaves and stem of *L. indica* by GC-MS analysis.

## Cardiac glycosides

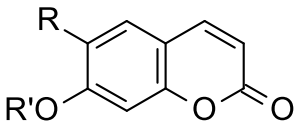
Dalu et al. (2014) and Rahman et al. (2013a,b) showed the presence of cardiac glycosides by preliminary qualitative tests for this type of compounds, but no cardiac glycosides have been isolated and identified from *L. indica* to date.

## Carotenoids

Carotenoids are one of the widely distributed compounds in plants, and often possess a high degree of antioxidant properties (Nahar and Sarker, 2019). Sing et al. (2019a,b) detected carotenoids in different solvent fractions obtained from a methanolic extract of the leaves of *L. indica*, but no purifications for carotenoids have ever been reported for this plant.

## Coumarins

Only one coumarin, esculetin (Figure 3), was reported from the leaves of *L. indica* based on LC-MS analysis (Singh et al., 2019a,b). The distribution of esculetin, like scopoletin, scoparone and umbelliferone, is quite widespread in the plant kingdom.




Esculetin R = OH, R’ = H; Scopoletin R = OMe, R’ = H;

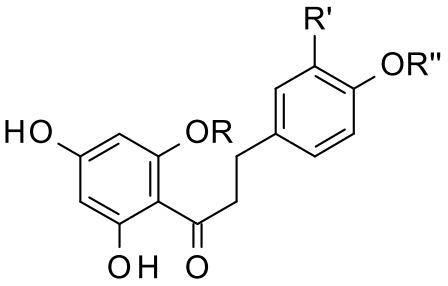
Scoparone R = OMe, R’ = Me; Umbelliferone R = R’ = H

**Figure 3.** Esculetin from the leaves of *L. indica*

## Dihydrochalcones

Singh et al. (2019a) reported dihydrochalcone, 4’,6’-dihydroxy-4-methoxydihydrochalcone 2’-*O*-β-D-glucopyranoside (Figure 4), from the leaves of *L. indica*. A repeated column chromatography approach was adopted for the isolation of this dihydrochalcone, which was identified comprehensively by spectroscopic means. A few other dihydrochalcones, 3-hydroxyphloridzin, phloridzin, 4’,6’-dihydroxy-4-methoxydihydrochalcone 2’-*O*-rutinoside, 4’,6’-dihydroxy-4-methoxydihydrochalcone 2’-*O*-glucosylpentoside, 4’,6’-dihydroxy-4-methoxydihydrochalcone 2’-*O*-(3’’-

*O*-galloyl)-β-D-glucopyranoside and 2',4',6'-trihydroxy-4-methoxydihydrochalcone (3-methylphloretin) (Figure 4), were identified by LC-MS analysis without isolation.




4',6'-Dihydroxy-4-methoxydihydrochalcone 2'-*O*-β-D-glucopyranoside, R = Glucopyranosyl; R' = H; R'' = Me

3-Hydroxyphloridzin R = Glucopyranosyl; R' = OH; R'' = H

Phloridzin R = Glucopyranosyl; R' = R'' = H

4',6'-Dihydroxy-4-methoxydihydrochalcone 2'-*O*-rutinoside, R = Rutinosyl; R' = H; R'' = Me

4',6'-Dihydroxy-4-methoxydihydrochalcone 2'-*O*-glucosylpentoside, R = Glucosyl-pentosyl; R' = H; R'' = Me

4',6'-Dihydroxy-4-methoxydihydrochalcone 2'-*O*-(3''-*O*-galloyl)-β-D-glucopyranoside, R = 3-galloyl-glucosyl; R' = H; R'' = Me

2',4',6'-Trihydroxy-4-methoxydihydrochalcone (3-methylphloretin), R = R' = H; R'' = Me

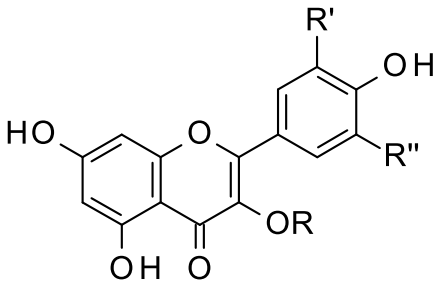
**Figure 4.** Dihydrochalcones from *L. indica*

## Fatty acids and fatty alcohols

Like long-chain alkanes and alkenes, fatty acids and alcohols are quite widespread in the plant kingdom, and they are usually not the subject of isolation and identification in any standard phytochemical work, unless the work specifically aims to purify these compounds for any particular reason. Nonetheless, in the process of isolating other secondary metabolites, some of these fatty acids and alcohols are inadvertently isolated and identified. Also, GC-MS based analysis of plant extracts often reveals the presence of these compounds in the extract. Methyl stearate, oleic acid, 9,12-octadecadienoic acid, 9-oxononanoic acid, palmitic acid and 9,12,13-trihydroxy-octadecadienoic acid, were reported as the major fatty acids in the leaves and stem of *L. indica* (Srinivasan et al., 2008; Harun et al., 2018; Singh et al., 2019a), while 1-eicosanol and farnesol were detected as two main fatty alcohols in the leaves of this plant (Srinivasan et al., 2008).

## Flavonoids

Flavonoids are a large group of phenolic compounds found in several plant families and possess various important medicinal properties (Nahar and Sarker, 2019). Emran et al. (2012a,b) established the presence of flavonoids in the leaves of this plant based on qualitative tests for flavonoids, but no isolation and identification of specific flavonoids was achieved. Similar qualitative result was obtained by a few other researchers (Rahman et al., 2013a,b; Dalu et al., 2014; Mishra et al., 2014; Chander and Vijayachari, 2016; Harun et al., 2016; Ghagane et al., 2017; Tareq et al., 2017). The presence of one of the most common flavonols, quercetin (Figure 5), in an ethanolic extract of the aerial parts of *L. indica* was confirmed by HPTLC analysis (Patel et al., 2017); previously this flavonol was isolated and identified from an ethanolic extract of the roots of this plant (Joshi et al., 2013). Sing et al. (2019a) isolated and identified two flavonoid glycosides, myricetin 3-*O*-rhamnoside and quercetin 3-*O*-rhamnoside from a methanolic extract of the leaves of *L. indica*, while identified several other flavonoids, including epicatechin, epigallocatechin, (-)-epigallocatechin 3-*O*-gallate, gallocatechin, kaempferol, kaempferol 3-*O*-arabinoside, kaempferol 3-*O*-rhamnoside, myricetin (2''-O-gllayl)-3-rhamnoside and quercitrin 2''-gallate, in this extract as a result of detailed LC-MS analysis (Figure 5).



Kaempferol R = R’ = R’’ = H

Kaempferol 3-*O*-arabinoside R = Arabinosyl, R’ = R’’ = H

Kaempferol 3-*O*-rhamnoside R = Rhamnosyl, R’ = R’’ = H

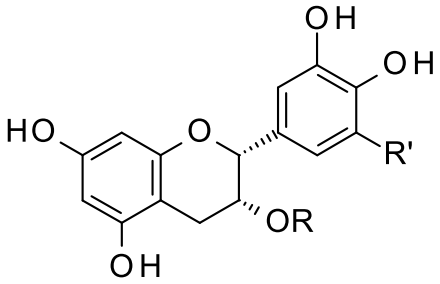
Myricetin 3-*O*-rhamnoside R = Rhamnosyl. R’ = R’’ = OH

Myricetin (2’’-*O*-gllayl)-3-*O*-rhamnoside R = (2’’-*O*-Galloyl)-3-*O*-rhamnosyl, R’ = R’’ = OH

Quercetin R = R’’ = H, R’ = OH

Quercetin 3-*O*-rhamnoside R = Rhamnosyl, R’ = OH, R’’ = H

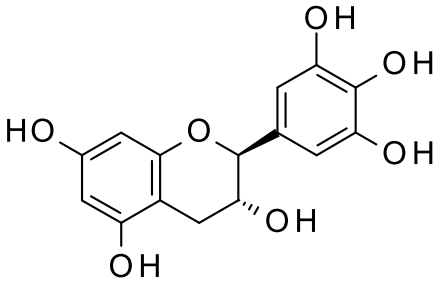
Quercitrin 2’’-gallate R = (2’’-*O*-Galloyl)-3-*O*-rhamnosyl, R’ = OH, R’’ = H



Epicatechin R = R’ = OH

(-)-Epigallocatechin R = H, R’ = OH

(-)-Epigallocatechin 3-*O*-gallate R = Galloyl, R’ = OH



Gallocatechin

**Figure 5.** Major flavonoids in *L. indica*

## Glycosides

Several authors reported the presence of unidentified glycosides in the leaves and stem of *L. indica* (Rahman et al., 2013a,b; Mishra et al., 2014; Ghagane et al., 2017; Tareq et al., 2017) based on qualitative chemical assays for glycosides. Some of these glycosides were eventually identified as mainly dihydrochalcone and flavonoid based glycosides (Singh et al., 2019a) as shown in Figures 4 and 5.

## Megastigmane

Megastigmanes represent a large group of C13 derivatives present in fruits and vegetables, as well as in non-edible plants (Nahar and Sarker, 2019). The only megastigmane that was identified to date in the leaves of *L. indica* is dehydrovomifoliol (Figure 6) (Singh et al., 2019a). However, no attempt was made to isolate and identify this compound from the extract.

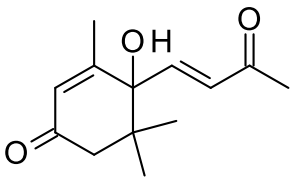


**Figure 6.** Dehydrovomifoliol, the only megastigmane reported from *L. indica*

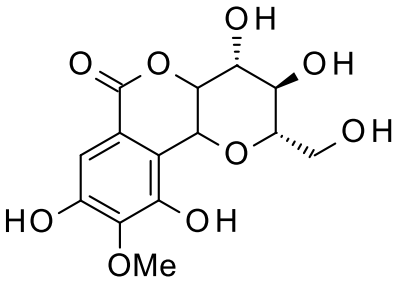
## Phthalic acid esters

Phthalic acid derivatives, including esters, are not necessarily the desired components in phytochemical investigations. Nonetheless, phytochemists often end up with isolating or identifying these compounds in various plant materials. Most often, these compounds are the artefacts that come from various plastic containers, impure

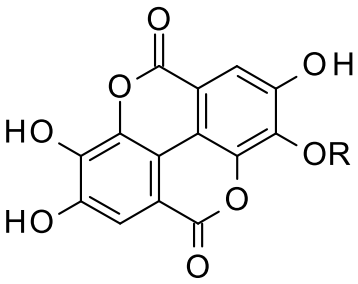
solvents and other sources that the plant materials come in contact with. Di-*n*-butyl-phthalate and di-*n*-octyl-phthalate were reported from the roots of *L. indica*, while di-isobutyl-phthalate, di-*n*-butyl-phthalate, *n*-butyl-isobutyl-phthalate and butyl-isohexyl-phthalate were found in the flowers (Srinivasan et al., 2009). Phthalic acid, di-*n*-butyl-phthalate, butyl-2-ethylhexyl-phthalate and isooctyl- phthalate were identified in the leaves of this plant (Srinivasan et al., 2008).

## Polyphenols

Polyphenols constitute one of the largest groups of bioactive phytochemicals, with high antioxidant capacities (Nahar and Sarker, 2019). In addition to dihydrochalcones, flavonoids and their glycosides, which have already been discussed in the earlier sections, there are several other more complex polyphenolic compounds, often in the form of tannins. There are also several simple polyphenolic compounds found in various plants. Emran et al. (2012a,b) established the presence of polyphenolic compounds like tannins in the leaves of this plant based on qualitative tests for tannins, but no isolation and identification of specific tannins was pursued. Gallic acid and methyl gallate (Figures 7) are two most prevalent simple polyphenolic compounds found in various plant parts of *L. indica* (Joshi et al., 2013; Srinivasan et al., 2008; Patel et al., 2017; Singh et al., 2019a). α-Tocopherol (Figure 7), another well-known natural antioxidant, was found in the roots of this plant (Joshi et al., 2013), while bergenin, ellagic acid and methyl-*O*-ellagic acid (Figure 7) were identified in the leaves by LC-MS (Singh et al., 2019a). Theasinensin A isomers, theasinensin A quinone and theasinensin F (Figure 8) are among the more complex polyphenols reported from the leaves of *L. indica* (Singh et al., 2019a).

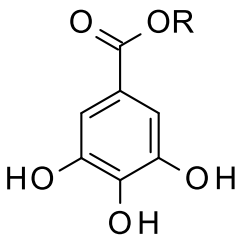



Bergenin



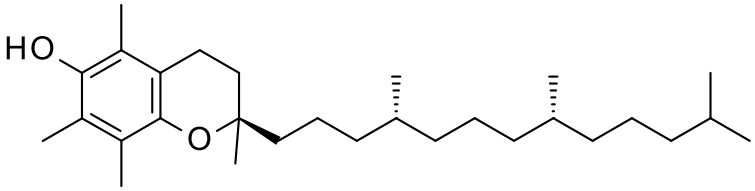

Ellagic acid R = H

Methyl-*O*-ellagic acid R = Me



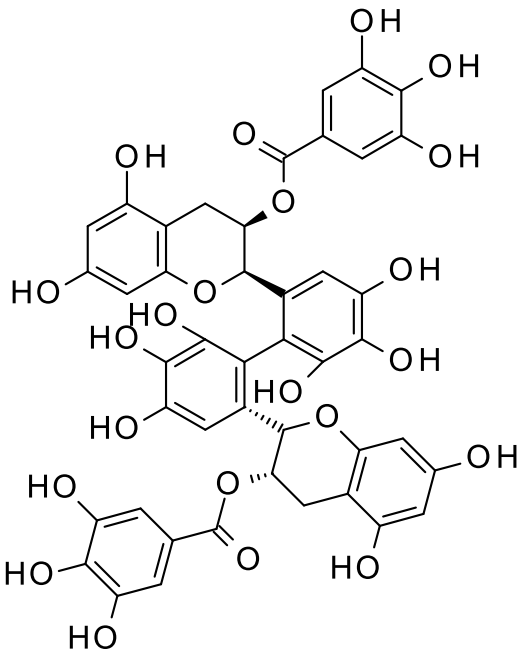

Gallic acid R = H

Methyl gallate R = Me

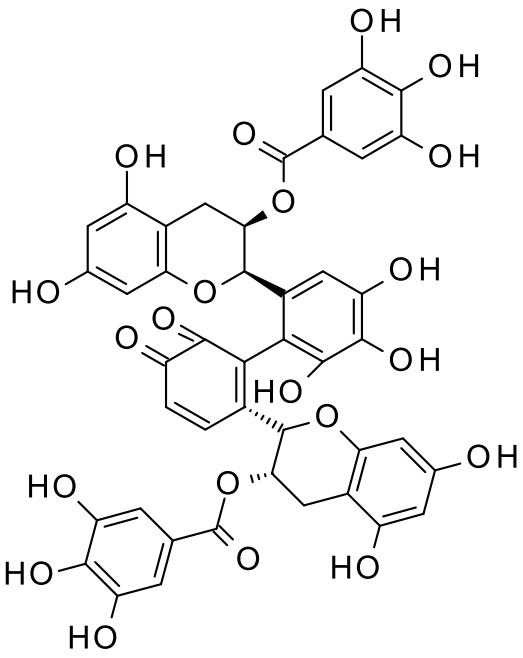



α-Tocophenrol

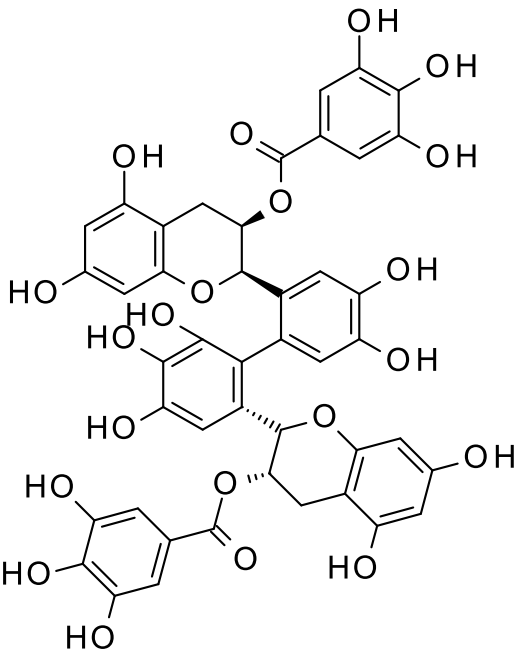
**Figure 7.** Simple polyphenolic compounds present in *L. indica*



Theasinensin A isomers



Theasinensin A quinone



Theasinensin F

**Figure 8.** Complex polyphenolic compounds present in *L. indica*

### Saponins

A number of researchers (Rahman et al., 2013a,b; Dalu et al., 2014; Harun et al., 2016) showed the presence of saponins in the leaves, stem and roots of this plant based on qualitative tests for saponins, but no isolation and identification of specific saponins was performed. It is interesting though, that Emran et al. (2012b) did not detect the presence of saponins in the leaves when they performed the same qualitative test.

### Steroids

Several researchers established the presence of plant sterols in the leaves of this plant based on qualitative tests for steroids, but no isolation and identification of specific steroids was achieved (Emran et al. 2012a,b; Rahman et al., 2013a,b; Dalu et al., 2014; Harun et al., 2016). Joshi et al. (2013) and Srinivasan et al. (2008) isolated β-sitosterol, which is the most distributed sterol in the plant kingdom, respectively, from the roots and leaves of *L. indica*. β-Sitosterol 3-*O*-glucoside was also reported from the roots of this plant (Singh et al., 2019a).

### Terpenoids

Emran et al. (2012a,b) established the presence of terpenoids in the leaves of this plant based on qualitative tests for terpenes without isolation and identification of specific terpenoids. Several other authors also reported the presence of terpenoids based on qualitative tests (Joshi et al., 2013; Dalu et al., 2014; Chander and Vijaychari, 2016; Harun et al., 2016, 2018). However, a few researchers isolated and identified β-amyrin, *O*-hexadecanoyl-β-amyrin, lupeol, mollic acid α-L-arabinoside, mollic acid β-D-xyloside, 2α,3α,23-trihydroxy-12-oleanen-28-oic acid and ursolic acid from various plant parts of *L. indica* (Table 1) (Figure 8) (Srinivasan et al., 2008; Wong et al., 2012; Joshi et al., 2013; Singh et al., 2019a,b).

Various other compounds

Harun et al. (2018) reported the presence of 3,8,8-Trimethoxy-3-piperidyl-2,2-binaphthalene-1,1,4,4-tetrone in the leaves, and 1-(hydroxymethyl)-1,2-ethanediyl ester in the stem of *L. indica*.

## THERAPEUTIC POTENTIAL

### Therapeutic potential of crude extracts and fractions

Pharmacological properties of the extracts and fractions of *L. indica* as established by several studies and published in the literature, are summarized in Table 2.

#### *Analgesic activity*

An ethanolic extract of the leaves of *L. indica* was found to exhibit central and peripheral analgesic effects in mice which could support its traditional uses in the management of pains. The assessment of the analgesic effect of this ethanolic extract was carried out by Emran et al. (2012a), who observed that the extract (200 mg/kg, p.o.) significantly ($p < 0.05$) inhibited the writhing response in acetic acid-induced writhing test compared to the known analgesic diclofenac sodium (40 mg/kg, i.p.). They also found that the extract could suppress the pain response (8.18%) in formalin-induced licking test compared to diclofenac sodium (66.45%; 0.5 mg/kg, i.p.).

#### *Antiangiogenic activity*

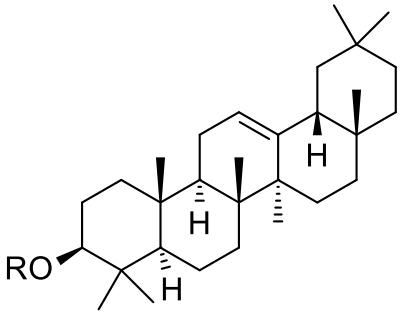
Recombinant vascular endothelial growth factor (rVEGF165) induced *in vivo* chorio alontoic membrane, rat corneal micropocket, and tumour-induced peritoneal angiogenesis assays were used for the preliminary screening of an ethanolic extract of the leaves of *L. indica*. It was found that the crude extract (50 mg/kg) could inhibit the sprouting vessels both in non-tumorigenic and tumorigenic conditions. Inhibition of VEGF expression by the extract contributed for tumour inhibitory effect. It was suggested that the presence of triterpenoids (Figure 8) in the extract might be a contributory factor for this angiomodulatory effect (Avin et al., 2014).

#### *Antidiabetic activity*

Antihyperglycemic activity of alcoholic and hydroalcoholic extracts of *L. indica* leaves was evaluated by the glucose tolerance test and alloxan-induced diabetes model in rats. Both extracts (200 and 400 mg/kg body weight) significantly decreased blood glucose level without displaying any acute toxicity (Dalu et al., 2014). As a result of oral treatment with the alcoholic and hydroalcoholic extracts (200 mg/kg and 400 mg/kg) for 21 days in alloxan-induced diabetic rats, the extracts were shown to have hypolipidemic activity by reducing triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol and elevated high density lipoprotein (HDL) levels (Dalu et al., 2014). Another study demonstrated that a hydroalcoholic extract

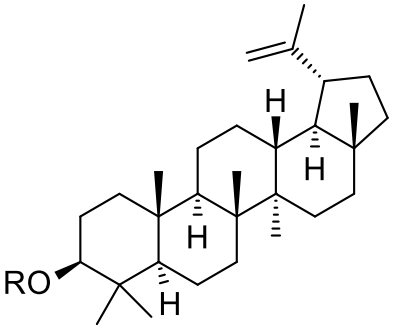
of *L. indica* leaves could significantly increase glucose uptake in isolated rat hemidiaphragm, improve glycogen content and inhibit α-glucosidase enzyme (Dalu and Dhulipala, 2016). A methanolic extract of *L. indica* leaves (200 mg/kg, p.o.) was found to reduce blood glucose levels in alloxan-induced diabetic rats (Patel et al., 2016). A methanolic extract of the leaves was accessed its effect on porcine pancreatic lipase activity, and it was observed that the extract could inhibit the activity of lipase by 48.5% (Ado et al., 2013).

It was suggested that the antihyperglycemic and hypolipidemic properties of *L. indica* could be due to the presence of ursolic acid (Figure 8) and gallic acid (Figure 7), as ursolic acid was reported as an effective insulin-mimetic agent and gallic acid was reported to be an insulin-secretagogue, antihyperlipidemic and antioxidant (Dalu et al., 2014 and Dalu and Dhulipala, 2016).

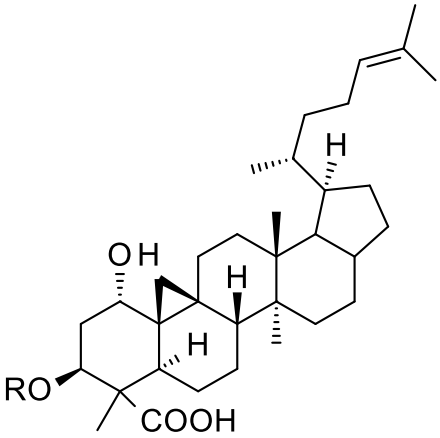



β-Amyrin R = H

*O*-Hexadecanoyl-β-amyrin R = Hexadecanoyl

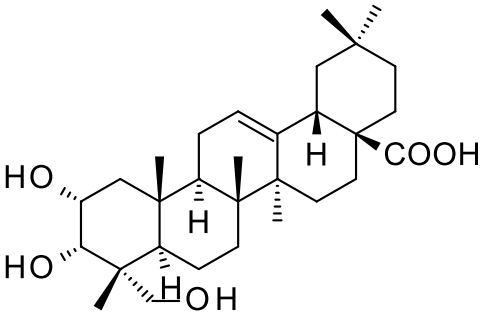



Lupeol

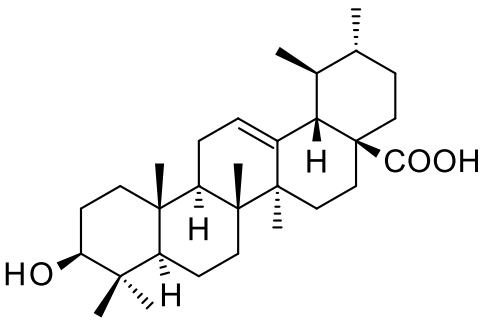



Mollic acid α-L-arabinoside R = Arabinosyl

Mollic acid β-D-xyloside R = Xylosyl




2α,3α,23-Trihydroxy-12-oleanen-28-oic acid




Ursolic acid

**Figure 8.** Major terpenoids present in *L. indica*

**Table 2**| Pharmacological properties of *L. indica*

| Pharmacological properties | Plant parts | Extracting solvents | References |
|---|---|---|---|
| **Analgesic** | Leaves | EtOH | Emran et al., 2012a |
| **Anti-angiogenic** | Leaves | EtOH | Avin et al., 2014 |
| **Antidiabetic** | Leaves | EtOH, MeOH and water extracts | Ado et al., 2013; Dalu et al., 2014; Dalu and Dhulipala, 2016; Patel et al., 2016 |
| **Antidiarrhoeal** | Leaves | MeOH extract | Tareq et al., 2017 |
| **Anti-inflammatory** | Whole plant and leaves | MeOH extract and its *n*-hexane fraction | Saha et al., 2004; Sakib et al., 2021 |
| **Antimicrobial** | Flowers, fruits, leaves, roots and stem | EtOH, MeOH, water and DCM extracts | A;I et al., 1996; Wiart et al. (2004); Srinivasan et al., 2009; Rahman et al., 2013a,b; Razak et al., 2014; Ramesh et al., 2015; Chander and Vijayachari, 2016, 2018;Harun et al., 2016; Rokhade and Taranath, 2016, 2017; Tareq et al., 2017; Mahboob et al., 2020 |
| **Antioxidant** | Whole plant, leaves, | EtOH, MeOH, water extracts, and *n*-hexane, EtOAc and water fractions, | Saha et al., 2004; Emran et al., 2012a,b; Raihan et al., 2012; Reddy et al., 2012; Rahman et al., 2013a,b; Ramesh et al., 2015; Chander and Vijayachari, 2016; Ghahane et al., 2017; Sulistyaningsih et al., 2017; Ismail et al., 2019; |
| **Antiproliferative** | Leaves | EtOH, MeOH, water extracts, and n-hexane, EtOAc and water fractions | Nurhanan et al., 2008; Wong and Kadir, 2011, 2012; Emran et al., 2012a,b; Paul and Saha, 2012; Rahman 2013a,b; Raihan et al., 2012; Reddy et al., 2012; Ghagane et al., 2017; Siew at all., 2019 |
| **Effect on the central nervous system** | Leaves | MeOH extract | Raihan et al., 2011; Sarris et al., 2013; Hosen et al., 2018; Chen et al., 2019 |
| **Hepatoprotective** | Stem bark | EtOH extract | Mishra et al., 2014 |
| **Larvicidal** | Leaves | MeOH extract | Sreedhanya et al., 2017 |
| **Phosphodiesterase inhibitory** | Roots | EtOH extract | Temkitthawon et al., 2008, 2011 |
| **Thrombolytic** | Leaves | EtOH, MeOH extracts and *n*-hexane fraction of MeOH extract | Rahman et al., 2013; Azad et al., 2018; Sakib et al., 2021 |
| **Wound healing** | Aerial parts | EtOH extract | Wan et al., 2016 |

### *Antidiarrhoeal activity*

The antidiarrhoeal activity of a methanolic extract of *L. indica* leaves was assessed by the castor oil-induced diarrhoea in mice (Tareq et al.2017). The extract at the doses of 500 mg/kg and 250 mg/kg significantly reduced the total number of stool as well as increased the latency period of defecation in comparison to the control groups. This appears to be the only antidiarrhoeal study reported on this plant to date.

### *Anti-inflammatory activity*

A methanolic extract of *L. indica* whole plant exhibited strong inhibitory effect of nitric oxide (NO) production in lipopolysaccharide and interferon-$\gamma$ induced mouse macrophage RAW 264.7 cells with percentage of NO inhibition 83.63, 80.42 and 74.91% at concentrations of 250, 125.5 and 62.5 µg/mL, respectively (Saha et al., 2004). Most recently, Sakib et al. (2021) reported that the *n*-hexane fraction of a methanol extract of *L. indica* leaves had a significant dose-dependent inhibition of haemolysis and protein denaturation compared to two non-steroidal anti-inflammatory drugs. This finding was in line with the traditional use of *L. indica* to relieve pain.

### *Antimicrobial activity*

There are a good number of antimicrobial studies with *L. indica* extracts reported in the literature, several of which, however, are of preliminary levels, and based only on agar diffusion assays (Wiart et al., 2004; Chander and Vijayachari, 2016, 2018); some of them showed some antimicrobial activities, whereas the others did not. A methanolic extract of *L. indica* leaves was found inactive against Gram-positive bacteria (*Bacillus cereus*, *Bacillus subtilis, Staphylococcus aureus* and *Staphylococcus epidermidis*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae, Proteus mirabilis, Shigella flexneri* and *Salmonella typhi*) along with fungal strains (*Candida albicans* and *Aspergillus niger*) (Wiart et al., 2004; Chander and Vijayachari, 2016, 2018). However, a similar extract was reported to have antimicrobial activity against four Gram-positive pathogenic bacteria (*B. subtilis*, *B. cereus*, *B. megateriuum* and *S. aureus*), four Gram-negative pathogenic bacteria (*P. aeruginosa*, *S. dysenteriae*, *S. sonnei* and *Vibrio cholera*) and five fungal species (*A. niger*, *Blastomyces dermatitidis*, *C. albicans, Trichophyton spp., Microsporum spp.* and *Cryptococcus neoformans*) (Tareq et al., 2017). Similarly, methanolic extracts of the leaves and stem bark of *L. indica* displayed antifungal activity against fungal strains namely *Colletotrichum capsici*, *Helminthosporium sp*. and *Curvularia sp*. (Ramesh et al., 2015). Inconsistencies in the antimicrobial activities in different studies might be due to the differences in extraction techniques and assay protocols.

An ethanolic extract obtained from leaves of *L. indica* at three different concentrations 1, 2, and 3 mg/disk showed significant ($P < 0.05$) zones of inhibition (9.0-12.0 mm) against Gram-positive bacteria including *B. subtilis*, *S. aureus*, *B. cereus* and *B. megaterium* and Gram-negative bacteria namely *Salmonella typhi*, *Salmonella paratyphi*, *P. aeruginosa*, *Vibrio cholerae*, *Shigella dysenteriae* and *E. coli*, compared to that for the antibiotic tetracycline and ampicillin (16-20 mm) at 30 µg/disc (Rahman, Imran and Islam, 2013a,b). Moreover, this extract at 10 mg/disc inhibited the growth of *Aspergillus flavus*, *C. albicans* and *Fusarium equisetii* by 38.09 ± 0.59%, 22.58 ± 2.22% and 61.82 ± 2.7%, (fluconazole 67.01 ± 1.8%, 40.00 ± 2.5% and 72.32 ± 2.3%, respectively at 100 µg/disc) The minimum inhibitory concentrations (MIC) of the extract for different bacterial strains ranged from 25 to 100 µl/mL.

The essential oil derived from the flowers of *L. indica* demonstrated good antibacterial activity against two Gram-negative bacteria (*E. coli* and *S. typhimurium*), moderate activity against three Gram-positive bacteria (*B. subtilis*, *B. cereus*, and *S. aureus*), good antifungal activity against *Pencillium notatum* and moderate antifungal activity against two fungal strains (*A. niger* and *F. monelliforme*) (Srinivasan et al., 2009). The three largest zones of inhibition were observed with *P. notatum, S. typhimurium*, and *E. coli* (21, 11 and 10 mm, respectively). It was suggested that the antimicrobial effect of the essential oil might be due to the presence of phthalates in higher percentage. A dichloromethane (DCM) extracts of *L. indica* roots, stems and leaves exhibited antibacterial effect against *S. epidermis* and *S. aureus* (Harun et al., 2016); The DCM extract of the leaves at concentration 200 mg/mL produced the largest zone of inhibition (18 mm) against *S. epidermis*. Aqueous extracts of *L. indica* leaves and fruits were used for the synthesis of silver nanoparticles, which exhibited antimicrobial activity in combination of silver nanoparticles with antibiotic against *E. coli*, *S. typhi*, *S. aureus* and *B. subtilis* (Rokhade and Taranath, 2016; Rokhade and Taranath, 2017).

The only antiviral activity of *L. indica* was reported from an ethanolic extract of the leaves against *Herpes simplex* virus type-1 with an MIC value of 0.05 mg/mL (Ali et al., 1996). However, the extract was ineffective against *vesicular stomatitis* virus.

### *Antioxidant activity*

A methanolic extract obtained from the whole plant of *L. indica* was analysed for antioxidant activity using the ferric thiocyanate, thiobarbituric acid and DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging methods, and strong antioxidant activity was observed in all assays (Saha et al., 2004). Similarly, an ethanolic extract of *L. indica* leaves, and its *n*-hexane, ethyl acetate and water fractions were assessed for antioxidant property by the DPPH radical-scavenging, reducing power and superoxide dismutase (SOD) activity assays. Water fraction showed the strongest

DPPH radical-scavenging activity with an $EC_{50}$ value of 48.0 µg/mL compared to that of ascorbic acid (AA) 15.0 µg/mL, a significantly ($p < 0.05$) higher reducing power with 2.70 ± 0.02 compared to AA 2.73 ± 0.03 at 0.8 mg/mL and the strongest inhibition rate ($p < 0.05$) in the SOD assay which could be attributed by the high content of phenolic compounds in water fraction (Reddy et al., 2012). Similar antioxidant activity of an ethanolic extract was also reported by Rahman et al., (2013a,b), where a strong DPPH-radical scavenging activity ($IC_{50}$ = 139.83 ± 1.40 µg/mL compared to AA $IC_{50}$ 1.46 ±0.06 µg/mL) was observed. Additionally, the ethanolic extract displayed $FeCl_3$ reduction with $IC_{50}$ = 16.48 ± 0.64 µg/mL compared to AA $IC_{50}$ = 14.04 ± 1.20 µg/mL and superoxide radical scavenging effect 49.54 ± 0.51% with $IC_{50}$ = 676.08 ± 5.80 µg/mL, compared to curcumin with $IC_{50}$ = 60.48 ± 0.53%, along with less potent iron chelating activity with $IC_{50}$ = 519.33 ± 16.96 µg/mL compared to AA $IC_{50}$ = 8.81 ± 0.90 µg/mL.

Ghagane et al. (2017) reported that the methanolic extract of the leaves of *L. indica* had higher antioxidant activity than the ethanolic and aqueous extracts in the DPPH, ferric ion reducing power and phosphomolybdenum assays. The aqueous and methanolic extracts of the leaves showed prominent effects in the DPPH assay with the $IC_{50}$ values of 0.27 and 0.28 mg/mL, respectively, using gallic acid as the control ($IC_{50}$ = 0.28 mg/mL) (Ismail et al., 2019). There are several other similar DPPH assay-based antioxidant activity assessments of *L. indica* reported in the literature (Emran et al., 2012; Raihan et al., 2012; Ramesh et al., 2015; Chander and Vijayachari, 2016; Sulistyaningsih et al, 2017 and Chen et al., 2019). Different research suggested that the antioxidant potential of *L. indica* could be due to the presence of phenolic compounds as well as some alkaloids, terpenoids, sterols, saponins (Emran et al., 2012; Reddy et al., 2012; Ghagane et al.,2017; Chen et al., 2019). It is well-established that phenolic compounds possess antioxidant activity due to their redox properties which allow them to act as reducing agents, hydrogen donors, singlet oxygen quenchers or metal chelators (Liang et al., 2010 and Luna-Guevara et al., 2018).

***Antiproliferative activity***

*In vitro* assessment of antiproliferative activity of plant extracts against cancer and tumour cell lines, often in the MTT or sulforhodamine-B assays, generally provides indications about their potential anticancer and antitumour activities. In a sulforhodamine-B assay, conducted by Nurhanan et al. (2018), using methanol extracts of the leaves and stem bark of *L. indica*, but no noticeable antiproliferative activity was observed against the MCF-7 and T47D breast cancer cell lines ($IC_{50}$ > 100 µg/mL in both cell lines). Similar inactivity was observed in several other studies using the MTT assay. A crude ethanol extract and its fractions (ethyl acetate, *n*-hexane and water) were tested against Ca Ski, MCF-7, MDA-MB-435, KB, HEP G2, WRL 68 and Vero cell lines by the MTT assay, and except for the activity of ethyl acetate (EtOAc) fraction of the ethanol (EtOH) extract against Ca Ski cervical cancer cells ($IC_{50}$ = 85.83 ± 6.01 µg/mL), none of the other fractions or extracts demonstrated significant activity against any of the cell lines as demonstrated by their $IC_{50}$ values of >180 µg/mL. However, the EtOAc fraction was found to decrease cell viability of MCF-7, KB, MDA-MB-435, KB, HEP G2 and WRL 68 cells, and to induce apoptosis via nuclear shrinkage, chromatin condensation, increase in sub-G1 cells, DNA fragmentation, intracellular GSH depletion and caspase-3 activation (Wong and Kadir, 2011). Extracts and fractions were evaluated against three human colon cancer cell lines, HT-29, HCT-15 and HCT-116, but no antiproliferative activity could be observed (Reddy et al., 2012). Similarly, an EtOH extract of the leaves of *L. indica* revealed no significant antiproliferative activity against Vero cells (Wong and Kadir, 2011) and HeLa cells (Ali et al.,1996). Nonetheless, a moderate cytotoxic activity was observed against MCF-7 cell line (Azad et al., 2018).

Ghagane et al. (2017), using the MTT assay, showed *in vitro* cytotoxicity of three different extracts (EtOH, MeOH and water) of the leaves of *L. indica* against two human prostate cancer cell lines, DU-145 and PC-3, while no cytotoxicity was observed on normal mice embryo fibroblast cell line (MEF-L929). Among the extracts, the methanolic extract inhibited human prostate cancer cell lines DU-145 and PC-3 with $IC_{50}$ values of 529.44 ± 42.07 µg/mL and 547.55 ± 33.52 µg/mL, respectively. The $IC_{50}$ values, although the authors claimed cytotoxicity, could not establish that the extracts were really cytotoxic, as the $IC_{50}$ values were well above 100 µg/mL, which would not usually be considered as cytotoxic for any anticancer drug development purposes.

In a recent study, the antiproliferative activity of seven medicinal plants including *L. indica* leaves using water soluble tetrazolium salt (WST-1) assay was evaluated on twelve human cancer cell lines derived from breast (MDA-MB-231, T47D), cervical (C33A), colon (HCT116), leukaemia (U937), liver (HepG2, SNU-182, SNU-449), ovarian (OVCAR-5, PA-1, SK-OV-3) and uterine (MES-SA/DX5) cancer. All leaf extracts of *L. indica* demonstrated strong or moderately strong antiproliferative activity against almost all cell lines tested. However, not all leaf extracts were active against leukaemic U937 cells. The most effective one was the methanolic extract of *L. indica* with the $IC_{50}$

values of 31.5 ± 11.4 µg/mL, 37.5 ± 0.7 µg/mL and 43.0 ± 6.2 µg/mL in cervical C33A, liver SNU-449, and ovarian PA-1 cancer cell lines, respectively (Siew at all., 2019).

An ethanolic extract of the leaves of *L. indica* displayed brine shrimp toxicity (not really cytotoxicity as described by the authors) at lethal concentrations ($LC_{50}$) of 2.48 µg/mL (Emran et al., 2012; Paul and Saha, 2012), 2.65 ± 0.16 µg/mL (Rahman et al., 2013a, 2013b) and 170.86 µg/mL (Azad et al., 2018). However, brine shrimp lethality assay, although not an assay that could provide any cytotoxicity data, is often incorrectly used to assess cytotoxicity of plant extracts and compounds. This assay merely shows the lethality against brine shrimp, which can be attributed by various factors, but not necessarily only because of cytotoxicity.

*In vivo* antitumour activity of a methanolic extract of the *L. indica* leaves was assessed against Ehrlich Ascites Carcinoma (EAC) cells in Swiss albino mice. The results demonstrated that the extract at a dose of 40 mg/kg, i.p. displayed maximum antitumour activity with 77.29% of cell growth inhibition compared to the positive control bleomycin with 92.02% of cell growth inhibition (0.3 mg/kg, i.p.). A reduction in the tumour weight (7.90 g) was also observed as was an enhancement of the life span by 69.33%. The positive control bleomycin at a dose of 0.3 mg/kg (i.p.) showed 7.05 g of tumour weight reduction and 94.66% ($p < 0.01$) increase in life span (Raihan et al., 2012).

***Central nervous system (CNS)- affecting activity***

A methanolic extract of the leaves of *L. indica* showed CNS-affecting properties as evidenced from its sedative and anxiolytic (Raihan et al., 2011) and anti-amnesic effects (Chen et al., 2019). Administrations of the extract at the doses of 200 and 400 mg/kg displayed dose-dependent anxiolytic effects (in hole cross and open-field tests), and suppression of motor activity and prolongation of thiopental-induced sleeping time. As *L. indica* leaves contain ursolic acid, eicosanol, farnesol and β-sitosterol which are γ-aminobutyric acid type A (GABAA) agonists, those phytochemicals could be responsible for the above CNS-depressant effects of this plant (Raihan et al., 2011). The extract at 500 mg/kg, p.o., exerted anti-amnesic effect on scopolamine-induced amnesia of Alzheimer's type in rats and significantly modulated the induced memory deficits, which could be related to its anti-acetylcholinesterase, antioxidant and anti-inflammatory activities (Chen et al., 2019). Combined molecular docking and molecular dynamics-based techniques were used to find a potent inhibitor of BACE1 (beta secretase 1) from the components derived from *L. indica*, and this study explored lupeol as a potential lead molecule for a new therapeutic agent for Alzheimer's disease (Hosen et al., 2018). However, the conclusion was somewhat premature as appropriate *in vitro* and *in vivo* studies are necessary before this *in silico* study-based assumption could be substantiated.

Sarris et al. (2013) reviewed plant-based medicines for anxiety disorders on the basis of preclinical trials and found that *L. indica* could be useful to treat this disorder. It was suggested that the plausible mechanism of action could involve GABA either via direct receptor binding or ionic channel or cell membrane modulation.

***Hepatoprotective activity***

Generally, plants that contain high amounts of antioxidant compounds tend to offer hepatoprotective activity through mitigating damages caused by oxidative stress. An ethanolic extract of the stem bark of *L. indica* displayed hepatoprotective activity against paracetamol-induced hepatotoxicity *in vivo* in rats. The treatment of mice with the extract at two doses (200 mg/kg and 400 mg/kg body weight) could significantly reduce the elevated levels of serum marker enzymes, bilirubin and triglycerides, when compared to the positive control group (Mishra et al., 2014). As this plant is known to produce antioxidant phytochemicals, it was inferred that those antioxidants could be responsible for the hepatoprotective effect observed in the study.

***Larvicidal activity***

Larvicidal activity is desirable for pest (insect) control, a good example of which is the larvicidal activity of a methanolic extract of the leaves of *L. indica* was against *Culex quinquefasciatus* mosquitos (Sreedhanya et al., 2017).

***Phosphodiesterase (PDE) inhibitory activity***

An ethanolic extract of the roots of *L. indica* was screened for its PDE inhibitory activity using a radioactive-assay (Temkitthawon et al., 2008). The extract at a concentration of 0.1 mg/mL showed high PDE-inhibitory effect with an $IC_{50}$ value of 2.62 ± 0.25 µg/mL, compared to that of the known PDE inhibitor 3-isobutyl-1-methylxanthine ($IC_{50}$ 0.68 ± 0.14 µg/mL). In addition, this extract displayed a 31.36 ± 7.47% PDE-5 inhibition in the two-step radioactive assay (Temkitthawon et al., 2011).

### *Thrombolytic activity*

Potential thrombolytic property of an ethanolic extract of the leaves of *L. indica* was assessed as the clot-lysis effect (39.3 ± 0.96%) and compared with the effect offered by the positive control drug streptokinase (Rahman et al., 2013). Later, Sakib et al. (2021) demonstrated that the *n*-hexane fraction from the MeOH extract could exhibit significant thrombolytic activity (32.58 ± 1.18%). Previously, however, another study revealed a moderate level of clot-lysis activity of an ethanolic extract (07.24 ± 0.15%) (Azad et al., 2018). It was suggested that the observed thrombolytic effects might be linked to the antibacterial activity of this plant (Rahman et al., 2013).

### *Wound healing activity*

An ethanolic extract of the aerial parts of *L. indica* was found to possess diabetic wound healing property, as revealed from the scratch assay using NIH 3T3 mouse fibroblast and Raw 264.7 mouse macrophage cells (Wan et al., 2012). The extract could enhance the migration of the cells towards the closure of the gap, and thus heal the wound. It was assumed that the activity might be associated with high antioxidant activity offered by tannins present in the extract.

### *Various other activities*

An *n*-hexane fraction of a methanolic extract of the leaves of *L. indica* leaves exhibited hair growth-promoting activity (Sakib et al. 2021). When applied on the mice skin at the concentrations of 10, 1, 0.1%, it demonstrated a significant increase in average hair length ($p < 0.001$) compared with untreated animals. This fraction at a concentration of 1% exhibited the highest percentage of hair regrowth on day 7, 14 and 21 (81.24, 65.60, and 62.5%, respectively). The DCM, MeOH and water extracts of *L. indica* leaves were tested for antiplasmodial activity against chloroquine resistant *Plasmodium falciparum* by using HRP2 assay, but the activities were weak or inactive ($EC_{50}$ > 15.7 µg/mL) (Mohammadd Abdur Razak et al., 2014). Nonetheless, the methanolic extract of *L. indica* leaves demonstrated antimalarial activity in a malaria-induced mice model (the 4-day suppressive test) (Sulistyaningsiha et al., 2017). Mahboob et al. (2020) reported amoebicidal activity of the water and butanol fractions of the EtOH extract of the leaves against trophozoites and cysts.

## Therapeutic potential isolated compounds

Most of the studies aiming at assessing the therapeutic potential of *L. indica* were confined to preliminary *in vitro*, and some *in vivo* animal assays with crude extracts and their solvent fractions, without any major efforts in conducting bioassay-guided isolation of active therapeutic agents from this plant. Phytochemical studies were mainly qualitative phytochemical screening for detecting the presence of certain groups of phytochemicals, with some GC-MS and LC-MS analyses of active extracts/fraction tentatively identifying the presence of some phytochemicals as discussed in the previous sections. Only a handful of reports are available on proper isolation and identification of active compounds from this plant. Also, there could hardly any attempts be observed to assess the therapeutic potential of purified compounds from active extracts/fractions.

One of the major bioactivity studies with isolated compounds from *L. indica* was conducted by Wong's group (Wong et al., 2012; Wong and Kader, 2012). Two cycloartane triterpenoid glycosides, mollic acid α-L-arabinoside and mollic acid β-D-xyloside (Figure 7) were isolated from the active EtOAc fraction of *L. indica* leaves. Both identified compounds inhibited the growth of Ca Ski cells with $IC_{50}$ value of 19.21 and 33.33 µM, respectively. Compared to the MRC5 cell line, both terpenoids were between 4-8 fold more cytotoxic, respectively, to Ca Ski cells. The cytotoxicity of mollic acid α-L-arabinoside was associated with a decrease in proliferating cell nuclear antigen gene expression, cell cycle arrest at S and G2/M phases, as well as induction of hypodiploid cells (Wong, Kadir and Ling, 2012). This compound induced mitochondrial-mediated apoptosis in Ca Ski cells by promoting upregulation of Bax and downregulation of Bcl-2 (Wong and Kadir, 2012). It is interesting to note that despite the extracts and fractions of *L. indica* not showing any significant antiproliferative activity ($IC_{50}$ = >100 µg/mL), these isolated triterpenes from weakly active EtOAc fraction of the methanolic extract showed quite prominent cytotoxicity against certain cell lines. Several other triterpenes (Figure 8) reported from *L. indica*, *e.g.*, α-amyrin, lupeol and ursolic acid, are well-known for their bioactivities including antiproliferative activity (Nahar and Sarker, 2019), and thus, their presence in *L. indica* might provide some rationale behind the traditional use of this plant in the treatment some forms of cancers and tumours. However, much more work is needed, especially structured pre-clinical and clinical trials before the true therapeutic efficacy of *L. indica* extracts and their major bioactive compounds can be established conclusively.

*L. indica* has been shown to possess several phenolic and polyphenolic compounds including dihydrochalcones, flavonoids and tannins, which are generally well-known for significant antioxidant property (Nahar and Sarker, 2019).

Although most of these compounds were identified by LC-MS data analyses, some of those compounds, *e.g.,* ellagic acid, gallic acid and quercetin, were purified and tested for *in vitro* antioxidant activities. However, some non-phenolic compounds were also isolated as the major contributors for the antioxidant property of the extracts of *L. indica*. For example, a recent investigation of the tentative antioxidative constituents from stem and leaves extracts of *L. indica* revealed the presence of 1-(hydroxymethyl)-1,2-ethanediyl ester (LI-1), 9-oxononanoic acid methyl ester, 9,12-octadecadienoic acid methyl ester and 3',8,8'-trimethoxy-3-piperidyl-2,2'-binaphthalene-1,1',4,4'-tetrone as antioxidant components (Baharom et al., 2020).

Antiamoebic activity of *L. indica* was attributed to gallic acid. Gallic acid encapsulated in the PLGA nanoparticles exhibited 90% inhibition against trophozoites and reduced cytotoxicity towards MRC-5 compared to gallic acid. In the assessment of antidiabetic potential of this plant, it was suggested that the antihyperglycemic and hypolipidemic properties of *L. indica* could be due to the presence of ursolic acid and gallic acid, as ursolic acid was reported as an effective insulin-mimetic agent and gallic acid was reported to be an insulin-secretagogue, antihyperlipidemic and antioxidant (Dalu et al., 2014 and Dalu and Dhulipala, 2016). Again, there is no report on any bioassay-guided isolation of antidiabetic compounds and subsequent assessment for antidiabetic therapeutic potential of those compounds. However, as one of the mechanisms for antidiabetic actions is directly linked to reduction of oxidative stress, the presence of high amounts of antioxidant compounds in *L. indica*, could be a major contributor for its antidiabetic activity.

In an *in silico* study, two triterpenoids, ursolic acid and lupeol, isolated from *L. indica*, were identified as potent BACE1 inhibitor from a manually curated dataset of *L. indica* molecules, which might offer a novel direction for designing novel BACE1 inhibitors as therapeutic options for Alzheimer disease (Hosen et al., 2018).

## CONCLUSIONS

Preliminary in vitro and some in vivo studies involving animal models with the extracts and fractions of L. indica provided some scientific basis for traditional therapeutic applications of this plant. The presence of certain bioactive compounds in the extracts and fractions could further support therapeutic potential and traditional medicinal uses of this plant. However, more extensive phytochemical work leading to isolation of active compounds, and subsequent assessment of their therapeutic efficacy in relation to certain disease conditions is still needed. Although this plant is still in use in traditional medicinal practices in Asia, and present in some of the traditional medicinal preparations, well-designed pre-clinical and clinical studies are essential before any recommendations could be made on the efficacy and safety of L. indica-based therapeutic interventions.

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## CONFLICT INTEREST

The author declares no personal or financial conflict of interest related to this work.

## AUTHORS CONTRIBUTION

(C.K.) (L.N.) (K.J.R.) (S.D.S.) Conceptualization, Methodology, Formal analysis, Investigation, Writing, Review & Editing.

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