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REVIEW ARTICLE

Pharmacological Activities of *Borassus flabellifer* L. Extracts and Isolated Compounds

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HIGHLIGHTS

> Clinical, in vivo, and in vitro scientific evidence is currently available for various pharmacological activities
> *B. flabellifer* possesses anthelmintic, antiarthritic, antibacterial, anticancer, antidiabetic, antifungal, anti-inflammatory, antioxidant, antipyretic, diuretic, hypersensitivity, immunomodulatory, and wound healing activities
> So far, eight pharmacological active compounds have been isolated (Six antidiabetic, one antioxidant, and one antibacterial compounds).

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ABSTRACT

The purpose of this systematic review work is to evaluate, summarize, and document the scientific findings of the pharmacological activities of *Borassus flabellifer* L. The major electronic databases (Web of Science, Scopus, ScienceDirect, and PubMed) have been employed to identify related publications published from 1900 to April 2021. In this review, only reported pharmacological activities-related publications were considered to extract the data. Clinical, in vivo, and *in vitro* pharmacological scientific evidence is currently available for this plant species, and various parts of *B. flabellifer* showed anthelmintic, antiarthritic, antibacterial, anticancer, antidiabetic, antifungal, anti-inflammatory, antioxidant, antipyretic, diuretic, hypersensitivity, immunomodulatory, and wound healing activities. Hitherto, seven bioactive compounds have been identified from *B. flabellifer*. Only, some uses of *B. flabellifer* in traditional medicine have scientific evidence at the moment. This review highlighted the reported pharmacological importance and discussed the more important reported pharmacological studies of *B. flabellifer*.

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1. Introduction

Borassus flabellifer L. [synonyms: *B. flabelliformis* L.; *B. sundaicus* Becc.; *B. tunicatus* Lour.; *Lontarus domestica* Gaertn.; *Pholidocarpus tunicatus* (Lour.) H.Wendl.; and *Thrinax tunicata* (Lour.) Rollisson] is a tree (Figure 1), that grows up to 20 m in height. This plant species belongs to the *Arecaceae* family. It is called Panai (பனை) in Tamil and palmyra palm in English. Furthermore, this plant species is native to Bangladesh, Cambodia, India, Sri Lanka, Vietnam, Myanmar, Laos, and Indonesia and has been introduced into Asian countries like Malaysia, Yemen, and Thailand, and Mauritania (Africa). *B. flabellifer* is usually distributed in the coastal areas and could be found in areas up to 800 m elevations from the sea level. This plant species prefers sandy or alluvial soils dominate the region with permanent soil moisture such as flood plains and river valleys [1].

B. flabellifer is a multipurpose tree and almost all parts of this plant species are used for different purposes such as food, medicine, and others. In terms of edible uses, the flowers are used to prepare different food items including palm wine, jaggery, treacle, sugar, soup, and curry [1–3] and the fruits are used to prepare pickle, curry, and drink [3–5]. Moreover, the leaves are used to produce salt [3, 6] and seeds are also used to prepare foods [3, 5]. Apart from these edible uses, the stems are used for construction and making boats and used as a fuel and charcoal making source [5, 7]. The leaves are used to prepare roof, wall, weaving, containers, writing materials, fiber, and fuel [2, 5, 7]. Also, the bark is used as dentifrice [8].

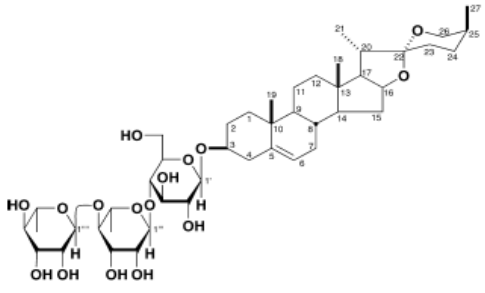
Various parts of *B. flabellifer* are used to treat various disorders in traditional medicines and they have been used to treat abscess, anemia, asthma, constipation, cough and various pulmonary complaints, dermatitis, diabetes, diarrhea, dysentery, dysuria, fever, flatus, general debility, gonorrhea, heartburn, hiccup, hyperdipsia, hypertension, indigestion, inflammations, liver problems, nasal complaints, nausea, phlegm, stomach pain, stomach ulcer, typhoid, and vomiting [4, 7–27]. Besides, compounds including borassoside A to F; uracil; nicotinamide; 2,3,4-trihydroxy-5-methyl acetophenone; and (17α)-23-(E)-dammara-20,23-diene-3β,25-diol have been isolated from *B. flabellifer* (Figure 2) [10, 28, 29].

The purpose of this systematic review work is to evaluate, summarize, and document the scientific findings of the pharmacological activities of *B. flabellifer*. This work will highlight the findings related to the pharmacological activities of this plant species. Further, this work will be useful for the researchers who are interested to conduct more pharmacological and phytochemical researches using various parts of this plant species.

Figure 1 A *B. flabellifer* tree at Palmyra Research Institute, Sri Lanka

2. Materials and Methods

The major electronic databases (Web of Science, Scopus, ScienceDirect, and PubMed) have been employed to identify related publications published from 1900 to April 2021. The accepted and synonym scientific name "*Borassus flabellifer*", "*Borassus flabelliformis*", "*Borassus sundaicus*", "*Borassus tunicatus*", "*Lontarus domestica*", "*Pholidocarpus tunicatus*" and "*Thrinax tunicata*" (enclosed with quotation marks) was used as the search term in this work. In this review, only reported pharmacological activities-related publications were considered to extract the data.



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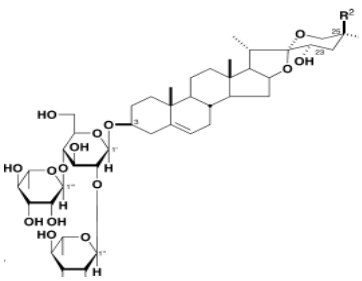

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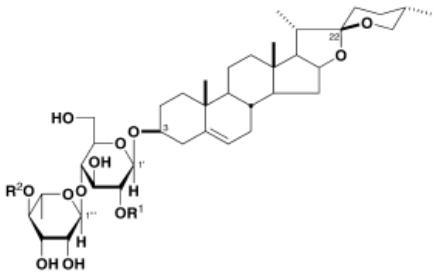
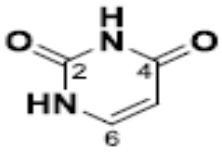


Borassoside D, E, F



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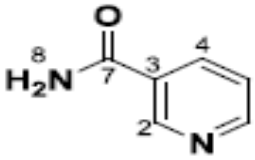
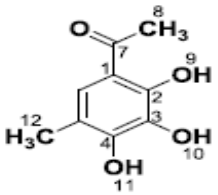
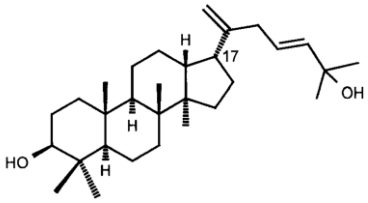


Nicotinamide



2,3,4-trihydroxy-5-methyl acetophenone



(17α)-23-(E)-dammara-20,23-diene-3β,25-diol

Figure 2 Isolated phytocompounds from various part of *B. flabellifer* [10, 28, 29]

3. Results and Discussion

3.1. Reported Pharmacological Activities of *B. flabellifer*

Level of scientific evidence, pharmacological activity, partly used, extract/compound, assay/model/human subject, dose/concentration, duration, positive control, and dose/concentration of positive control of reported pharmacological activities of *B. flabellifer* are presented in Table 1. Clinical, in vivo, and in vitro scientific evidence is currently available in various parts of this plant species. Although, there is more in vitro evidence followed by *in vivo* and clinical evidence.

Moreover, various parts of *B. flabellifer* showed anthelmintic [30], anti-arthritic [31], antibacterial [10, 32–38], anticancer [39], antidiabetic [28, 40–45], antifungal [35, 36], anti-inflammatory [31, 46–49], antioxidant [8, 34, 36, 45, 50–56], antipyretic [48], diuretic [57], hypersensitivity [29], immunomodulatory [58, 59], and wound healing [32, 60] activities. Anyhow, antioxidant activity has the highest number of studies.

Flower, fruit, leaf, root, seed, and tuber of this plant species exhibited pharmacological activities. However, the flower showed the greatest number of pharmacological activities including antibacterial, antioxidant, anti-arthritic, antidiabetic, anti-inflammatory, antipyretic, and immunomodulatory activities. Various extracts such as acetone, chloroform, ethanol, ethyl acetate, hexane, petroleum ether, methanol, and water unveiled pharmacological activities. Anyway, ethanol extract displayed pharmacological activities in the majority of studies. So far, seven bioactive compounds have been identified from *B. flabellifer* and 2,3,4-trihydroxy-5-methyl acetophenone exposed antibacterial and antioxidant activities [10], and borassosides A to F revealed antidiabetic activity [28].

Some uses of *B. flabellifer* in traditional medicine have scientific evidence at the moment. For example, both flower and root are used to treat diabetes in traditional medicine [23, 61], provided scientific evidence by exhibiting antidiabetic activities [13, 31, 41, 42, 45, 47, 48]. On one hand, there is no scientific evidence for some of the traditional medicinal uses of *B. flabellifer*. For example, anemia, asthma, constipation, convalescent, hemorrhage, hypertension, indigestion, and malaria. On the other hand, there is scientific evidence for few reported traditional medicinal uses. For example, anti-arthritic, anticancer, and immunomodulatory activities. Only remarkable reported pharmacological activities which have the highest level of scientific evidence at the reduced concentrations/doses are discussed in detail below.

3.2. Clinical Studies

3.2.1. Antidiabetic activity

An extract from immature endosperm at a concentration of 200mL was administered against randomly selected 30 numbers of type 2 diabetic patients for twenty-eight days and discovered that immature endosperm is a good diet for diabetic patients. In this study, the positive control used was not mentioned [62].

Table 1 Reported pharmacological activities of *B. flabellifer*

Level of scientific evidence	Pharmacological activity	Part used	Extract / compound	Assay / model / human subject	Dose / concentration	Duration	Positive control	Dose / concentration	Reference
Clinical	Antidiabetic	Seed	Methanol: ethanol (1:1)	Type 2 diabetic patient	200 mL	4 week	Not stated (NS)	NS	[62]
Clinical	Wound healing	Fruit	NS	Patient with wound	4 mg/mL	1 week	Metronidazole	NS	[60]
In vivo	Antiarthritic	Flower	Ethanol	Freund's complete adjuvant-induced poly arthritis	200 mg/kg	21 d	Diclofenac sodium	100 mg/kg	[47]
In vivo	Anticancer	Root	Methanol	Human colorectal cancer cell	1 µg/mL	4 week	NS	NS	[39]
In vivo	Anticancer	Root	Methanol	Mouse	12.5 µg/mL	4 week	Docetaxel	20 mg/kg	[39]
In vivo	Antidiabetic	Flower	Ethanol	Rat	200 mg/kg	10 d	Glibenclamide	2.5 mg/kg	[45]
In vivo	Antidiabetic	Flower	Borassoside A, Borassoside B, Borassoside C, Borassoside D, Borassoside E, and Borassoside F	Rat	250 mg/kg	30 min	Dioscin	12.5 mg/kg	[28]
In vivo	Antidiabetic	Fruit	Methanol	Streptozotocin-induced diabetic	100 mg/kg	21 d	Glibenclamide	5 mg/kg	[43]
In vivo	Antidiabetic	Root	Ethanol	Alloxan-induced diabetic	250 mg/kg	21 d	Glibenclamide	10 mg/kg	[41]
In vivo	Antidiabetic	Root	Ethanol, petroleum ether	Alloxan-induced diabetic	100 mg/kg	28 d	Glibenclamide	5 mg/kg	[42]
In vivo	Anti-inflammatory	Flower	Ethanol	Acetic acid-induced writhes	150 mg/kg	15 min	Indomethacin, Morphine	10 mg/kg	[57]
In vivo	Anti-inflammatory	Flower	Ethanol	Carrageenan-induced	150 mg/kg	3 h	Diclofenac Sodium	100 mg/kg	[31]
In vivo	Anti-inflammatory	Flower	Ethanol	Nystatin-induced rat paw edema	200 mg/kg	72 h	Diclofenac sodium	100 mg/kg	[47]
In vivo	Anti-inflammatory	Leaf	Chloroform	Mouse	200 mg/kg	6 d	Diclofenac	10 mg/kg	[46]
In vivo	Antipyretic	Flower	Ethanol	Mouse, rat	150 mg/kg	5 h	Aspirin	200 mg/kg	[48]
In vivo	Diuretic	Tuber	Ethanol	Rat, mouse	200 mg/kg	5 h	Furosemide	100 mg/kg	[57]
In vivo	Antidiabetic	Flower	Aqueous, chloroform, petroleum ether	Streptozocin-induced diabetic	150 mg/kg	2 h	Glibenclamide	10 mg/kg	[40]
In vivo	Immunomodulatory	Flower	Ethanol	Mouse	300 µg/mL	26 d	Dextran	300 µg/mL	[59]
In vivo	Immunomodulatory	Tuber	NS	Rat	33 µg/mL	7 week	NS	NS	[58]
In vivo	Wound healing	Leaf	Methanol	Rabbit	10% (w/w)	15 d	Cetrimide	0.5% w/w	[32]
In vivo	Hypersensitivity	Tuber	Ethyl acetate	Mouse	0.04 mg/kg (ED50)	5 h	Cyclosporin A	NS	[29]
In vitro	Anthelmintic	Leaf	Methanol	Pheretima posthuma	10 mg/mL	NA	Albendazole	10 mg/mL	[30]

Level of scientific evidence	Pharmacological activity	Part used	Extract / compound	Assay / model / human subject	Dose / concentration	Duration	Positive control	Dose / concentration	Reference
In vitro	Antibacterial	Flower	2,3,4-trihydroxy-5-methylacetophenone	*Bacillus cereus, Escherichia coli, Klebsiella pneumoniae, Mycobacterium smegmatis, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus simulans*	2 mg/mL	NA	Ampicillin	10 mg/disc	[10]
In vitro	Antibacterial	Flower	NS	*Salmonella typhimurium, Staphylococcus aureus*	NS	NA	NS	NS	[63]
In vitro	Antibacterial	Fruit	Ethanol	Escherichia coli, Staphylococcus aureus	50 mg/mL	NA	Ciprofloxacin	50 µg/mL	[37]
In vitro	Antibacterial	Fruit	Methanol	Alteromonas sp., Pseudomonas sp.	15 mg/mL	NA	NS	NS	[38]
In vitro	Antibacterial	Leaf	Methanol	*Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhi, Staphylococcus aureus, Staphylococcus epidermidis,*	100 µg/mL	NA	Amoxicillin, ciprofloxacin	100 µg/mL	[36]
In vitro	Antibacterial	Leaf	Methanol	*Bacillus subtilis, Escherichia coli, Plesiomonas shigelloides, Proteus fluorescens, Proteus vulgaris, Salmonella paratyphi, Serratia marcescens, Staphylococcus aureus, Staphylococcus lutrae, Vibrio alginolyticus, Vibrio cholera, Vibrio harveyi, Vibrio mimicus*	NS	NA	Streptomycin	NS	[32]
In vitro	Antibacterial	Seed	Methanol	*Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae, Serratia marcescens, Staphylococcus aureus*	0.78 mg/mL	NA	Penicillin	NS	[33]
In vitro	Antibacterial	Seed	Methanol	*Enterococcus faecalis, Salmonella typhi, Shigella dysenteriae, Vibrio cholerae*	10 µg/µl	NA	Ampicillin	30 µg/µl	[34]
In vitro	Antibacterial	Seed	Aqueous, ethanol, methanol	*Bacillus subtilis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus*	50 mg/mL	NA	Streptomycin	50 mg/mL	[35]
In vitro	Antidiabetic	Fruit	Aqueous	α-Amylase inhibitory	NS	NA	NS	NS	[44]
In vitro	Antidiabetic	Fruit	Aqueous	α-Glucosidase inhibitory	NS	NA	NS	NS	[44]
In vitro	Antifungal	Leaf	Methanol	*Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Candida albicans, Candida blanki, Microsporum canis, Saccharomyces cerevisiae, Vestilago myditis*	100 µg/mL	NA	Griseofulvin	100 µg/mL	[36]
In vitro	Antifungal	Seed	Aqueous, ethanol, methanol	*Aspergillus brasiliensis, Aspergillus fumigatus, Candida albicans*	50 mg/mL	NA	Nystatin	50 mg/mL	[35]
In vitro	Anti-inflammatory	Root	Ethanol	Heat, hypotonicity induced hemolysis	200 µg/mL (IC_{50})	NA	Diclofenac	1 mg/mL	[49]
In vitro	Antioxidant	Flower	Ethanol	DPPH radical scavenging	10 µg/mL (IC_{50})	NA	BHT	10 µg/mL	[45]

Level of scientific evidence	Pharmacological activity	Part used	Extract / compound	Assay / model / human subject	Dose / concentration	Duration	Positive control	Dose / concentration	Reference
In vitro	Antioxidant	Flower	2,3,4-trihydroxy-5-methyl acetophenone	DPPH radical scavenging	20.02 µM (IC_{50})	NA	Ascorbic acid, gallic acid	NS	[10]
In vitro	Antioxidant	Fruit	Aqueous, ethanol	DPPH radical scavenging	0.03 mg/mL	NA	BHA, BHT	10 mg/mL	[56]
In vitro	Antioxidant	Fruit	Ethanol	DPPH radical scavenging	NS	NA	Trolox	100 µM/mL	[52]
In vitro	Antioxidant	Fruit	Methanol	DPPH radical scavenging	200 µg/mL	NA	NS	NS	[51]
In vitro	Antioxidant	Leaf	Methanol	DPPH radical scavenging, H2O2 radical scavenging	20 µg/mL (IC_{50})	NA	Ascorbic acid	20 µg/mL	[36]
In vitro	Antioxidant	Leaf	NS	DPPH radical scavenging	6.7 µg/mL	NA	Ascorbic acid	0.01 µg/mL	[54]
In vitro	Antioxidant	Seed	Methanol	ABTS radical scavenging, DPPH radical scavenging	1 µg/mL (IC_{50})	NA	Ascorbic acid	1 µg/mL	[34]
In vitro	Antioxidant	Seed	Acetone, chloroform, methanol, petroleum ether	ABTS radical scavenging	1 mg/mL	NA	Trolox	15 µM	[8]
In vitro	Antioxidant	Seed	Acetone, chloroform, methanol, petroleum ether	DPPH radical scavenging	1 mg/mL	NA	Quercetin, BHA, BHT, α-tocopherol	NS	[8]
In vitro	Antioxidant	Seed	Acetone, chloroform, methanol, petroleum ether	FRAP radical scavenging	1 mg/mL	NA	NS	NS	[8]
In vitro	Antioxidant	Seed	Acetone, chloroform, methanol, petroleum ether	OH radical scavenging	1 mg/mL	NA	BHT, Rutin	NS	[8]
In vitro	Antioxidant	Seed	Acetone, chloroform, methanol, petroleum ether	Phosphomolybdenum radical scavenging	1 mg/mL	NA	NS	NS	[8]
In vitro	Antioxidant	Seed	Aqueous, ethanol	DPPH radical scavenging	10 µg/mL	NA	Ascorbic acid	10 µg/mL	[53]
In vitro	Antioxidant	Seed	Ethanol	DPPH radical scavenging, H2O2 scavenging, OH radical scavenging	20 µg/mL	NA	Ascorbic acid	20 µg/mL	[55]
In vitro	Antioxidant	Fruit	Ethanol	DPPH radical scavenging	0.3125 mg/mL	NA	Vitamin C	0.3125 mg/mL	[50]
In vitro	Antioxidant	Seed	Ethanol	DPPH radical scavenging	0.3125 mg/mL	NA	Vitamin C	0.3125 mg/mL	[50]

3.2.2. Wound healing activity

One another preliminary human trial was carried out to determine the efficacy of the local application of *Flabelliferin b.* (FB) at selected 7 volunteers to show the wound healing property of fruit extract at the concentration of 4 mg/mL for one week. The prepared FB ointment resulted in wound healing without any adverse effects and the Metronidazole was used as the positive control in this study [60].

3.3. *In-vivo* Studies

3.3.1. Antiarthritic activity

An ethanolic extract at the dose of 200 mg/kg from the flower was employed using Freund's Complete Adjuvant (FCA) induced polyarthritis model for twenty-one days to screen antiarthritic potential. Results showed significant antiarthritic activity, as compared to control (Diclofenac sodium) at 100 mg/kg [47].

3.3.2. Anticancer activity

Hong et al. studied the anticancer activity of root methanol extract at the concentration of 1 µg/mL in human colorectal cancer cell lines for twenty-eight days. They found that Trans-Scirpusin A inhibited the growth of colorectal cancer Her2/CT26 cells in mice and it is not stated the positive control used in this study [39].

3.3.3. Anti-inflammatory activity

An extract at the concentration of 150 mg/kg was prepared from the flower using ethanol and applied to acetic acid-induced writhes. Eventually, the extract was able to prevent damage to red blood cell membranes and promote the stabilization of the membrane. In this study, indomethacin and morphine were used as positive controls at the concentration of 10 mg/kg [57].

3.3.4. Antipyretic activity

An ethanolic extract at a dose of 150 mg/kg from the flower was tested on yeast-induced pyrexia in mice and rats and results showed that the extract significantly reversed hyperthermia and this was compared with aspirin at 200 mg/kg concentration [48].

3.3.5. Diuretic Activity

The diuretic effect of tuber using the ethanol extract at the concentration of 200 mg/kg was investigated in albino rat and mouse for 5h period and the result was compared with standard drug furosemide (100 mg/kg) and extract has shown a significant increase in the urinary level of Na^+, K^+, and Cl^- [57].

3.3.6. Immunomodulatory activity

Ma'Unatin et al. investigated the immunomodulatory effect in mice for the ethanol extract extracted from the flower at the concentration of 300 µg/mL for twenty-six days. The results indicated that the exopolysaccharides produced by two strains of *Leuconostoc mesenteroides* have immunomodulatory activity. This was compared with Dextran using the same concentration [59].

3.3.7. Hypersensitivity

An ethyl acetate extract of tuber was tested in the mouse at the concentration of 0.4 mg/kg (effective dose) (ED_{50}) to study the potent immunosuppressant activity for five hours and this was compared with cyclosporin A [29].

3.4. *In-vitro* Studies

3.4.1. Anthelmintic activity

Jamkhande et al. investigated the anthelmintic property of leaf extract extracted using methanol in *Pheretima posthuma* at the concentration of 10 mg/mL and the results revealed that extract has effective anthelmintic activity against Indian adult earthworms. In this study, albendazole was used as the positive control at the same concentration [30].

3.4.2. Antibacterial activity

A methanol extract at the concentration of 100 µg/mL from leaf was tested for its antibacterial property against *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumonia*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*, and the extract revealed significant inhibition of growth of selected bacterial strains. In this study, the researchers used amoxicillin and ciprofloxacin as a positive control at the concentration of 100 µg/mL [36].

3.4.3. Antifungal activity

The methanol extract of leaf showed the antifungal property against selected fungal strains (*Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, *Candida albicans*, *Candida blanki*, *Microsporum canis*, *Saccharomyces cerevisiae*, Vestilago) at the concentration of 100 µg/mL and results were compared with standard griseofulvin (100 µg/mL) [36].

3.4.4. Antioxidant activity

An extract was prepared using seed and methanol exhibited antioxidant effects in 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical scavenging at a concentration of 1 µg/mL (The half-maximal inhibitory concentration) (IC50), and compared with ascorbic acid at the same concentration [34].

3.5. Toxicity Studies

Determination of median lethal dose (LD50) was done for fixing the therapeutic dose using ethanolic flower extract. This acute toxicity study revealed that even at the higher dose (2000 mg/kg) there were no mortality or any toxic reactions with oral administration of the extract recorded [57].

4. Conclusion

This review article summarized the available scientific evidence based on pharmacological activities of *B. flabellifer*. From this study, it was identified that only a few traditional medicinal uses have been supported by the scientific evidence and only a few phytochemical compounds have been isolated. Therefore, a greater number of *in vitro*, *in vivo*, and clinical studies would be needed to conduct to provide more scientific evidence of this plant's traditional medicinal uses. In addition to that, studies emphasized the toxicity for various extracts and isolated compounds were limited and these should be evidenced by well-structured in vivo or clinical study to prove no side effects associated with it. In the future, further studies on phytochemical compounds should be emphasized to discover the potentially active pharmacological compounds. Moreover, a better understanding of the mode of action of the extracts and isolated compounds would expose these in

safely treating various disorders. This will reveal new drug discoveries for various syndromes. The importance and benefits of this plant species are known for a limited group of people and the significance of *B. flabellifer* should be understood to sustain this invaluable resource.

Declaration of Conflict of Interest

The authors declare no conflict of interest.

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