



## *In vitro* antidiabetic and anti-inflammatory activities of bark of *Alangium salvifolium* and *Alangium lamarckii*

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### ABSTRACT

The greatest disadvantage in the presently available potent synthetic antidiabetic and anti-inflammatory drugs lies in their toxicity and reappearance of symptoms after discontinuation. As a result, people are going back to natural products in the search of security and safety. Several species of *Alangium* have been reported to have therapeutic properties. The present study aims to assess the antidiabetic and anti-inflammatory activity of methanolic, ethanolic and petroleum ether extracts of bark of *Alangium salvifolium* and *Alangium lamarckii* in vitro. The in vitro bioassay consisted of assaying the effect of the extracts against  $\alpha$ -amylase activity for lowering the levels of hyperglycaemia. and the effect of the extracts against denaturation of protein (egg albumin) for anti-inflammatory activity. Acarbose is a common drug used as standard in in vitro antidiabetic assay and diclofenac sodium used as a standard drug for anti-inflammatory assay. The in vitro study of methanolic extracts of bark of *A. salvifolium* and *A. lamarckii* showed a better antidiabetic activity of  $81.02 \pm 0.79\%$  and  $81.42 \pm 1.68\%$ , respectively at  $250 \mu\text{g/ml}$  concentration than other solvent extracts. Similarly, the in vitro anti-inflammatory study, exhibited a better activity in methanolic extract of bark of *A. lamarckii* with inhibition of  $93.63 \pm 0.79\%$  at  $250 \mu\text{g/ml}$ . The methanolic bark extract of both *A. salvifolium* and *A. lamarckii* showed potent antidiabetic and anti-inflammatory activities.

**Keywords:** Antidiabetic, anti-inflammatory, *A. salvifolium*, *A. lamarckii*, bark.

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### INTRODUCTION

Diabetes mellitus is a metabolic disease, involving increased levels of blood glucose. Diabetes mellitus has several categories, including type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes and neonatal diabetes. Type 2 diabetes (T2D), which is characterized by hyperglycaemia and impaired glucose metabolism, is a leading cause of morbidity and mortality globally and a significant economic burden [1]. About 382 million people worldwide had diabetes in 2013, according to the International Diabetes Federation, and by 2035 those numbers are projected to quadruple [2]. The majority (>95 %) of the newly diagnosed diabetics have type 2 diabetes (T2D), which is brought on by pancreatic beta-cell failure and insulin resistance [3]. The onset and progression of T2D challenges have been reported to be significantly influenced by postprandial blood glucose levels [4]. Inhibiting  $\alpha$ -amylase is one of the treatment methods for treating postprandial hyperglycaemia [5]. Synthetic medications like acarbose and miglitol have potent anti-amylase and anti-glucosidase effects, but they can also cause abdomen discomfort, vomiting, and diarrhoea [6]. Advanced glycation end products (AGE) and excessive non-enzymatic glycation of proteins are additional consequences of hyperglycaemia. By causing nephropathy, cataracts, vasculopathy, and atherosclerosis, the glycation changes can exacerbate the pathology of diabetes [7]. Numerous studies and reviews have revealed that phytochemicals such phenolics have the ability to treat concerns associated with diabetes and other complications inhibiting effects on amylase [8-12]. Medicinal plants that maintain low blood glucose, lower blood pressure, increase the body's antioxidant defences, and regulate insulin are a safer alternative for treating T2D [13]. For ages, type 2 diabetes and metabolic diseases have been treated using infusions and decoctions of traditional medicinal plants [14]. Reactive oxygen species (ROS) can cause diabetes, although plants rich in antioxidant chemicals can shield these cells from ROS [13]. Living tissues response to harm is inflammation. Normally, it is a defence system that is activated in reaction to unpleasant stimuli, injury, or illness to safeguard the body and speed up the healing process. However, an unchecked reaction causes inflammatory illnesses that are persistent. For the

treatment of inflammation, a wide variety of steroids and non-steroidal anti-inflammatory medications are sold on the market, even though their treatment effectiveness appears to be constrained because they are frequently linked to severe unpleasant side effects like gastrointestinal discomfort, ulcers, nephrotoxicity, metabolic problems, metabolic disorders and nephrotoxicity [15]. The metabolism of arachidonic acid plays a significant part in a number of events that make up the mechanisms of inflammation. It is metabolized by the 5-lipoxygenase pathway to eicosanoids and leukotrienes, which are known to operate as chemical mediators in a range of inflammatory processes, as opposed to the cyclooxygenase (COX) pathway to prostaglandins and thromboxane A<sub>2</sub> [16]. Despite having harmful side effects, the anti-inflammatory medications that are currently accessible limit enzyme activity while also providing symptom alleviation. Hence, it is crucial to use anti-inflammatory medications with minimal adverse effects. Over 3000 plants are officially recognized as having therapeutic use in India. Over 6000 plants are reportedly used in India for traditional, folk, and herbal medicine, which accounts for about 75% of the medical requirements of third world nations. The plants *Alangium salvifolium* and *Alangium lamarckii* are among them [17]. The monogeneric plant genus *Alangium* belongs to the Alangiaceae family. The size of *Alangium salvifolium* varies from a small shrub to a deciduous tree that is between 3 and 12 feet tall. Alternate, unequal, oblong, lanceolate, or oval leaves are pubescent on veins beneath and 3-6 pairs of oblique veins are acuminate and obtuse at the apex. white or yellow flowers with aroma. Fruit drupe with one to two seeds with calyx lobes on top [18]. Western Africa, Madagascar, Southern and Eastern Asia (China, Malaysia, Indonesia, India, and Philippines), tropical Australia, the islands of the Western Pacific Ocean, and New Caledonia are its natural regions. It is a well-known folk remedy whose antifertility [19], anti-inflammatory [20], antimicrobial [21], antioxidant [22], antitumor [23] and anti-ulcer [24] properties have all been investigated. There are many pharmacological studies reported on *Alangium salvifolium* and *Alangium lamarckii*. But there were no studies about *in vitro* antidiabetic and anti-inflammatory activities of bark of *Alangium salvifolium* and *Alangium lamarckii*. The above points in mind, the present study was aimed to determine the *in vitro* antidiabetic and anti-inflammatory activities of bark of *Alangium salvifolium* and *Alangium lamarckii*.

## **MATERIAL AND METHODS**

### **Plant extract preparation**

*Alangium salvifolium* and *Alangium lamarckii* barks were collected from the banks of river cauvery near Kumbakonam, Thanjavur District, Tamilnadu, India. The collected barks of plants were washed with water and rinsed with distilled water and finally shade dried. The dried material of each plant was made into fine powder. Each plant material is extracted using solvents ethanol, methanol and petroleum ether by using soxhlet apparatus. After the extraction completed, the solvent was evaporated and dried at 40 °C till the solvent was completely evaporated. Finally, the dark brown residue was obtained and used for *in vitro* antidiabetic and anti-inflammatory studies.

### **Phytochemical evaluation**

Methanolic, ethanolic and petroleum ether extracts of *A. salvifolium* and *A. lamarckii* were studied for its phytoconstituents such as alkaloids, steroids, triterpenoids, tannins, flavonoids, carbohydrates and cardiac glycosides by using different phytochemical tests [25].

### ***In vitro* antidiabetic activity**

The *in vitro* antidiabetic activity of methanolic, ethanolic and petroleum ether extracts of bark of *A. salvifolium* and *A. lamarckii* was analysed by 3,5-dinitrosalicylic acid (DNSA) method and it was used to determine the  $\alpha$ -amylase inhibition capacity [26]. The extract dissolved in buffer (Na<sub>2</sub>HPO<sub>4</sub>/NaH<sub>2</sub>PO<sub>4</sub> (0.02 M), NaCl (0.006 M) at pH 6.9) to give concentrations ranging from 50 to 250  $\mu$ g/ml. The extract was added with 200  $\mu$ l of  $\alpha$ -amylase solution (2 units/ml), which was then incubated for 10 min at 30 °C. Each tube then added with 200  $\mu$ l of the starch solution (1 % in water (w/v), which was then incubated for 3 min. 200  $\mu$ l of the DNSA reagent (12 g of sodium potassium tartrate tetrahydrate in 8.0 ml of 2 M NaOH and 20 ml of 96 mM 3,5-dinitrosalicylic acid solution) was added to the reaction to stop it, and it was then heated for 10 minutes at 85–90 °C in a water bath. The mixture was diluted with 5 ml distilled water and allowed to cool to room temperature and tested for absorbance at 540 nm with a UV-Visible spectrophotometer. The blank was made by substituting 200  $\mu$ l of buffer for the plant extract to have 100 % enzyme activity. Acarbose (150  $\mu$ g/ml) was used as positive control and the reaction was carried out in a manner identical to that of the above-mentioned reaction without plant extract. The following equation was used to compute the percent inhibition of the  $\alpha$ -amylase inhibitory activity

$$\text{Percentage inhibition} = (\text{Abs}_{\text{control}} - \text{Abs}_{\text{sample}}) / \text{Abs}_{\text{control}} \times 100$$

### ***In-vitro* anti-inflammatory activity**

The *in vitro* anti-inflammatory activity of methanolic, ethanolic and petroleum ether extracts of bark of *A. salvifolium* and *A. lamarckii* was analysed by protein denaturation inhibition assay [27]. The reaction

mixture contained 0.2 ml of fresh hen's egg albumin, 2.8 ml of phosphate buffered saline (pH 6.4), and 2 ml of test extract at different quantities, resulting in concentrations of 50, 100, 150, 200 and 250 µg/ml. As a control, the same volume of DMSO was used. The mixtures were incubated for 15 minutes at 37 °C ± 2 °C and then heated at 70°C for 5 minutes. After cooling, their absorbance at 660 nm was measured using a vehicle as a blank. Diclofenac sodium at the concentration of 150 µg/ml was used as standard drug and treated similarly as above for determination of anti-inflammatory activity. The following formula was used to determine how much protein denaturation was inhibited:

$$\% \text{ inhibition} = 100 \times ([Vt/Vc] - 1).$$

Where, Vt = absorbance of test sample, Vc = absorbance of control.

#### Statistical analysis

The results were subjected to statistical analysis and the values were expressed as mean ± Standard deviation of triplicates.

### RESULT AND DISCUSSION

Preliminary phytochemical investigations of the methanolic, ethanolic and petroleum ether extracts of bark of *A. salvifolium* and *A. lamarckii* revealed that the presence of flavonoids, tannins, phenolic compounds, alkaloids, glycosides, and carbohydrates and are shown in Table 1 and 2. It is widely known that plant phenols and flavonoids in general are powerful antioxidants and free radical scavengers. The use of polyphenol and flavonoids in treating and preventing a variety of illnesses, particularly those primarily brought on by free radicals, is common.

**Table 1: Preliminary phytochemical screening of methanolic, ethanolic and petroleum ether extracts of bark of *Alangium salvifolium***

Name of phytoconstituents	Name of the solvent extract		
	Methanol	Ethanol	Petroleum ether
Alkaloids	+	+	+
Flavonoids	+	+	+
Saponins	+	+	-
Tannins	+	+	+
Terpenoids	+	+	+
Triterpenoids	+	+	+
Phenolic compounds	+	+	+
Quinones	+	+	+
Steroids	-	-	-
Glycosides	-	-	-
Coumarins	-	-	+
Sugar	+	+	-
Proteins	+	-	+
Phlobatannins	+	+	+
Emodins	+	+	+
Polyphenols	-	+	+
Carbohydrates	+	+	-
Cardiac glucosides	+	+	+
Anthraquinones	+	+	+
Anthocyanins	-	-	-

- Absent; + Present

**Table 2: Preliminary phytochemical screening of methanolic, ethanolic and petroleum ether extracts of bark of *Alangium lamarckii***

Name of phytoconstituents	Name of the solvent extract		
	Methanol	Ethanol	Petroleum ether
Alkaloids	+	+	+
Flavonoids	+	+	+
Saponins	-	-	-
Tannins	+	+	+
Terpenoids	+	+	+
Triterpenoids	+	+	+
Phenolic compounds	+	+	+
Quinones	+	+	+
Steroids	-	-	-
Glycosides	-	-	-

Coumarins	-	+	+
Sugar	+	+	-
Proteins	+	+	+
Phlobatannins	+	+	+
Emodins	-	+	-
Polyphenols	+	+	+
Carbohydrates	+	+	-
Cardiac glucosides	+	+	-
Anthraquinones	+	+	-
Anthocyanins	-	-	-

- Absent; + Present

### ***In vitro* antidiabetic activity**

A metabolic problem brought on by an absolute or relative insulin insufficiency, which results in an unbalanced glucose, lipid, and protein metabolism. Diabetes mellitus (DM) is a complicated disease [28, 29]. Numerous people with diabetes mellitus experience severe side effects such as nephropathy, retinopathy, neuropathy, and cardiovascular conditions [30]. The intestinal enzyme  $\alpha$ -amylase is crucial for the breakdown of carbohydrates and the absorption of glucose. Digestion of starch and oligosaccharides would be delayed if the activity of digestive enzymes like  $\alpha$ -amylase were suppressed. This would diminish the absorption of glucose and, in turn, lower blood sugar levels. Due to their capacity to bond with proteins, polyphenolic chemicals found in plants block the activities of carbohydrate hydrolysing enzymes including  $\alpha$ -amylase and  $\alpha$ -glucosidase [31]. In the present study, the potential of *Alangium salvifolium* and *Alangium lamarckii* as an antidiabetic supplement was investigated by using DNSA as a substrate in determining the  $\alpha$ -amylase inhibitory activities of the different crude extract and its fractions. The methanolic extracts of *Alangium salvifolium* exhibited significantly higher activity than other bark extracts and the results were indicated in Table 3. The studies performed on the methanolic extracts of bark of *A. salvifolium* and *A. lamarckii* at concentrations of 50, 100, 150, 200 and 250  $\mu$ g/ml showed the percentage of inhibition as 55.23  $\pm$  1.39, 60.46  $\pm$  0.96, 73.68  $\pm$  1.51, 76.11  $\pm$  1.01 and 71.02  $\pm$  0.79 % and 47.47  $\pm$  1.35, 52.63  $\pm$  1.50, 60.60  $\pm$  1.20, 73.68  $\pm$  1.20, 71.42  $\pm$  1.68 %, respectively. Ethanolic extract of *A. salvifolium* and *A. lamarckii* at the dose of 50, 100, 150, 200 and 250  $\mu$ g/ml showed the percentage of inhibition as 49.97  $\pm$  1.15, 57.69  $\pm$  1.86, 57.99  $\pm$  1.51, 60.32  $\pm$  1.90 and 65.95  $\pm$  2.15 % and 44.77  $\pm$  1.25, 54.89  $\pm$  1.68, 63.23  $\pm$  1.20, 68.05  $\pm$  0.72 and 66.06  $\pm$  0.83 %, respectively. Petroleum ether extract of both plants showed less inhibition compared with other extracts. Maximum inhibition of petroleum ether extract of *A. salvifolium* was 60.50  $\pm$  1.68 % at the concentration of 250  $\mu$ g/ml. Acarbose, a standard antidiabetic drug showed the maximum inhibition, 83.16  $\pm$  1.20 % at the concentration of 150  $\mu$ g/ml. Similarly, aqueous extract of *Agrimonia eupatoria* showed inhibition of 46.31  $\pm$  8.76  $\mu$ g/ml [32] and Capsaicin isolated from *Capsicum frutescens* showed weak  $\alpha$ -glucosidase inhibition of 48.8 %  $\pm$  2.8 % and inhibited the  $\alpha$ -amylase to 55.5  $\pm$  1.58 % [33]. Ethanolic seed extracts of *Coriandrum sativum* showed an IC<sub>50</sub> of 0.294 mg/ml against  $\alpha$ -amylase [34]. The inhibition percentage of  $\alpha$ -amylase was found to be 85.73 % by water extracts and 84.23 % by methanolic stem extracts of *Taraxacum officinale* and water extracts of root showed inhibition of 79.93 %. It is known that the polyphenols interact with the enzyme by non-specific binding, which inhibits the activity of the enzyme. The molecular weight and degree of polymerization of the polyphenols tend to increase their ability to block  $\alpha$ -glucosidase [35]. Amylase and glucosidase are two enzymes that hydrolyse carbohydrates, break down dietary starch and convert its oligosaccharides to glucose, causing a postprandial glucose spike. Therefore, one of the key strategies for treating hyperglycaemic situations in T2D patients is to limit the activities of glucosidase and amylase. The most often prescribed  $\alpha$ -amylase inhibitor is Acarbose [36].

### ***In vitro* anti-inflammatory activity**

Rheumatoid arthritis, asthma, and atherosclerosis can all be caused by inflammation, which is the body's natural immunological response to infection or tissue damage [37]. Despite the development of numerous steroidal and non-steroidal anti-inflammatory treatments, plant-derived medications have proved essential in the treatment of inflammatory illnesses [38]. According to pharmaceutical statistics, 12 of the 40 anti-inflammatory medications that were approved worldwide between 1983 and 1994 were based on phytochemicals found in plants [39]. Protein denaturation is a well-researched contributor to inflammation. Anti-inflammatory medications such as phenylbutazone, salicylic acid and flufenamic acid have demonstrated dose-dependent capacity to prevent thermally induced protein denaturation [40]. The potential of the extract to suppress protein denaturation was investigated as part of present study into the mechanism of the anti-inflammatory effect. As indicated in Table 4, it was efficient at preventing heat-induced albumin denaturation at various doses. The methanolic extracts of *Alangium salvifolium* exhibited

significantly higher activity than other solvent extracts and the results were indicated in Table 4. The studies performed on the methanolic extracts of bark of *A. salvifolium* and *A. lamarckii* at concentrations of 50, 100, 150, 200 and 250 µg/ml showed inhibition % as 26.66 ± 1.20, 33.73 ± 1.93, 47.03 ± 1.78, 60.27 ± 1.03 and 79.30 ± 1.48 % and 39.63 ± 1.35, 46.33 ± 0.76, 52.73 ± 1.31, 73.93 ± 1.40 and 93.63 ± 0.79 %, respectively. Ethanolic extract of *A. salvifolium* and *A. lamarckii* at the doses of 50, 100, 150, 200 and 250 µg/ml resulted in 33.40 ± 1.30, 39.97 ± 2.25, 53.60 ± 1.81, 66.69 ± 2.45 and 86.73 ± 2.40 % reduction and 40.33 ± 1.00, 52.33 ± 2.00, 57.56 ± 2.01, 80.43 ± 0.84 and 86.26 ± 0.87 % reduction, respectively. Petroleum ether extract of both plants showed less inhibition compared with other extracts. Maximum inhibition of bark of petroleum ether extract of *A. salvifolium* was 60.67 ± 1.33 % at the concentration of 250 µg/ml. Diclofenac sodium, a standard anti-inflammatory drug showed the maximum inhibition, 86.66 ± 2.36 % at the concentration of 150 µg/ml. Leukocytes play a crucial part in the inflammatory response, which makes cellular infiltration an important aspect of that reaction. Leukocytes release their lysosomal enzymes, such as proteases, during inflammation as part of their protective activities, which leads to further tissue damage and subsequent inflammation [41]. By way of lipid peroxidation caused by free radicals, cell membrane damage will make the cell even more vulnerable to secondary damage [42]. Through membrane proteins, sodium and potassium ion transport can be regulated to govern cell volume and water content, and membrane damage will impact this function [41]. Inhibiting red blood cell haemolysis may provide light on the inflammatory process because the red blood cell membrane resembles the lysosomal membrane [42]. According to a different study, *Albuca setosa* aqueous extract, at the concentration of 125 - 500 µg/ml, may be able to prevent the lysis of the erythrocyte membrane brought on by a heat solution [42]. Though the interaction of extract chemicals with membrane constituents seems most likely, the particular process of membrane stability is unknown. According to Aitdafoun [43], certain plant extracts have the ability to stabilize membranes and inhibit the release of inflammatory mediators in their early stages by stopping the release of phospholipases, which is what causes the formation of inflammatory mediators. Furthermore, it is possible that plant extracts may alter the cells' surface area to volume ratio by membrane expansion, cell shrinkage, or interactions with membrane proteins [44]. Only a few reports on *A. salvifolium* and *A. lamarckii* were found in the literature review, and there are no studies on the *in vitro* anti-inflammatory and anti-diabetic activities of bark. The methanolic extract of bark of *A. salvifolium* and *A. lamarckii* showed higher antidiabetic and anti-inflammatory activities, which suggest that it a major concentration of compounds with potential antidiabetic and anti-inflammatory activities.

**Table 3: *In vitro* antidiabetic activity of methanolic, ethanolic and petroleum ether extracts of bark of *A. salvifolium* and *A.lamarckii***

Concentration of plant extract (µg/ml)	<i>In vitro</i> antidiabetic activity (% inhibition)					
	Methanol		Ethanol		Petroleum ether	
	<i>A. salvifolium</i>	<i>A. lamarckii</i>	<i>A. salvifolium</i>	<i>A. lamarckii</i>	<i>A. salvifolium</i>	<i>A. lamarckii</i>
50	55.23 ± 1.39	47.47 ± 1.35	49.97 ± 1.15	44.77 ± 1.25	42.10 ± 1.20	31.40 ± 1.96
100	60.46 ± 0.96	52.63 ± 1.50	57.69 ± 1.86	54.89 ± 1.68	47.39 ± 1.77	34.11 ± 1.35
150	73.68 ± 1.51	60.60 ± 1.20	57.99 ± 1.51	63.23 ± 1.20	52.60 ± 1.25	36.87 ± 1.55
200	76.11 ± 1.01	73.68 ± 1.20	60.32 ± 1.90	68.05 ± 0.72	52.66 ± 1.45	36.74 ± 1.99
250	81.02 ± 0.79	81.42 ± 1.68	75.95 ± 2.15	76.06 ± 0.83	60.50 ± 1.68	49.97 ± 1.04
Acarbose (150µg/ml)	83.16 ± 1.20					

Values are expressed as mean ± standard deviation of triplicates

**Table 4: *In vitro* anti-inflammatory activity of methanol, ethanol and petroleum ether extracts of bark of *A. salvifolium* and *A. lamarckii***

Concentration of plant extract (µg/ml)	<i>In vitro</i> anti-inflammatory activity (% inhibition)					
	Methanol		Ethanol		Petroleum ether	
	<i>A. salvifolium</i>	<i>A. lamarckii</i>	<i>A. salvifolium</i>	<i>A. lamarckii</i>	<i>A. salvifolium</i>	<i>A. lamarckii</i>
50	26.66 ± 1.20	39.63 ± 1.00	33.40 ± 1.30	40.33 ± 1.00	19.97 ± 2.25	33.33 ± 1.02
100	33.73 ± 1.93	46.33 ± 0.76	39.97 ± 2.25	52.33 ± 2.00	34.03 ± 1.39	33.33 ± 1.39
150	47.03 ± 1.78	52.73 ± 1.31	53.60 ± 1.81	57.56 ± 2.01	39.67 ± 0.95	40.00 ± 0.79
200	60.27 ± 1.03	73.93 ± 1.40	66.69 ± 2.45	80.43 ± 0.84	49.67 ± 0.67	46.66 ± 2.35
250	79.30 ± 1.48	93.63 ± 0.79	86.73 ± 2.40	86.26 ± 0.87	60.67 ± 1.33	60.00 ± 1.78
Diclofenac sodium (150 µg/ml)	86.66 ± 2.36					

Values are expressed as mean ± standard deviation of triplicates

## CONCLUSION

The methanolic extract of bark of *A. salvifolium* and *A. lamarckii* exhibited strong antidiabetic and anti-inflammatory activities and may confer a beneficial effect against inflammation. Based on the results of *in vitro* assay, the antidiabetic activity of bark of *A. salvifolium* was due to its phytochemicals. Nevertheless, the optimal treatment protocol for use in humans remains to be found in further clinical studies.

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