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Antiulcer effects of the methanolic root extracts of *Paulownia elongata* on indomethacin-induced peptic ulcer in male albino rats

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Abstract

Medicinal plants have been the basis of treatment of various diseases in African traditional medicine as well as other forms of treatment from diverse cultures of the world. The aim of this study is to evaluate the Antiulcer Effects of the Ethanol Root Extracts of *Paulownia elongata* on Indomethacin-Induced Peptic Ulcer in Male Albino Rats. A total of sixteen (20) male albino rats gotten from the HEMA animal Farm, Federal Housing Estate Bajabure Gerie, ulcer was induced by administration of indomethacin (30 mg/kg, orally, Clinical isolates of four bacteria (*Staphylococcus aureus, Pseudomonas aeruginosa, and Clostridium Bolulinum and Escherichia coli*). The well method of the agar dilution was used to determine the antibacterial activity of the plant extracts. Were used for the antibacterial evaluation, and Gas Chromatography-Mass Spectrometry (GC-MS) analysis was used for phytochemical profiling. The study determined the phytochemical profile of methanol extracts of Paulownia elongate roots using GC-MS as displayed 20 chemical constituents, the antibacterial potential of the roots extract showed higher activity at 300 mg/kg/bwt with 18.12 + 0.9 mm on Salmonella typhi and at 400 mg/kg/bwt with inhibition rate 20.14+ 0.0 mm on Klebsiella pneumonia. The anti-ulcer potential was observed higher at 400 mg/kg/bwt in group 7 with potential of 87.71%. This activity of the crude roots extract was possible as a result of the chemical constituent observed. Thus this extract should be used as an agents to cutile diseases such as anti-microbials, anti-ulcer and well as diseases as cancer, HIV in the near feature with more research to isolate the active compounds.

Keywords: Ulcer; Extract; Albino Rats; *Paulownia Elongata*; Indomethacin

1. Introduction

Peptic ulcer disease (PUD) is described as the upper gastrointestinal tract mucosal rupture caused by acid peptic digestion which results in ulcer development that spreads over the muscularis mucosae through the submucosa (Hao, 2019; Hilton *et al*., 2001; Matthewson *et al*., 1988). It is most usually found in the stomach and first portion of the duodenum, although it can also be found in the distal oesophagus, distal duodenum, jejunum, and Meckel's diverticulum with heterotrophic gastric mucosa (Lanas and Chan, 2017). The ulcer can range in size from 5 mm to multiple centimetres. Erosion, on the other hand, is superficial, less than 5 mm in size, and restricted to the mucosa. PUD is one of the most prevalent conditions we see in our therapeutic practice. The term "peptic" refers to the hormone pepsin, which is responsible for mucosal breakdown. Peptic ulcer bleeding (Yuan and Leontiadis, 2019) is the most prevalent reason for upper gastrointestinal bleeding in the developed nations of the globe, resulting in high morbidity, death, and healthcare expenditures (Adam and Barkun, 2008). PUD is a benign illness that is readily treated with medication treatment and seldom necessitates surgery.

PUD impairs at least 5 million people each year and costs the healthcare system around $3.3 billion per year (Sandler *et al*., 2002). PUD prevalence changes in relation to *Helicobacter pylori* (*H. pylori*) infection. According to a study

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conducted in the United States, the seroprevalence of *H. pylori* infection changes with age, ranging from 16.7% in the young (20-29 years) group to 56.9% in the elderly (>70 years). It also varies by ethnicity: non-Hispanic whites have 26.2%, non-Hispanic blacks have 52.7%, and Mexican Americans have 61.6% (Everhart *et al*., 2000). In underdeveloped nations like as Nigeria, infection rates might reach 90% (Salih, 2009). Based on a systematic assessment of the literature from industrialized nations, the worldwide rate and frequency of physician-diagnosed PUD were estimated to be 0.10-0.19% and 0.12-1.50%, respectively. However, with the widespread use of acid suppressant medication and a decrease in the frequency of Helicobacter pylori infection due to increased socioeconomic position and elimination of *H. pylori* infection after identification, the incidence and prevalence of PUD have reduced (Sung *et al*., 2009).

The majority of PUD cases are caused by *H. pylori* infection and nonsteroidal anti-inflammatory medications (NSAIDs). *H. pylori* is present in more than 90% of duodenal ulcers and more than 70% of stomach ulcers (O'Connor, 1994). A prospective research from Turkey discovered that *H. pylori* infection was solely responsible for PUD in 75% of cases, *H. pylori* infection plus NSAIDs were responsible in 50% of cases, and NSAIDs alone were responsible in 10% of incidents (Uyanikoglu *et al*., 2012). According to a Japanese research, long-term usage of low-dose aspirin can develop PUD in 6.2% of patients. Diabetes patients and those using anticoagulants are at a higher risk (Uyanikoglu *et al*., 2012). Both NSAIDs and aspirin block the cyclooxygenase pathway and reduce prostaglandin synthesis, which is important for gastric mucosa cytoprotection by boosting mucus and bicarbonate secretion and enhancing mucosal blood flow (Kawamura *et al*., 2013). Certain risk factors, such as age over 65, heart disease, previous episodes of PUD, and co-management of corticosteroids, antiplatelets, and anticoagulants, enhance the likelihood of developing NSAID-induced PUD (Silen, 1988). All NSAIDs have the potential to produce gastrointestinal problems such as inflammation, erosions, ulcerations, and haemorrhage. The relative risk varies: piroxicam and ketorolac have the highest danger; indomethacin and naproxen have a high risk; diclofenac, meloxicam, and ketoprofen have an intermediate risk; and ibuprofen and celecoxib have a low risk (Drini, 2017). NSAIDs are used on a regular basis by around 11% of the US population. Although symptomatic upper gastrointestinal problems can occur in 1.5-4.5% of individuals taking NSAIDs, 15-30% of them exhibit PUD on endoscopy (Laine, 2001). Aside from NSAIDs and low-dose aspirin, few additional drugs have been linked to PUD. Clopidogrel (in conjunction with NSAIDs), corticosteroids (also in conjunction with NSAIDs), potassium chloride, bisphosphonates, spironolactone, mycophenolate mofetil, sirolimus, hepatic artery infusion of 5-fluorouracil, and selective serotonin reuptake inhibitors are examples (Dall *et al*., 2010).

Peptic ulcer caused by the ingestion of NSAIDs (indomethacin) is a major health concern affecting the population all over the world. Indomethacin, one of the most commonly used NSAIDs because of its antipyretic effect and its use for patients with cardiovascular disease has an ulcer inducing properties. Researchers all over the world are committed in developing drugs from medicinal plants that can ameliorate peptic ulcers and can also, heal other ulcers. Thus, an investigation into the antioxidants and antiulcer effects of the roots extract of empress tree (*Paulownia elongata*) on indomethacin-induced peptic ulcer in male albino rats will provide the information on the effectiveness of this plant part on peptic ulcer. The aim of this research is to evaluate antiulcer effects of the roots extract of empress tree (*Paulownia elongata*) from a histopathology study of the stomach of treated and untreated indomethacin-induced peptic ulcerated male albino rats.

2. Materials and methods

2.1. Chemicals and reagents

Distilled water, detergent, dimethyl sulfur oxide and indomethacin.

2.2. Equipment and apparatus

Conical flask, laboratory mortar and pestle, whatman filter paper, refrigerator, water bath, sterile petri plates, masking tapes, separating funnel, hand gloves, cotton wool, nose mask, analytical weighing balance, micro pipette, test tubes, samples bottles, glucometer and gas chromatography-mass spectrometry instrument.

2.3. Plant Collection

The roots of *P. elongata* were collected from Wukari Local Government Area of Taraba State. It was washed under a running water with an intensive care and was air-dried for about 5 weeks for easy grinding. Identification and authentication were done at the herbarium in the Department of Plant Sciences of Modibbo Adama University Yola, Nigeria (see Fig. 1 & 2).

Figure 1 *Paulownia elongata* leaves on tree (photo taken in September 2022)

Figure 1 *Paulownia elongata* (photo taken in September 2022)

2.4. Plant Extraction

The air-dried roots of *P. elongata* were grinded to a smooth powdered form. Then 150g of the sample (roots of *P. elongata*) was weighed with an analytical weighing balance and put into a 1000mL container. 800mL of methanol was then added into the 1000mL container and was left for 48 hours for proper absorption. After 48 hours, the liquid sample was extracted and was evaporated in a water thermostat.

2.5. Breeding of animal (albino rats)

A total of sixteen (20) male albino rats gotten from the HEMA animal house, Federal Housing Estate Bajabure Gerie, Adamawa State will be used for this research. They were kept in five different cages and fed with the appropriate feed and water ad libitum. This was aimed to allow them gain weight and look healthy according to the animal house committee.

2.6. Chemical and Reference Drug

Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) used to treat chronic musculoskeletal pain and to close a hemodynamically important patent ductus arteriosus in preterm newborns. NSAIDs are made up of structurally unrelated compounds; indomethacin's NSAID chemical categorization is an indole-acetic acid product with the chemical name 1- (p-chlorobenzoyl)25-methoxy-2-methylindole-3-acetic acid (Gedeon *et al*., 2006). It was delivered orally to the albino rats using an orogastric syringe.

2.7. Experimental Protocol

Twenty (20) albino wistar rats weighing 100-200g (males and females) were separated into seven groups, each group containing four animals (n=5) and kept in aluminium cages. After it was allowed to fast for 24 hours. All animals except the normal control animal were given indomethacin (30 mg/kg, oral) to produce ulcers. Treatment with the plant extract was administered daily for 14days.

Group 1: Normal control (diet/water)
Group 2: Rats (induced ulcer indomethacin 25mg/kg/bwt +diet /water)
Group 3: Rats (induced ulcer indomethacin 25mg/kg/bwt +diet/water + Omeprazole)
Group 4: Rats (induced ulcer indomethacin 25mg/kg/bwt +diet /water +100mg/kg/bwt extracts)
Group 5: Rats (induced ulcer indomethacin 25mg/kg/bwt +diet /water +200mg/kg/bwt extracts)
Group 6: Rats (induced ulcer indomethacin 25mg/kg/bwt +diet /water +300mg/kg/bwt extracts).
Group 7: Rats (induced ulcer indomethacin 25mg/kg/bwt +diet /water +400mg/kg/bwt extracts)

2.8. Determination of the Minimum Concentration of extracts (MIC)

The MIC of the methanolic extracts of the plant specimen were determined through the agar diffusion method outlined by Baker and Breach (1980): one milliliter of different concentration of each of the extracts was added to about 14ml of nutrient agar to make the final concentration ranging from 12.5% w/v to 100% w/v of the products in the agar. Standardized inocula were streaked on the agar in petri dishes containing various concentration of the extracts. The plates were incubated at 37^0C for 24hours. The least level of each extracts inhibiting the development of the test organism was taken as the MIC.

3. Results

3.1. Effect of *Paulownia elongata* Root Extract on Indomethacin

The animals were treated orally with omniprazole and of *Paulownia elongata* roots Methanol Crude Extract at 400 mg/kg/wt for 14 days and the effect of *P. elongata* root extract across all experimental groups of albino rats is shown in Table 1 below.

Table 1 Effect of Paulownia elongata Root Extract on Indomethacin

S/N	Group	Methanol	Percentage
1	Negative Control	2.93 ±0.70	0.00
2	Positive control	0.11±0.05	96.25
3	50 mg/kg/bwt	1.86±0.20	36.51
4	100 mg/kg/bwt	1.60±0.10	45.25
5	200 mg/kg/bwt	0.99±0.09	66.70
6	300 mg/kg/bwt	0.76±0.03	76.04*
7	400 mg/kg/bwt	0.36±0.01	87.71*

Result is Mean ± SD. N = 5; *= significant activity was observed. Concentration of standard is 25 µg/mL of Omniprazole

Histopathology of gastric mucosa stained with H&E of the rats subjected to induction of ulcer by indomethacin

As shown in Fig. 1 below, the blue arrow indicated the absence of epithelial layers (ulcer area internal) and the black arrow indicated epithelial layers remaining (ulcer edge). The yellow showed healing portion of the ulcerated area. The microphotographs depict the activity of the crude at 400mg/kg/bwt in the group's magnification of 200µg.

Negative control | Positive control (Omniprazole) | 400mg/kg/bwt extract

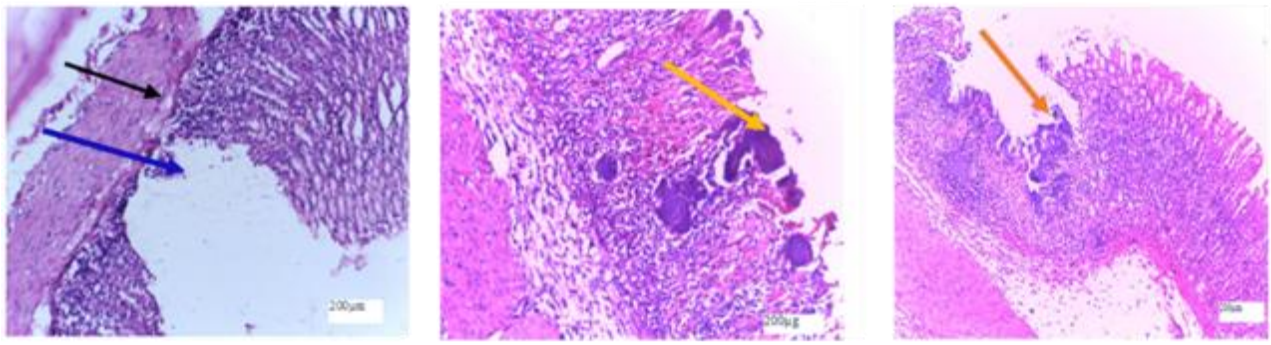

Figure 3 Histopathology of gastric mucosa stained with H&E of the rats subjected to induction of ulcer by indomethacin

4. Discussion

An imbalance in gastrointestinal defence factors such as prostaglandins, mucus, and bicarbonate, as well as potentially damaging substances such as pepsin, acid, and *H. pylori* infection, causes peptic ulcer (Lacy, 2000; Meyer, 2012). Flavonoids, a type of phytochemical found in *Paulownia elongata*, have been shown to have anti-ulcer effects by enhancing defence mechanisms (antioxidant enzymes, bicarbonate, prostaglandins, mucus, and so on) and refusing aggressive components (gastric acid, pepsin, *H. pylori*, NSAIDs, oxidative stress, and so on). Figure 2 (Anami, 2004; Barton *et al*., 2007). Dai *et al*. (2015) recently published a study that found six flavonoids (quercetin 3-O--d-glucoside, apigenin, quercetin, apigenin-7-O--d-glucoside, tricin-7-O--d-glucopyranoside, and 3'-methoxyluteolin-7-O--dglucoside) in rat plasma following oral administration of *P. tomentosa* flower extract. Another recent study found twenty-three distinct C-Geranylated Flavanones from *P. tomentosa* fruits, at least five of which demonstrated antiinflammatory action potentially impacting the NF-B signalling system (Dai *et al*., 2015), specifically by reducing TNF- mRNA production.

Flavonoids have anti-ulcer properties through controlling gastric secretion pathways. The stomach normally secretes a variety of substances, including pepsin, gastric acid, and gastric mucus. Stomach acid and pepsin aid digestion, while gastric mucus shields epithelial cells from harm caused by stomach acid and pepsin (Engel *et al*., 1995). A high quantity of stomach acid, on the other hand, exacerbates irritation of the mucus membrane in peptic ulcer (Shamburek and Schubert, 1993). As a result, inhibiting excessive stomach acid output is critical in the treatment of peptic ulcers. Gastrointestinal hormones control gastric acid secretion. The major hormones that trigger parietal cells to release acid include acetylcholine, gastrin, and histamine. Additionally, somatostatin inhibits acid secretion and exerts a tonic restraint on parietal, enterochromaffin-like, and gastrin cells via acting on sst_2 receptors (Shamburek and Schubert, 1993; Schubert, 1999). More crucially, H+K+-ATPase, a proton pump within the membrane of parietal cells, catalyses H+ transfer at the expense of ATP hydrolysis in the penultimate phase of gastric acid production.

Flavonoids have anti-ulcer actions by inhibiting acid secretion, boosting stomach mucus and bicarbonate production, and decreasing pepsin levels and activity. Flavonoids also improve mucosal antioxidative, cytoprotective, antibacterial, and anti-inflammatory defences against peptic ulcer. Typically, a single flavonoid can have anti-ulcer effects via numerous pathways (Foster & Duke 2000; Akyildiz & Kol 2010). The abundance of flavonoids, notably apigenin, in *P. tomentosa* flower extracts has piqued the curiosity of researchers. Apigenin, a plant-produced flavone, has been demonstrated to have substantial antioxidant, anti-inflammatory, and anticarcinogenic effects. In recent years, significant advancement is being made in the research of apigenin's biological effects at both the cellular and molecular levels. Although human clinical trials investigating the efficacy of apigenin supplementation as a cancer chemopreventive drug have not been conducted (Patel *et al*., 2007), apigenin offers significant potential for development as a cancer chemopreventive agent.

Flavonoids extracted from *P. tomentosa* leaves show anti-oxidant and cell-protective properties (Tables 1 and 2). Aqueous extracts of fresh *P. elongata* leaves and silage show *in vitro* antimicrobial activity against *Candida albicans, Streptococcus pyogenes, Staphylococcus aureus, Pseudomonas aeruginosa, Paenibacillus alvei,* and *Salmonella enterica.* The inhibitory effect is more pronounced against gram-negative bacteria (Popova and Baykov, 2013). In in vitro tests on cervical and breast cancer cell lines, the leaves of *P. tomentosa* (misidentified as *P. coreana*) contained isoatriplicolide tiglate (PCAC), which triggered apoptosis (Jung *et al*., 2012). Varlyakov *et al*. (2013) investigated the effect of *P. elongata* leaf consumption on blood parameters in three yearling sheep, Stara Zagora x Pleven Blackhead hybrids. Their findings demonstrated a considerable decline in erythrocyte and leukocyte counts, with the most marked decrease occurring in the postprandial hours. Furthermore, their research revealed that the leaves of *P. elongata* had the capacity to drastically lower blood glucose levels. Flavonoids derived from *Paulownia* flowers have been proven to inhibit asthmatic trachea inflammation, and the essential oil from the flowers has also been demonstrated to treat allergic airway inflammation in rats (Chen and Li, 2007). Similarly, in *Cavia porcellus*, *Paulownia* flower extract exhibited potential effectiveness against bronchial asthma (Zhang *et al*., 2002). *P. tomentosa* sesquiterpene derivatives may have neuroprotective benefits by reducing glutamate toxicity (Kim *et al*., 2010).

Although the xylem of *Paulownia* wood includes paulownin and d-sesamin (Park *et al*., 1991; Ayan *et al*., 2002; Zhu *et al*., 1986), nothing is known about the wood's real therapeutic use. From the stems and roots of *P. tomentosa* (misidentified as *P. coreana*), elements of syringin, paulownin, and eleostearic acid have been named, and these chemicals contribute to the numerous therapeutic applications (Park *et al*., 1991). Aside from its traditional use in haemorrhoids or to kill worms, information on the medical use of the bark are scarce. There is one account of it being used to treat wild bee stings (Zhao, 2003), and antioxidant activity of *P. tomentosa* var. tomentosa bark extracts has also been established (Jiang, 2003; Si *et al*., 2013), which may lead to medical uses. According to the later study, isocampneoside II plays an important function in neuroprotection by serving as a source of free radicals and antioxidant.

Paulownia roots have been used to treat chronic retrograde inflammation of the shoulder joint capsule and associated ligaments, muscles, tendons, and bursa mucosa, commonly described in medical terminology as scapulohumeral periarthritis (Zhao, 2003).

P. elongata and *P. fortunei* methanolic leaf extracts have strong antioxidant activity (Yadav *et al*., 2008). *P. fortunei* leaves (the two newly harvested and dried) have a greater total polyphenol content, averaging 250 mg/g GAE, than *P. elongata* (75 mg/g GAE). *P. fortunei* leaf extract also had a greater flavonoid concentration than *P. elongata*. Furthermore, the TEAC (TROLOX equivalent antioxidant capacity) analysis of the leaf extracts demonstrated that *P. fortunei* has a higher average TEAC value (2000 mol/g) for both fresh and dried methanolic extracts than *P. elongata* (1375 mol/g) (Yadav *et al*., 2008). *P. tomentosa* (misidentified as *P. coreana*) seed acetone extract has been used to treat diabetic problems. According to one research, the identified active molecule, phenylethanoid glycoside isocampneoside II, inhibits aldose reductase and blocks the polyol pathway (Kim *et al*., 2011). *Paulownia* seeds may also be utilised in an unconventional way to produce oil rich in bioactive components such as sterols and tocopherols for nutritional reasons (Angelova-Romova *et al*., 2011).

Table 2 A comprehensive list of ailments for which various plant parts of Paulownia species have been used

#	Species	Plant parts	Used for	References
1	*Paulownia tomentosa*	Stem bark	Gonorrhea and erysipelas	Kang *et al*., 1999
2	*P. tomentosa*	Fruit, leaf and wood	Bronchitis	Zhu *et al*., 1986
3	*P. tomentosa*	Fruit and leaf	Hair regeneration and scalp stimulant	
			Tonsillitis, bronchitis, asthmatic attack, and bacterial infections such as enteritis or dysentery	Kang et al., 1999; Jiang et al., 2004; Šmejkal et al., 2007
4	*P. tomentosa*	Leaf	Antiradical and cell protective effects	Zima et al., 2010; Šmejkal et al., 2007
5	*P. tomentosa*	Fruit	Airway inflammation	Chen and Li, 2007
			Antioxidant activity	Zima et al., 2010
			Inhibitory activity against bacteria and yeast	Šmejkal et al., 2007
			Antibacterial and antileishmanial activity	Navrátilová et al., 2015
		Fruit	Anti-inflammatory and antiphlogistic potential	Hanáková et al., 2015
		Fruit (unripe)	Reduction of symptoms of colitis in male Wistar rats	Vochyánova et al., 201
		Fruit	Hypotensive effect	Duke et al., 1985
		Wood	Bacterial infection	
6	*P. tomentosa*	Flower	Anti-viral activity against EV71 and CAV 16 - caused hand, foot and mouth disease	Ji *et al*., 2015
			Antioxidant activity	Meng *et al*., 2014
			Antimicrobial activity; Antibacterial activity	Ibrahim *et al*., 2013
			Against Acne vulgaris	Guo *et al*., 2011
			First to second-degree empyrosis	Luo *et al*., 2010
8	*P. tomentosa*	Flower	Hypotensive, anti-inflammatory, antispasmodic, anti-oxidant and	Loizzo *et al*., 2007; Gerritsen *et al*., 1995; Ko *et al*., 2004;

			vasorelaxant activities; Anti-tumorigenic effect in vitro as well as in vivo	Capasso *et al*., 1991; Cos *et al*., 1998; Zhang *et al*., 2000; Czyz *et al*., 2005; Parajuli *et al*, 2009
			Bacterial inhibitor	Wei *et al*., 2006
			Neuroprotective effects	Kim *et al*., 2010
7	*P. elongata*	Leaf	Antimicrobial activity	Popova and Baykov, 2013
			Decreasing erythrocyte and leukocyte counts; Reducing blood glucose	Varlyakov *et al*., 2013
8	*P. fortunei*	Seed	Diabetes and its complications	Kim *et al*., 2011
9	*P. tomentosa var. tomentosa*	Bark	Antioxidant activity	Jiang, 2003; Si *et al*., 2013
		Bark, fruit, xylem, and leaf	Hemorrhoid; Carbuncle; Inflammatory bronchitis; Gonorrhea; Upper respiratory tract infection; Parotitis; Asthma; Traumatic bleeding; Erysipelas; Bacteriological diarrhea; Swelling; Bronchopneumonia; Enteritis; Conjunctivitis; Hypertension; Tonsillitis	Jiang, 2003; Jiangsu New Medical College, 1977
			Anti-inflammatory and analgesic properties; Boosting immunity; Lowering blood glucose	Li *et al*., 2007
	P. coreana	Leaf	Anticancer activity against breast and cervical cancer cell lines	Jung *et al*., 2012
	P. tomentosa	Fruits	Anticancer activity against human lung adenocarcinoma cells	An *et al.*, 2014
	P. tomentosa	Extract	Anti-inflammatory	Hošek *at al*., 2010
	P. tomentosa	Extract	Anticancer agent	Kollár *et al*., 2011
10	*Paulownia sp.*	Leaf and flower	Fertilizer; Fodder	Rahman *et al*., 2013
		Leaf	Frostbite; Leg ulcers	Zhao, 2003
	Paulownia sp.	Flower	Bronchial asthma	Zhang *et al*., 2002
	Paulownia sp.	Flower	Asthmatic trachea inflammation;	Chen and Li, 2007
		Bark	Hemorrhoids; Insecticide; Swelling; Hair growth induction;	The Editorial Committee of Flora of China, 1979
11	*Paulownia sp.*	Extract	Antibacterial; Anti-inflammatory; Thirst-quenching; Diuretic; Antihypertensive; Hemostatic, Insecticidal effects	Qu *et al*., 2011
			Hemostasis	Cao *et al*., 2008
			Tinea pedis	Guo *et al*., 2011
		Fruit	Inhibitory activity against gram-positive bacteria	Si *et al*., 2009
		Bark	Wild bee stings	Zhao, 2003

5. Conclusion

Paulownia elongate is a medicinal plant that contains some bioactive ingredients. The roots of *paulownia elongate* was used in this study to determine the histopathology gastric muscosa of rats injected with indomethacin at varying dose. The study revealed that *Paulownia elongate* roots extract demonstrated potential anti-ulcer activity in ulcer rats.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to disclosed.

Statement of ethical approval

All ethical considerations as approved by the Department of Biochemistry, Federal University Wukari as regard animal studies were strictly followed in this research.

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