

Analgesic, antipyretic and antiulcer activities of *Ailanthus altissima* (Mill.) Swingle

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Abstract

Traditionally, medicinal plants have been used in folk medicine throughout the world to treat various diseases, specially pain, fever and gastric ulcer. *A. altissima* is used in traditional medicine for treatment of dysentery, gonorrhoea, haemorrhoids and a remedy for cough, gastric and intestinal upsets. The bark of *A. altissima* is prescribed to treat anaemia, diarrhoea, haemorrhage and spermatorrhea. It is also used as antispasmodic, antiasthmatic, cardiac depressant, astringent and for treatment of epilepsy. The diethyl ether and chloroform extracts of *A. altissima* stem bark of Egyptian origin were evaluated for their analgesic, antipyretic and antiulcer activities. Analgesic and antipyretic activities were evaluated by using hot plate test at doses of 50 mg/kg and 100 mg/kg of the extracts. The extracts have similar analgesic activity and the ether extract showed good analgesic activity at 30 min. Also extracts showed a decrease on rectal temperature that means an hypothermic activity of the plant extracts with longer effect for the ether extract. The extracts at doses of 50 mg/kg and 100 mg/kg proved significant an antiulcerogenic effect related to cytoprotection activity. Phytochemical analysis revealed that the extracts are rich with biologically active chemical constituents, quassinoids (highly oxygenated triterpenes) and alkaloids.

Keywords: *Ailanthus altissima*, stem bark, analgesic, antipyretic, anti-ulcer, quassinoids, alkaloids

Introduction

The practice of herbal medicines dates to the very earliest of known human history. Pain, fever and ulcers are very common complications in human beings. The great variety of plants and their popular use with medical purpose, in special for the low income population, justifies the study of these as potential drugs source. Analgesia is the inability to feel pain while still conscious, fever is the body's natural function to create an environment where infectious agents or damaged tissues can not survive (Chattopadhyay et al. 2005). Normal body

temperature is regulated by a center in the hypothalamus that ensures a balance between heat loss and production. Fever occurs when there is a disturbance of this hypothalamic (thermostat), which leads to the set-point, the temperature regulating mechanisms (dilation of superficial blood vessels, sweating etc.) then operate to reduce temperature (Anonymous, 1976). Most of antipyretic drugs inhibit COX-2 expression to reduce the elevated body temperature by inhibiting PGE₂ biosynthesis (Cheng et al., 2005).

Peptic ulcer disease is a very common global health problem today. Peptic ulcer is a lesion of gastric or duodenal mucosa. Gastric ulcers occur commonly at old age and in lower socio-economic class of individuals. Although the exact cause of ulceration is not known, hydrochloric acid and pepsin are responsible for maintaining the lesion once it is produced. Peptic ulcers also occur at the lower end of the esophagus, on the jejunal side of a gastroenterostomy and in Meckel's diverticulum (Boyd 1970). The current therapeutic approach to gastric ulceration is to achieve inhibition of gastric secretion, promotion of gastric protection, blockage of apoptosis, and epithelial cell proliferation for effective healing (Edwin et al. 2007).

In recent years, focus on plant research has increased worldwide and several studies had showed immense potential of medicinal plants and several plants are claimed and proved to possess analgesic, antipyretic and antiulcer properties. *Ailanthus altissima* (Mill.) Swingle is a deciduous tree belonging to Simaroubaceae family and widely distributed in Asia and north Australia. Its native origin is China and it is known as tree of heaven (Adamik and Brauns 1957) and then it is introduced to Europe and the United States because people admired the beautiful foliage of these fast growing trees and for over a century have been planted as an ornamental. *A. altissima* is used in traditional medicine for treatment of dysentery, gonorrhoea, haemorrhoids and a remedy for cough, gastric and intestinal upsets (Perry 1980). The bark is prescribed to treat anaemia, diarrhoea, haemorrhage and spermatorrhea (Perry 1980), it is also used as antispasmodic, antiasthmatic, cardiac depressant, astringent and for treatment of epilepsy (Watt and Breyer 1962). Previous phytochemical studies on *A. altissima* have demonstrated the presence of quassinoids (Casinovi et al. 1983; Chiarlo and Pinca 1965, Furuno et al. 1981; Niimi et al. 1987; Kubota et al. 1996) as well as indole alkaloids (Ohmoto et al. 1981; Varga et al. 1981; Ohmoto 1984; Souleles and Waigh 1984; Souleles and kokkalou 1989) lipids and fatty acids (Chiarlo and Tacchino 1965; Bory and Clair-Maezulajty 1989; Kapoor et al. 1990; Kucuk et al. 1994), phenolic derivatives (Souleles and Philianso 1983; Barakat 1998; El-Baky et al. 2000) and volatile compounds (Mastelic and Jerkovic 2002) isolated from *A. altissima* leaves. Extracts of *A. altissima* and some isolated compounds have demonstrated medicinal properties such as antituberculosis, antimalarial, antitumor and antiherpes activities (Hwang et al. 2002; Crespi et al. 1988; Kraus et al. 1994; Rahman et al. 1997; Bray et al. 1987; Tamura et al. 2000; Ohmoto et al. 1989; Ohmoto et al. 1983; Ohmoto et al. 1985). A great amount of analgesic, anti-inflammatory and antipyretic drugs already exist. Most of which present, as the main adverse effect, the production of nuisances and lesions at gastric level, for that reason, research on compounds that have the effect to reduce the temperature and analgesia combined with a protection of gastrointestinal tract could be of great importance. In order to clarify several aspects of the biological activities of *A. altissima* stem bark, a preliminary study was carried out to evaluate the analgesic, antipyretic and antiulcer activities of ether and chloroform extracts.

Materials and Methods

Plant material

Stem bark of *Ailanthus altissima* was collected from Orman garden, Giza, Egypt in April 2010. The plant was identified by Prof. Dr. Kamal El Batanony, professor of Taxonomy and Botany, Faculty of Science, Cairo University. A voucher specimen No.13245 is deposited in the herbarium of Orman garden, Giza, Egypt.

Extraction

500 g of powdered of *A. altissima* stem bark was extracted with diethyl ether and chloroform in a continuous extraction apparatus (soxhlet apparatus). Each extract was concentrated under reduced pressure to give 9 gm of diethyl ether and 10.5 gm of chloroform extracts respectively. Each extract of *Ailanthus altissima* was phytochemically screened according to the following (Connolly et al. 1970 for sterols and/or triterpenes (quassinoids); Wolf et al. 1962 for carbohydrates and saponins; Harbone 1973 for flavonoids and alkaloids; Farnsworth 1966 for coumarins; Geissman 1962 for tannins)

Pharmacological studies

The extracts were given by i.p. and p.o. in analgesic and antipyretic activities in different doses and by gavage in antiulcerogenic activity in a constant volume of 0.2 ml/30g body weight in doses equivalents of 100 mg/kg and 50 mg/kg. All experiments were performed on male Swiss mice, Glaxo (Charles River), weighing 30 ± 5 g, kept in controlled stabilized conditions were used. The animals were fed a standard diet with free access to tap water, and were housed in a 12 h light/dark cycle at humidity of 50% and a temperature of 24 ± 1 °C. The experimental protocols were approved by the Animal Use and Care Committee of Complutense University of Madrid. A statistical analysis of the results was made by calculating the arithmetic mean \pm SE and the significance of difference was determined by Student's *t*-test, U of Mann Whitney and Newman Keuls test taking $p < 0.05$ and $p < 0.01$ as significant.

Analgesic and Antipyretic activities

Hot plate test

(The Eddy and Leimbach 1953) method, modified by (Turner and Hebborn 1965), was used and the extracts (50 mg/kg and 100 mg/kg of ether and chloroform extracts of *A. altissima* and controls (vehicle, 100 mg/kg ASA, 5 mg/kg morphine sulphate) assayed on groups of nine mice. The reaction time of the animals to pain stimulus when placed on a metallic hot plate kept at 54 ± 0.5 °C was measured. The readings were taken before, and ½h, 1h, 1 ½h and 3h after administration of the extracts and controls. The rectal temperature was taken before and during the assay in order to know if the extracts modified the temperature. Rectal temperatures were recorded in a Panlab multichannel electric thermometer at the same time intervals from administration of the extracts and controls.

Antiulcerogenic activity

Ethanol-induced ulcer and determination of ulcerative lesions, acidity and pH values

The antiulcerogenic activity of the two extracts obtained from *A. altissima* in this model was assessed in mice, as described by (Slowing 1992; Delgado 1993) with some modifications. This is an experimental model of gastric ulcer induction which is independent of gastric juice secretion and exhibit a drug cytoprotection activity and enhance mucosal defensive mechanism. Mice were divided into 6 groups of seven animals which were treated for one week (seven days consecutives) to oral dosing with vehicle 0.6% Tween 80 (10 ml/kg), omeprazole (20 mg/kg), Diethyl ether (100 and 50 mg/kg), Chloroform (100 and 50 mg/kg). Mice were fasted for 24 h prior to the last oral dosing. Thirty minutes after the treatments, all animals received orally 0.2 ml of Ethanol 98%. Animals were killed by cervical dislocation 1 h after the administration of EtOH. The stomachs were removed, inflated by an injection of saline (2 ml) and the gastric content collected to determine the total amount of gastric juice acid (ml) and pH values. EtOH induced gastric damage which was observed in the gastric mucosa as elongated black - red lines parallel to the long axis of the stomach of the mice. The lesion index was determined according to Marhuenda's Index as the sum of the erosion length. The stomachs were excised and opened along the greater curvature and then were fixed and the ulcerative lesions were observed. The ulcerative lesions index (ULI) was calculated (Alarcon et al. 1992; Pascual 2001; Slowing 1992).

$$\% \text{ Inhibition} = \frac{\text{U.L.L.c} - \text{U.I.I.p}}{\text{U.I.c}} \times 100$$

Where, U.L.I.c = Control ulcerative lesion index, and U.L.p = problem substance or standard ulcerative lesion index. The gastric content collected were used to determine the acidity and pH values according to the method described by (Vela et al. 1997). Two ml of distilled water were added to each tube with the gastric content and measured the pH values. Total acid in the gastric secretion was determined by titration with 0.01 N NaOH and phenolphthalein as indicator. The expression of results were in mEq/l.

Determination of sulphidryl groups (SH) in gastric mucosa

The assay was performed according to the methodology described previously by (Hissin and Hilf 1976) with some modifications. This assay was made suitable in plates of 96 wells and o-phthalaldehyde (OPT) was used as a reagent for a fluorometric assay of reduced glutathione (GSH). This method consist in GSH ability to react with OPT at pH 8, yielding a highly fluorescent product that could be activated at 350 nm with an emission peak at 420 nm.

Tissue preparation

Mice were killed by cervical dislocation; stomachs were removed, opened along the curvature and washed gently. The tissue was homogenized on ice using a Polytron homogenizer with a concentration of 100 mg of tissue/ ml of phosphate-EDTA buffer and 10 µl of 60% HClO₄ for each ml of homogenizer, which was used as a protein precipitant. The total

homogenate was centrifuged at 4°C at 10,000 rpm for 10 min to obtain the supernatant and stored cold until sulphidryl assay

GSH assay

For determination of GSH 10 µl of the supernatant in each well and phosphate-EDTA buffer until final volume of 200 µl, was added. At the final mixture 20 µl of PTO was added for the reaction with GSH present in the sample. After thorough mixing and incubation at room temperature and darkness for 15 min. Fluorescence at 420 nm was determined with activation at 350 nm. The fluorescence intensity for the OPT-GSH reaction was directly related to SH (sulphidryl groups) concentration and was linear over the concentration range. The results was expressed as µg SH/mg of tissue.

Results

Analgesic and Antipyretic activities

We have conducted a study of the potential analgesic and antipyretic activity of plant extracts, using the “hot plate test” and the measure of the rectal temperature, as a simple methods of analysis. To study the analgesic activity, standards with central and peripheral analgesic activity (morphine and acetyl salicylic acid) were used.

The results indicated that extracts considered for analysis have similar analgesic activity than those from AAS group, but only, in the case of the ether extract which shows good analgesic activity at 30 min although the maximum is reached 1 hour after administration, with high stability. Some pattern than aspirin but this one has a higher effect (66.55%). This indicates that plant extracts are less potent active as analgesic agent at popular level (Table 1).

Results also shown a decrease on rectal temperature that means an hypothermic activity of the plant extracts with longer effect for the ether extracts although the instauration period is longer than the chloroform extract. The decrease on temperature follows the same pattern that the analgesic activity (a maximal effect after 30 min of administration) but in contrast these effect is not stable for a long time. In this case the chloroform extract takes longer to act reaching its maximal activity after 3 hours with a more stable effect. That indicates that plant extracts are less potent active as antipyretic agent at popular level (Table 1).

Table 1. analgesic and antipyretic activity of *A. altissima* extracts.

Treatment	Temperature Drop (°C) ±SD.				
	Dose	1/2h	1h	1 1/2h	3h
Control		0,1 ± 0,01	0,1 ± 0,02	0,2 ± 0,03	0,1 ± 0,02
AAS	100 mg/kg	1,2 ± 0,24*	0,7 ± 0,10*	0,9 ± 0,17*	1,0 ± 0,11*
Morphine	5 mg/kg	1,5 ± 0,32*	1,3 ± 0,22*	1,1 ± 0,23*	1,0 ± 0,15*
E.Ether	50 mg/kg	1,0 ± 0,19*	0,4 ± 0,04	0,4 ± 0,07	0,3 ± 0,05
E.Chloroform	50 mg/kg	0,4 ± 0,06	0,8 ± 0,17*	0,8 ± 0,13*	1,3 ± 0,21*

* Significant P < 0,01 vs control; Test t-Student-Newman-Keuls.

Table 2. Antiulcer activity of *A. altissima* extracts.

Treatment	Dose	I.U.	% I	SH No P
Control		6 ± 0,61	0	301,2± 36,47
Omeprazol		1,2 ± 0,61*	78,5	340,2 ± 38,99
E.Ether	100mg/Kg	2,82± 0,69*	53	406,7 ± 36,47*
E.Ether	50mg/Kg	2,30± 0,72*	61,67	345,9 ± 36,47*
E.Chloroform	100mg/Kg	3,75± 0,66*	37,5	405,3 ± 38,99*
E.CHloroform	50mg/Kg	3,23± 0,63*	46,17	358,6 ± 36,47

I.U.: Index of ulceration of the substance in study±SD, according to scale of Marhuenda. (%I): percentage of inhibition with respect to the index of ulceration of the lot control. SH. N. P: Sulphidryls non protein±SD.* Significant with respect to L1 (Control), P< 0,01.

Antiulcer activity

Ethanol-Induced Ulcer and determination of ulcerative lesions, acidity and pH values

Ether extracts showed a gastric ulcer protection activity for doses of 100 mg/kg as well as 50 mg/kg with higher activity in this case, that means that the effect is non doses dependant. (Table 2). The acidity and pH of the gastric juice is not affected.

Determination of sulphidryl groups (SH) in gastric mucosa

Ether and chloroform extracts (50 and 100 mg/kg) shown a significant results (350 and 400 µg/mg tissue) of sulphidryl groups in gastric mucosa which act as endogenous protection factor and whose gastric ulcer protection activity is very well known. The results of phytochemical screening of *Ailanthus altissima* stem bark extracts are compiled in Table 2.

Discussion

Plant extracts are some of the most attractive sources of new drugs and have been shown to produce promising results in different pharmacological activities. This plant is a source of several classes of compounds, which include alkaloids which were detected with Dragendroff's reagent (Table 3) and according to (Harbone 1973), as well as, primarily, the bitter components known as quassinoids (highly oxygenated triterpenes), a group of substances be-

Table 3. Phytochemical analysis of extracts from *A. altissima* stem bark.

Constituents	Diethyl ether	Chloroform
Triterpenes and /or Sterols (Quassinoids)	++	+
Carbohydrates and/or glycosides	-	-
Flavonoids	-	-
Coumarins	-	-
Alkaloids and/or nitrogenous compounds	+	+
Tannins	-	-
Saponins	-	-

++ presence of constituents in considerable amounts; + presence of constituents; - absence of constituents

longing to the terpenes class and their detection was achieved by spraying a 3% H₂SO₄ solution in methanol under UV light at 254 nm and heating for 5 minute at 115°C. Quassinoids afforded a red color when sprayed with 3% H₂SO₄ solution in methanol and produced a brown color after heating at 115°C (Connolly et al. 1970). To evaluate the potential gastric ulcer protection activity, a model of ulcer induction by ethanol was used, which is independent of the secretion of gastric juice. This allows to evaluate the cytoprotective activity of a drug (increasing the defence mechanisms). (Slowing, 1992; Delgado, 1993). Omeprazole as a commonly used drug in ulcer therapy, was used as an anti-ulcer agent, which is an inhibitor of the bomb ATPase H⁺/K⁺. EtOH manifests its harmful effects either through direct generation of reactive metabolite, including free radical species that react with most of the cell components changing their structures and functions or by contributing to other mechanism that finally promote enhanced oxidative damage. Ethanol induced gastric mucosal capillaries and increased vascular permeability. Mucosal capillary, necrosis, vascular congestion and thrombosis in the sub-epithelial microvasculature accompany disruption of the gastric mucosal barrier. In addition to the direct injurious effects of EtOH on gastric mucosa, other factors are also thought to be involved in the pathogenesis of injury. This activity does not seem to be due to an inhibition of the gastric secretion, as the acidity of the gastric juice is not affected, the effect can be due to the implication of mechanisms that originate and increase of the content of SH of the mucosa which act as endogenous protection factor and whose gastric ulcer protection activity is very well known. Although, it is possible that the drug also acts on other factors as prostaglandins, etc. All these results make consider of special interest the study in depth of all the possible mechanisms that could be implied in the anti-ulcer activity. This results show that *A. altissima* extracts have an antiulcerogenic effect related to cytoprotection activity (Morimoto et al. 1991; Hiruma et al. 1996a, Hiruma et al. 1996b; Pascual 2001) but exact mechanisms are not clear yet and need further investigations. It is possible that the inhibitory effects of extracts are due, at least partly, to the presence of terpenoids (quassinoids). These compounds were associated to antiulcerogenic activity in other plants (Toma et al. 2002). Some triterpenes are known as antiulcer and their action has been suggested to be due to the activation of cellular protection, metabolism cytoprotective action and reduction of gastric vascular permeability.

Conflict of interest

There is no conflict of interest associated with the authors of this paper.

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