Abortifacient activity of *Aegle marmelos* and *Laurus nobilis* leaf extracts

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Abstract

Rapid elevation of population in India is the one of the major problems, which directly influence the economy of country and may lead to poverty. Government implemented number of family planning programs through the various surgical operations (tubectomy and laproscopy) and oral contraceptives. Usage of oral contraceptive pills may lead serious complications, and may induce congenital abnormalities. The primary goal of this research is to assess the abortifacient activity in rat models of two historically used medicinal plants, *Laurus nobilis L.* and *Aegle marmelos* (L.) Corr. Restructure the paragraph as the study included 18 female wistar rats (150-200 g) and six male wistar rats (male wistar rats were used only for copulation). Female rats in proestrous phase were isolated and allowed to mate with males of proven fertility using the mass mating technique in a 3:1 ratio for an overnight. Control animals received an equivalent volume of the dosing vehicle (1% tween 80) orally. Aqueous extract of *Laurus nobilis* (AQLN) leaves and Ethanolic Extract of *Aegle Marmelos* leaves (EEAM) at doses of 175 mg/kg and 250 mg/ kg of were orally administrated daily for 10 days from day 0 of pregnancy to day 9. On day 20th of pregnancy, all the animals were sacrificed under euthanasia and the uterine horns were isolated, later they were examined for number of abortifacient sites and deformities of fetuses. The number of live fetuses in animals treated with EEAM at two doses was substantially lower in Group-4 at 175mg/kg (2.63 + 0.36) and Group-5 at 250mg/kg (1.87 + 0.40) compared to the vehicle control group (p 0.05, p 0.01). The survival ratio decreased considerably from 52.2% to 28.8% as the dose increased. Similarly, the abortion rate was higher in group 5 compared to Group-4. AQLN demonstrated to have 100% abortifacient efficacy at 250mg/kg, while EEAM has 83.3%.

Introduction

Plants are abundant in ecologically formed secondary metabolites and physiologically active molecules with a variety of pharmacological and therapeutic properties. The use of herbal plants for contraception has been widely utilized over the past decade (both male and female), and it is still done in tribal communities due to a lack of conventional prescription for oral contraception. Over 7500 plant species were estimated to be employed by ethnic communities of human and veterinary healthcare in India, notably in distinct traditional and folk regions. Plants are abundant in ecologically formed secondary metabolites and physiologically active molecules with a variety of pharmacological and therapeutic properties. The use of herbal plants for contraception has been widely utilized over the past decade (both male and female), and it is still done in tribal communities due to a lack of conventional prescription for oral contraception. Over 7500 plant species were estimated to be employed by ethnic communities of human and veterinary healthcare in India, notably in distinct traditional and folk regions.[1] Herbal medicines are commonly used by tribal people rather than allopathic medicine for a variety of ailments such as monthly irregularities, birth disorders, birth control, sterility, and abortion. Abortion, sterilization, and contraception are the three methods of population control. The most common method employed by indigenous people is abortion.[2] Abortifacients are medications or substances that cause abortion, or the permanent expulsion of a fetus, during a life-threatening pregnancy, or in women who are unable to carry a pregnancy in order to preserve the mother's life and prevent the delivery of a deformed infant. Herbal medicines are commonly used by tribal people rather than allopathic medicine for a variety of ailments such as monthly irregularities, birth disorders, birth control, sterility, and abortion. The use of these synthetic abortifacients has been followed to avoid conception in industrialized countries, although they may induce the complications in babies who are born from mothers who regularly use of oral contraceptive pills. Misoprostol is frequently used as a synthetic abortifacient to induce abortion under the care of a gynecologist during abnormal fetal growth. However, the time required to accomplish the pregnancy termination is longer than when the medicine

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is given in conjunction with mifepristone. Furthermore, abortion is frequently painful and associated with greater side effects than when taken with mifepristone.[3] The side effects of synthetic abortifacients include down syndrome, muscular dystrophy, and anencephaly, among others.[3]

The laurel, *Laurus nobilis L*., also commonly called bay-leaves, is an evergreen tree or shrub belonging to the family Lauraceae, is native to the south parts of Europe and the Mediterranean area. The dried leaves and the oil from leaves are used as a valuable spice and flavoring agent in culinary and food industry.[4] Leaves of *L. nobilis* are also used in folk medicine.[5] It increases gastric fluid production and suppresses various digestive difficulties, including flatulent colics, bacterial and fungal growth.[6,7] The leaf has been utilized as a herbal remedy due to its anti-oxidant, antibacterial, anti-fungal, anti-diabetes, and anti-inflammatory properties.[8] Oxygenated monoterpenes account for 48.6% of the EO, with 1.8-cineole (31.9%), sabinene (12.2%), and linalool (10%) constituting the primary constituents. Similarly, it increases gastric fluid production and suppresses various digestive difficulties, including flatulent colics, bacterial and fungal growth.[6,7] The leaf has been utilized as an herbal remedy due to its anti-oxidant, anti-bacterial, anti-fungal, anti-diabetes, and anti-inflammatory properties.[8] Oxygenated monoterpenes account for 48.6% of the EO, with 1,8-cineole (31.9%), sabinene (12.2%), and linalool (10%) constituting the primary constituents. The fruits traditionally have been used for treating skin rashes, rheumatism, earaches, sprains and to promote perspiration as a carminative, diaphoretic, stimulant, cough, cardiac diseases, viral infections, diarrhea, indigestion and as a general gastric secretion stimulant, emetic, emmenagogue, abortifacient, antiseptic, and insect repellent.[9,10]

More than 100 phytochemical substances, including phenols, flavonoids, alkaloids, cardiac glycosides, saponins, terpenoids, steroids, and tannins, have been identified from various portions of Bael (*Aegle marmelos*). However, bioactive substances found in Bael's fruits, bark, leaves, seeds, and roots include coumarin, xanthotoxol, imperatorin, aegeline, and marmeline. These substances have antidiabetic, anticancer, antifertility, antibacterial, immunogenic, and insecticidal properties. They possess biological activity against a variety of chronic diseases, including cancer, cardiovascular disease, and gastrointestinal disorders.[11-14] The leaf is one of the most accumulative sections of the plant, including bioactive chemicals that are generated as secondary metabolites.

There was no evidence available about the abortifacient activity of *Laurus nobilis* or *Aegle marmelos*. The abortifacient effect of an Aqueous Extract of *Laurus Nobilis* (AELN) and an Ethanolic Extract of *Aegle Marmelos* (EEAM) leaves on rats was thus thought to be of interest.

Materials and Methods

The leaves of *Laurus nobilis* and *Aegle marmelos* were collected from rural area of Guntur district, Andhra Pradesh, India. The plants were authenticated by Dr. P. Satyanarayana Raju (Plant taxonomist) of Department of Botany at Acharya Nagarjuna University, Guntur, Andhra Pradesh.

The leaves of *Laurus nobilis* were cleaned with purified water to remove dust. To remove moisture from leaves, they are sun-dried. The powdered leaves were then subjected to three hours of hydro distillation. The oil was removed and separated from the mixture before being kept at 4 degrees Celsius. On the other hand, *Aegle marmelos* was extracted using the Soxhlet method with ethanol as the solvent. The extraction was conducted for 72 hours at a temperature below the boiling point of the solvent at room temperature. Utilizing solvent evaporation, the dry weight of the plant extracts was determined.

Phytochemical characterization

The *Laurus nobilis* aqueous extract and *Aegle marmelos* ethanolic extract were subjected to various phytochemical tests to confirm the presence of major chemical substance, by using the standard methods.

Animals

For our investigation, 8-10-week-old Wistar albino rats of either sex (150-200g) were selected. The experimental animals had free and unrestricted access to a regular rat pellet diet and water, and they were housed in polypropylene cages six animals per cage. Standard laboratory conditions (room temperature of - 24o + 1oC, relative humidity of 60%, and a light/dark cycle of 12 hours) were maintained. Prior to the trial, the animals were given seven days to acclimate to the laboratory environment. The experimental procedure was approved by the Institutional Animal Ethical Committee (IAEC) of Chalapathi Institute of Pharmaceutical Sciences in accordance with the CCSEA guidelines (CCSEA Reg. No. 1048/PO/Re/S/07/CCSEA; Protocol approval No. 06/IAEC/CLPT/2018-19).

Acute toxicity study

The healthy female albino rats, starved for 3-4 h were subjected to acute toxicity studies as per OECD 423 (OECD, 2002) guideline. The rats were observed for behavioral, neurological and autonomic profile and lethality or death for 24, 48 and 72 hr.

Abortifacient activity

8–10-week-old female Wistar rats weighing between 150 and 200 g were chosen for investigation, along with 6 male Wistar rats (male Wistar rats were used only for copulation). To select animals with a consistent estrous cycle of 5-6 days, the vaginal smear of each female rat was examined daily for 12 days to determine the degree of epithelial cornification. The rats in proestrus were identified and separated from the remaining rats to enable for mating with males proved to be fertile using the mass mating procedure.[15] By keeping both male and female rats in the same cage overnight in a 1:3 ratio. The vaginal smears from each rat were then collected using the swab smear technique,[16] and examined under the microscope to confirm copulation as well as the presence of spermatozoa till the next morning. The rats with spermatozoa were termed pregnant positive and were marked and placed in separate cages; this period was considered day 0 of pregnancy. Pregnant animals were divided into three groups and regularly treated with vehicle (Control), AQLN (175 mg/kg and 250 mg/kg) EEAM (175 mg/kg and 250 mg/kg) respectively for 10 days (day 0 to day 9). The control group animals were treated orally equal volume of the dosing vehicle (1% tween 80). 175 mg/kg and 250 mg/kg of AQLN were suspended in 1% v/v Tween 80 and administered orally daily to the animals in Group II, while Group III was treated with EEAM (175 mg/kg and 250 mg/kg) for 10 days, from pregnancy onset to the 9th day. On 20th day caesarian delivery was performed to all animals under anesthesia with thiopental sodium at a dose of 40mg/kg. Observed rats for changes in food/water intake, presence of vaginal bleeding, and behavior, as well as recorded the number of corpora lutea, implantations in each ovarian horn, and the correlation between fetal placement in each ovarian horn. For evaluating the efficacy of the plant extract, the total number of fetuses were counted, as well as (live/dead) fetuses, (early/late) resorptions, body weight (grams) of each fetus and body length (cm) from crown to rump of each fetus.

All fetuses were stored in 70% alcohol for 24 hours to detect any exterior abnormalities. If an abnormality was detected or suspected in a fetus, it should be referred to

skeletal investigations to determine the cause.[17] The remainder of the fetus was processed for slicing to examine gross histological examinations.[18]

Evaluation of blood hormone levels

Blood samples were collected from each animal via cardiac puncture in order to estimate the hormone levels in the blood. The blood samples were allowed to stand for 30-45 minutes to coagulate before being separated from the blood by centrifugation at 3000 rpm for 15 minutes. The serum was separated and placed in micro centrifuge tubes, which were then stored at -200C until the estimation of Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) was performed.

Statistical analysis

All data is expressed as mean ± SEM. The data of each experimental group was analyzed using one-way Analysis Of Variance (ANOVA) followed by Dunnett's multiple comparison test. $p < 0.001$ and $p < 0.01$ was considered as a significant when compared to the control.

Results

Phytochemical characterization

Phytochemical screening revealed the presence of alkaloids, carbohydrates, flavonoids, terpenoids, tannins, proteins, aminoacids, steroids, glycosides, fixed oils, and fatty acids in aqueous extract of *Laurus nobilis* leaves and in ethanolic extract of *Aegle marmelos* leaves (Table 1). Plants with active phytochemical constituents have already been shown to be effective in preventing pregnancy.[19,20]

Acute toxicity study

Acute toxicity testing for AQLN and EEAM was carried out using wistar rats in accordance with OECD Guideline 423. Aside from occasional clustering of the rats in one corner of the cage, the results of the acute toxicity test revealed no lethal or other treatment-related effect in all groups. Animals were clinically observed to determine changes in their eyes, skin and fur, mucous membranes, circulatory, autonomic, respiratory, and central nervous systems, as well as their behaviour patterns, somatomotor activity, convulsions, tremors, salivation, lethargy, sleep, and coma. Based on this finding, it was determined that both extracts are safe up to 2000mg/kg with no toxicity or fatality.

Abortifacient activity

Effect of AQLN and EEAM on foetal development of Rats

In Group-2, which received 175 mg/kg of AQLN, the number of live fetuses was reduced (1.17+0.31), but in Group-3, which received 250 mg/kg, there were no live fetuses (6.66+1.86). Survival rates of 21.95% and 0% were obtained for 175 mg/kg and 250 mg/kg, respectively, however a high number of litters were seen in the control group (100%). The litters born from the animals treated with AQLN did not show any physical deformities. It shows a plant extract without teratogenic effects at the indicated dose. Significant abortifacient action was detected in Group-3 animals (250 mg/kg), whereas Group-2 animals had a modest impact. 175mg/kg induced abor-

Table 1. Phytochemical Characterization of AQLN and EEAM.

Phytoconstituents	Chemical tests	AQLN	EEAM
Alkaloids	Wagner's test	+	+
	Hager's test	+	+
Carbohydrates	Fehling's test	+	+
	Benedict's test	+	+
	Barfoed's test	+	+
Flavonoids	Shinoda test	+	+
	Sulphuric acid	+	+
	Lead acetate	+	+
	Sodium hydroxide test	+	+
Phenols	Lead acetate test	+	-
	Ferric chloride test	+	-
Saponins	Foam test	-	-
Sterols	Liebermann burchard test	+	+
	Salkowski test	+	+
Tannins	Ferric chloride test	+	+

+(present), -(negative).

Table 2. Effect of AQLN and EEAM on foetal development.

Parameters	Control	AQLN (175 mg/kg body weight)	AQLN (250 mg/kg body weight)	EEAM (175 mg/kg body weight)	EEAM (250 mg/kg body weight)
Foetal body weight (g)	5.00 ± 0.34	2.79±0.13	2.33±0.41	2.79 ± 0.14	2.82 ± 0.12
Foetal body length (cm)	3.93 ± 0.37	2.94 ± 0.06	2.15±0.35	2.82 ± 0.13	2.94 ± 0.09
No. of live foetus	6.66 ± 1.86	1.17 ± 0.31	0	2.63±0.36	1.87 ± 0.40
No. of dead foetus	0	4.16±0.48**	5.33±0.76***	5.00±2.8**	4.61±1.18**
Survival ratio of foetus (%)	100	21.95	0	52.6	28.8
No. of rats that aborted	0	4	6	3	5
%of rats that aborted	0	66.7	100	50	83.3
No. of implantation sites	10.67 ± 0.99	6.81 ± 0.30**	4.26 ± 0.54***	4.80 ± 0.74**	4.09 ± 1.21**
No. of corpora lutea	11.67 ± 0.95	7.37 ± 0.30**	5.83 ± 0.36***	5.46 ± 0.21**	5.13 ± 0.33**
Implantation index (%)	91.4	92.4	73.1	87.9	79.7
Resorptions	0	3.66 ± 0.21**	2.16 ± 0.18***	4.16 ± 0.62**	2.83 ± 0.38**

All values are Mean ± SEM, and statistically analyzed using One Way Analysis of Variance (ANOVA) followed by Dunnet's multiple comparison test n=6, ***p<0.001, **p<0.01.

tions in 66.7% of animals. The formation of corpora lutea was dramatically reduced as the dose of AQLN extract was raised. Implantation index was not significantly different between the (175 mg/kg) extract treated group and the normal control group, however, the 250 mg/kg extract treatment decreased the implantation index. Similarly, the extract significantly decreased the number of resorptions.[21]

The number of live fetuses in animals treated with EEAM at two doses was substantially lower in Group-4 at 175mg/kg (2.63 + 0.36) and Group-5 at 250mg/kg (1.87 + 0.40) compared to the vehicle control group (p 0.05, p 0.01). The survival ratio decreased considerably from 52.2% to 28.8% as the dose increased. Similarly, the abortion rate was higher in group 5 compared to Group-4 (Table 2). By increasing the amount of extract, the number of corpora lutea in mice treated with EEAM is substantially increased.

In cases where pregnancy continued despite drug administration, fetuses exhibited various skeletal defects (flattened mouth, everted claw, shoulder, knee, and ankle joint defects, valgus deformities, syndactyly and ectrodactyly, wrist drop, clubbing of limbs, kinking of tail, bent claw) in addition to visceral defects. The details of the birth defects caused by plant are included in Tables 2, 3, and 4.

Hormonal analysis

Blood levels of LH and FSH were measured to determine their impact on the regulation of pregnancy, as an imbalance of these hormones may result in abortion. Reduced levels of FSH in the blood indicate a deviation in the ovulation and estrus cycle. LH is crucial for maintaining the proper functioning of the corpus luteum. All animals in the group that got two doses of AQLN and EEAM exhibit a reduction in LH blood levels. However, the FSH level does not alter significantly (Table 5). The suppression of the serum progesterone concentration in our study could be attributed to inadequate activation of LH release as well as a decrease in LH's action on ovarian follicles, as suggested by the lowering of hormone levels in the blood.

Discussion

Our interest in herbal medications stems from our search for safe, effective, and convenient abortion options. There is a wealth of ethnobotanical evidence on the use of medicinal herbs as abortifacients, although the most of it is not scientifically validated.

Table 3. Effect of AQLN and EEAM on macroscopic development in Rat foetuses.

% Incidence	AQLN	EEAM
Foetuses Examined (N)	12	18
Everted claw	0	0
Kinking of tail	0	66.67
Ankle joint defect	70.83	0
Foot drop	0	0
Syndactyly	0	72.22
Ectrodactyly	0	72.22
Clubbing of right-hand limb	0	0
Left wrist drop	79.17	60.55
Right wrist drops	83.3	88.62
Wrinkled skin	0	0
Valgus deformity	0	0
Hip joint defect	70.83	0
Elbow joint defect	0	0
Knee joint defect	0	20.54
Retarded growth	0	0

Table 4. Effect of AQLN and EEAM on Visceral development in Rat foetuses.

% Incidence	AQLN	EEAM
Foetuses Examined (N)	12	18
Partial cleft palate	45	67.2
Full cleft palate	0	55.2
Neural canal enlargement	0	0
Neural pore	0	0
Abnormal left kidney	0	0
Brain cavity hollow	0	0

Table 5. Effects of AQLN and EEAM on skeletal development in rat foetuses.

% Incidence	AQLN	EEAM
Foetuses Examined (N)	12	18
Non-ossification of skull bones	0	58.2
Ribs bent inside	0	0
Humerus absent	0*	0*
Ribs attached to sternum	0	0*
Ribs short	25.8	0
Non-ossified ribs	0*	0*
Tarsal fused	0	0
Intercoastal space in ribs	0	0
Non-ossification of cervical region	0	0
Non-ossified facial bones	0	67.7

Table 6. Effect of AQLN and EEAM on LH & FSH levels.

Group	Treatment	Dose	Hormone level	
			LH (miU/mL)	FSH (miU/mL)
1	Control (Tween 80)	-	7.38 ± 2.53	9.26 ± 2.50
2	AQLN	175 mg/kg	6.00 ± 1.47	9.16 ± 2.05
3		250 mg/kg	4.12 ± 0.9	8.38 ± 0.53
4	EEAM	175 mg/kg	5.87 ± 1.42	8.87 ± 2.41
5		250 mg/kg	4.93 ± 0.45	7.93 ± 0.95

The leaves of *Aegle marmelos* and *Laurus nobilis* that have been reported in folklore literature as abortifacient but have yet to be experimentally proven. So, in this investigation, we attempted to investigate the abortifacient potential of AQLN and EEAM in Wistar rats.

A variety of phytoconstituents derived from natural sources have been shown to be effective abortifacient agents. Many investigations on the antifertility activity of flavonoids, alkaloids, glycosides, tannins, flavonoids, and saponins have been published. Beal leaves contain alkaloids, mermesinin, rutin, phenylethyl cinnamides, anhydromarmeline, and aegelinosides, sterols, and essential oils. The extracts' abortifacient activity was assessed using fetal development indicators associated with hormone levels. The decrease in the number of live fetuses in pregnant rats treated with AQLN or EEAM shows abortifacient action. The findings were further confirmed by a drop in the implantation index represents the number of fetuses aborted, whereas an increase in the resorption index indicates that the pregnancy was interrupted after implantation.[22-24] These findings indicated that AQLN and EEAM can be used to terminate a pregnancy. The levels of FSH and LH were measured as a sign of a failed pregnancy. The process of luteolysis preceding to parturition may involve a reduction in LH levels. Reduced LH levels may be associated with ovarian follicle lutenization inactivation, which may be responsible for low serum progesterone levels. Progesterone is essential during ovulation, implantation, and pregnancy.[25] In cases where pregnancy was continued despite AQLN and EEAM administration, the fetuses had various skeletal defects (flattened mouth, everted claw, shoulder, knee, and ankle joint defects, valgus deformities, syndactyly and ectrodactyly, wrist drop, clubbing of limbs, kinking of tail, bended claw) as well as other visceral defects.[24,25] These findings suggested that AQLN and EEAM have abortifacient activity.

Conclusions

The current investigation confirmed the uterine abortifacient potential of *Laurus nobilis* and *Aegle marmelos*, which may be due to the presence of various phytochemicals. The activity was more obvious at 250 mg/kg of both extracts rather than 175 mg/kg of both extracts, as verified by the hormonal analysis. The study shows that both plants have abortifacient activity at high doses.

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