Algerian Journal of Natural Products 6:1 **(2018)** 573-583

OPEN ACCESS

Online ISSN: 2353-0391

Algerian Journal of Natural Products

www.univ-bejaia.dz/ajnp

Type of the Paper (Article)

Teratogenic Effects of Ethanol Leaf Extract of *Dryopteris filix-mas* L. Schott

Earnest Oghenesuvwe Erhirhie [1,]*, Oluchi Nzubechukwu Ezemokwe [1] and Emmanuel Emeka Ilodigwe [1]

[1]Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Agulu, Nigeria.

**Author to whom correspondence should be addressed; * Email: erhirhieochuko@yahoo.com*
Tel.: +234-7060434974

Received: 02/02/2018 Revised: 05/04/2018 /Accepted:06/08/2018

Abstract:
This study evaluated the teratogenic profile of ethanol leaf extract of *Dryopteris filix-mas*. Thirty-two (32) female virgin albino mice were grouped into control and treatment groups (250, 500 and 1000 mg/kg of extract). Oestrus female mice were mated with males and pregnant female mice were administered the extract from the 6th until the 15th day of pregnancy. Morphological parameters as well as histopathologies of the femur, liver, kidneys, lungs and heart of pups in treatment and control groups were carried out. Administration of 250, 500, 1000 mg/kg of the leaf extract did not cause significant alteration ($p>0.05$) in morphological parameters in pups when compared with control group. There was no alteration in histo-architecture of the lungs, femurs, liver, heart and kidneys but there was poor mineralization in metaphysis of pups femur in high dose of the extract when compared to control group.
Key words: *Dryopteris filix-mas,* Teratogenic profile, poor mineralization in femur, mice.

I. Introduction

From prehistoric times, medicinal plants have been identified as alternative agents for treatment of various diseases. Plant parts including barks, roots, leaves, seeds among others were used against illnesses before the era of conventional drugs [1]. However, the fact that medicinal plants are from natural sources does not guarantee that they are completely free from deleterious effects [2].
Congenital defects are structural or functional anomalies that occur during the intra-uterine life. It can be identified before birth, at birth or after birth [3]. According to Lozano [3], congenital disorders resulted in about 510,000 deaths in humans globally in 2010. The patronage of herbal medicines is on the rise among the population including pregnant women [4]. Literatures had revealed that the use of herbal medicines by pregnant women in the Middle East of Nigeria varied between 22.3% and 82.3% [4]. A study conducted in Aminu Kano Teaching Hospital on the use of herbal medicines by pregnant women revealed that 31.4% of them used herbal medicines during pregnancy [5]. A socio-demographic study carried out among pregnant women at Imo State University Teaching Hospital (Orlu, South-East Nigeria) showed that 36.8% of pregnant women used herbal medicines [6].
Evaluation of potential teratogenic effect of chemicals has been an important area of investigation, following the Thalidomide disaster that occurred in 1957 [7-8]. Teratogenic data from animal studies are required for the regulatory authorities' approval of any new drug [9].
Dryopteris filix-mas (Figure 1), belonging to the family of Dryopteridaceae is an evergreen fern growing up to 60-150 cm. It is native to Europe, Asia, and North America. It grows near streams, moist environments, stones, brick walls and open ground. Its growth is mostly favoured by damp and

shady environments. The leaves are bipinnated and consist of 20-35 pinnae on each side of the rachis [10]. It is commonly called male fern. Other names include; aspidium, bear's paw, knotty brake and shield fern. Homeopatically, it is called mother tincture [12]. It is locally recognized as Eraketa and Okpaka or Akolor by Urhobo and Igbo speaking tribes respectively. Historical source revealed that *Dryopteris filix-mas* is one of the medicinal plants used to cure spleenomegaly in malaria infection, feverish condition as well as dropsy [12]. Its decoction is also applied topically in the treatment of mumps, carbuncles, abscesses, boils and sores provoked by severe burns [13]. It is used among the lebanese rural dwellers in the treatment of neuralgia and rheumatic disorders [13]. In Nigeria, it is used in various parts of Edo and Delta State, in the treatment of gastrointestinal disorders, management of rheumatic disorders, boils and sores. The cooked young frond is eating as an aid in losing weight [11].

Previous studies on its phytochemical constituents and antidiarrheal activity [11], anti-microbial activity against both gram-positive and gram-negative bacteria [14] had been carried out.

There is increase in the report of birth defects due to the indiscriminate consumption of some medicinal plants [15]. Since the teratogenicity profile of *Dryopteris filix-mas* has not been scientifically validated, we decided to evaluate its teratogenic effect in this study.

Figure 1: *Picture of Dryopteris filix mas*

II. Materials and Methods

II.1 Plant materials

Fresh leaves of *Dryopteris filix-mas* were collected between 6:30 and 8:00 am in the month of March, 2016 from a swampy area beside the Horticulture botanical garden Amawbia, Awka South L.G.A, Anambra State, Nigeria. The plant was authenticated by Dr. Akinnigbosun H.I., a plant taxonomist in the Department of Botany, Faculty of Life Sciences, University of Benin, Edo State. It was deposited in the herbarium of the Department and Voucher number "UBH_d285A" was assigned to it.

II.2 Plant extraction

Plant was carried out using maceration method described by Anosike and Obidoa [16]. Fresh leaves of *Dryopteris filix-mas* were air-dried at room temperature for one week. The crisply dried leaves were pulverized using a mechanical grinding machine. Afterwards, 335.71 g of the powdered leaves was macerated in 1010 mL of 80% ethanol. The mixture was agitated continually for 48 hours and was filtered using a muslin cloth. The filtrate recovered was concentrated to a paste-like form using a

water bath at 45^{0}C. A greenish paste-like extract weighing 31.94 g (9.51% w/w, percentage yield) was recovered after extraction.

II.3 Equipment and Apparatus

The apparatus used in this study include; Thermostatic water bath (Equitron Mumbai India), Analytical weighing balance (Ohaus Corp. Pine Brook, NJ USA) and Top electronic weighing balance (Scout Pro SPU401, Ohaus Corp. Pine Brook, NJ USA).

II.4 Chemicals and reagents

Chemicals and reagents used in this study include; Formaldehyde 40 %w/v (May and Baker Ltd, Dagenham England, MUO124), Ethanol (absolute), (JHD, Guangdong Guanghua Schi-Tech. Ltd China) All reagents used were of analytical grade

II.5 Animals

Six weeks old male and virgin female mice used for this study were procured from University of Nigeria Nnsukka. They were acclimatized in the animal house, Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Agulu. Animals were given feed and water *ad libitum* and were handled in compliance with the National Institute of Health Guidelines for care and use of laboratory animals for research purpose (Pub No. 85-23, revised 1985).

II.6 Phytochemical screening

This test was carried out using standard methods of Trease and Evans, Harborne and Sofowra as described by Yadav and Agarwala [17]. Two grams of extract was dissolved in 20 mL of ethanol and was used for the determination of flavonoids, saponins, tannins, sterioids, cardiac glycosides, alkaloids, terpenoids, anthranquinones and reducing sugar.

II.7 Oral acute toxicity test

Miller and Tainter method described by Randhawa [18] was employed for the LD_{50} study. Sixty albino mice, 23.47 ± 0.35 g of either sex were randomnized into groups (control, 100, 1000, 2000, 3000 and 5000 mg/kg body weight of extract. The control group received 10 ml/kg of distilled water. After administration, special attention was given during the first 4 hours and after 24 hours for signs of toxicity or death. Animals were further observed for 2 weeks for signs of delayed toxicity and death.

II.8 Teratogenic study

This test was carried out following the methods described by Golalipour *et al.,*[19] and Saleem *et al.,* [9]. A total of thirty two virgin adult female albino mice and twenty adult male mice (23.70 ± 0.55 g) were used for this study. Visual method described by Richard *et al.* [20] was used for determination of estrous (ovulation) stage of estrus cycle based on the appearance of the external genitalia characterized by gaping vagina, light pink and less moist tissue with pronounced striation. Twenty six (26) female mice were selected and were mated with male adult mice (2 males to 3 female mice in the same cage) overnight (7 pm to 7 am). The following morning, mating was confirmed by checking for the presence of plug in vagina of female mice. Females with plugs were confirmed to be pregnant (day 0 of pregnancy). Twenty (20) mice with evidence of plug were randomly divided into four groups (n = 5). Group 1 (control) received 10 ml/kg of distilled water), groups 2 (low dose), 3 (medium dose) and 4 (high dose) were dosed once daily with 250, 500 and 1000 mg/kg of extract respectively from the 6th - to 15th day of gestation period (period of organogenesis).
Animals were allowed to give birth between the 20th and 21st day. The pulps were weighed and then examined for gross malformations or deviations from normal growth. The Liver, kidney, heart, lung

and femur of pulps from each group were harvested and fixed in 10% buffered saline for histopathology analyses using the method described by Bancroft and Gamble [21].

II.9 Data analysis

The results obtained were expressed as mean ± standard error of mean (SEM). Comparison of control and treatment groups was made by One-way Analysis of Variance (ANOVA) using Statistical Package for Social Sciences (SPSS-20). $p< 0.05$ was considered to be statistically significant.

III. Results

III.1 Oral acute toxicity

Acute toxicity test revealed no signs of toxicity or death at various doses (100, 1000, 2000, 3000 and 5000 mg/kg) when compared to the control group. The LD_{50} was estimated to be above 5000 mg/kg (Table 1).

Table 1: *Results of the oral acute toxicity on mice.*

Dose (mg/kg)	SEX	**Number of animals per group**	**Sign of toxicity**	**Number of death per group**	**Overall death per group**
Control	**Male**	5	Nil	0/5	0/10
	Female	5	Nil	0/5	
100 mg/kg	**Male**	5	Nil	0/5	0/10
	Female	5	Nil	0/5	
1000 mg/kg	**Male**	5	Nil	0/5	0/10
	Female	5	Nil	0/5	
2000 mg/kg	**Male**	5	Nil	0/5	0/10
	Female	5	Nil	0/5	
3000 mg/kg	**Male**	5	Nil	0/5	0/10
	Female	5	Nil	0/5	
5000 mg/kg	**Male**	5	Nil	0/5	0/10
	Female	5	Nil	0/5	

From LD_{50} result above, there were no signs of toxicity and death recorded at various doses (100, 1000, 2000, 3000 and 5000 mg/kg) for the mice when compared to the control group.

III.2 Phytochemical screening

Phytochemical screening on the extract revealed presence of tannins, reducing sugars, flavonoids, saponins, steroids, alkaloids, terpenoids and cardiac glycosides (Table 2).

Table 2: *Phytochemical constituents of the extract*

Phytochemicals	Result
Tannins	++
Flavonoids	+++
Saponins	++
Steroids	++
Alkaloids	++
Terpenoids	++
Anthranquinones	-
Cardiac glycosides	+
Reducing sugars	+

"-":absent, "+" :trace "++" : moderate and "+++": abundant.

III.3 Effect of extract on maternal body weight

There was no statistically significant difference ($p>0.05$) in body weight of mice treated with extract when compared with control group on days : 0, 16, before delivery and after delivery (Table 3).

Table 3: *Effect of extract on maternal body weight*

	Day 0	Day 16	Before delivery	After delivery
Control	21.88 ± 0.75	31.24 ± 2.20 (29.96 %)	37.64 ± 1.24 (41.87 %)	29.18 ± 0.77 (25.02 %)
250 mg/kg	23.28 ± 1.38	35.86 ± 1.10 (35.08 %)	38.06 ± 0.80 (38.83 %)	28.02 ± 0.71 (16.92 %)
500 mg/kg	24.70 ± 0.90	34.80 ± 0.31 (29.02 %)	36.00 ± 0.71 (31.39 %)	29.76 ± 0.88 (17.00%)
1000 mg/kg	24.06 ± 1.58	36.42 ± 1.02 (33.94 %)	39.74 ± 0.52 (39.46 %)	29.22 ± 0.74 (17.66 %)

Values are presented as mean ± standard error of mean (SEM), n =5. p>0.05: Not significantly different from control group. Values in parenthesis indicate percentage weight gain relative to Day 0.

III.4 Effects of extract on body weight, tail length, crown rump length (CRL) and number of pups whose mothers were treated with extract.

Administration of leaf extract of *Dryopteris filix-mas* at 250, 500 and 1000 mg/kg did not cause significant alteration ($p>0.05$) in average body weight, tail length and crown rump length of pups when compared to control group (Table 4).

Table 4*: Body weight, tail length, crown rump length (CRL) and number of pups whose mothers were treated with extract*

	Average number of pups	Average Fetal body weight (g)	Average Tail length (cm)	Average Crown rump length (CRL) (cm)
Control	5.60 ± 0.24	1.65 ± 0.03	1.25 ± 0.02	3.05 ± 0.03
250 mg/kg	5.60 ± 0.40	1.48 ± 0.06	1.11 ± 0.11	2.91 ± 0.11
500 mg/kg	5.80 ± 0.58	1.47 ± 0.09	1.22 ± 0.01	2.91 ± 0.17
1000 mg/kg	5.40 ± 0.68	1.42 ± 0.07	1.11 ± 0.06	2.97 ± 0.05

Values are presented as mean ± Standard error of mean (SEM). p>0.05: Not statistically significantly different from control group.

III.5 Effects of extract on congental parameters status and general appearance of pups

There was absence of middle ear disease (MED), absence of open eye (OE) and absence of polydactyl in control and extract treated groups. General appearance of pups in all groups was normal (Table 5).

Table 5: *Congenital parameters status and general appearance of pups whose mothers were treated with extract*

	Middle ear disease (MED)	Open eye (OE)	Polydactyl	General appearance
Control	-	-	-	Normal
250 mg/kg	-	-	-	Normal
500 mg/kg	-	-	-	Normal
1000 mg/kg	-	-	-	Normal

"-"Indicates absence of deformity.

III.6 Effects of extract on histology of pups' liver, kidney, heart, lung and femur

There were no observable toxicities in the liver, kidney, heart and lung architecture of pups whose mothers were exposed to 250, 500 and 1000 mg/kg doses of extract (Figures 2-5). There was no observable toxicities in histo-architecture of pups femur whose mothers were treated with 250 and 500 mg/kg of extract. However, there was poor mineralisation in the histo-architecture of pups femur whose mothers were treated with 1000 mg/kg of extract (Figure 6).

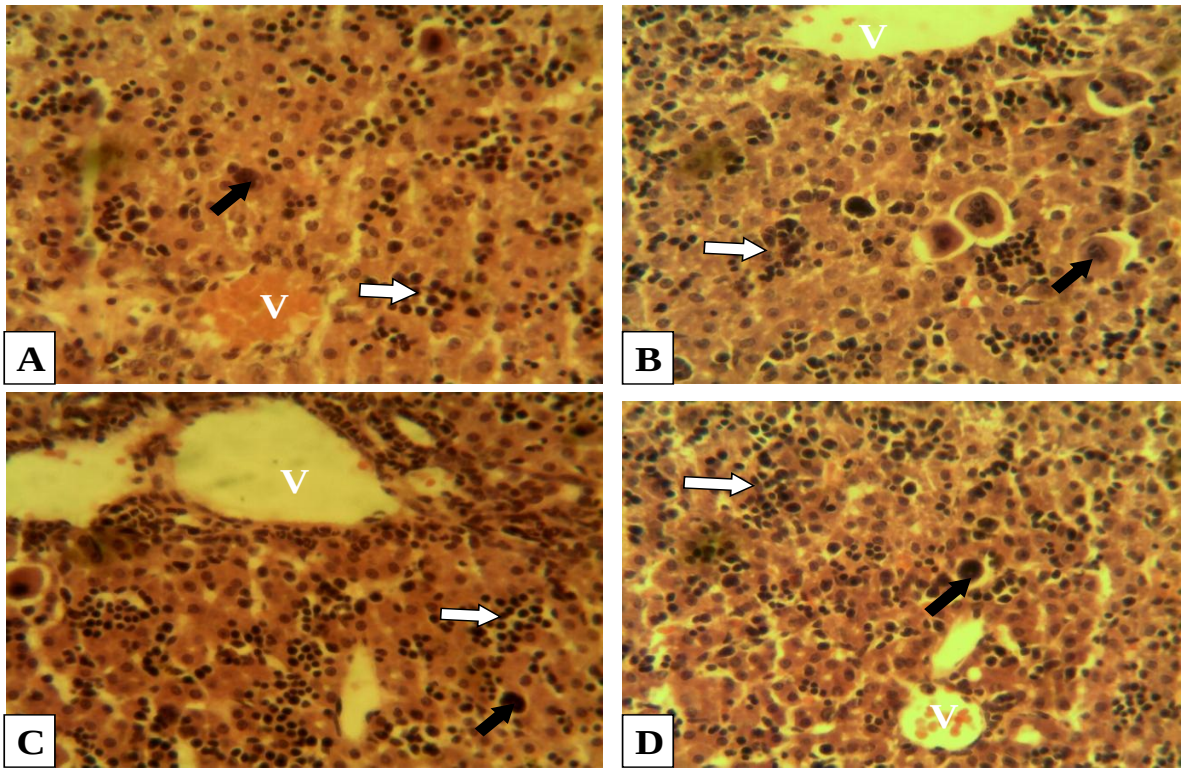

Figure 2*. Photomicrographs of pups liver sections. Control (**A**), low dose (**B**), medium dose (**C**) and high dose (**D**) groups showing the central vein (V). There is evidence of fetal hematopoiesis (blood cell formation) by the presence of megakaryocytes (black arrows) and aggregation of erythrocyte precursor cells (white arrows). There is no observable adverse reaction or lesion in all the groups. H and E x 400.*

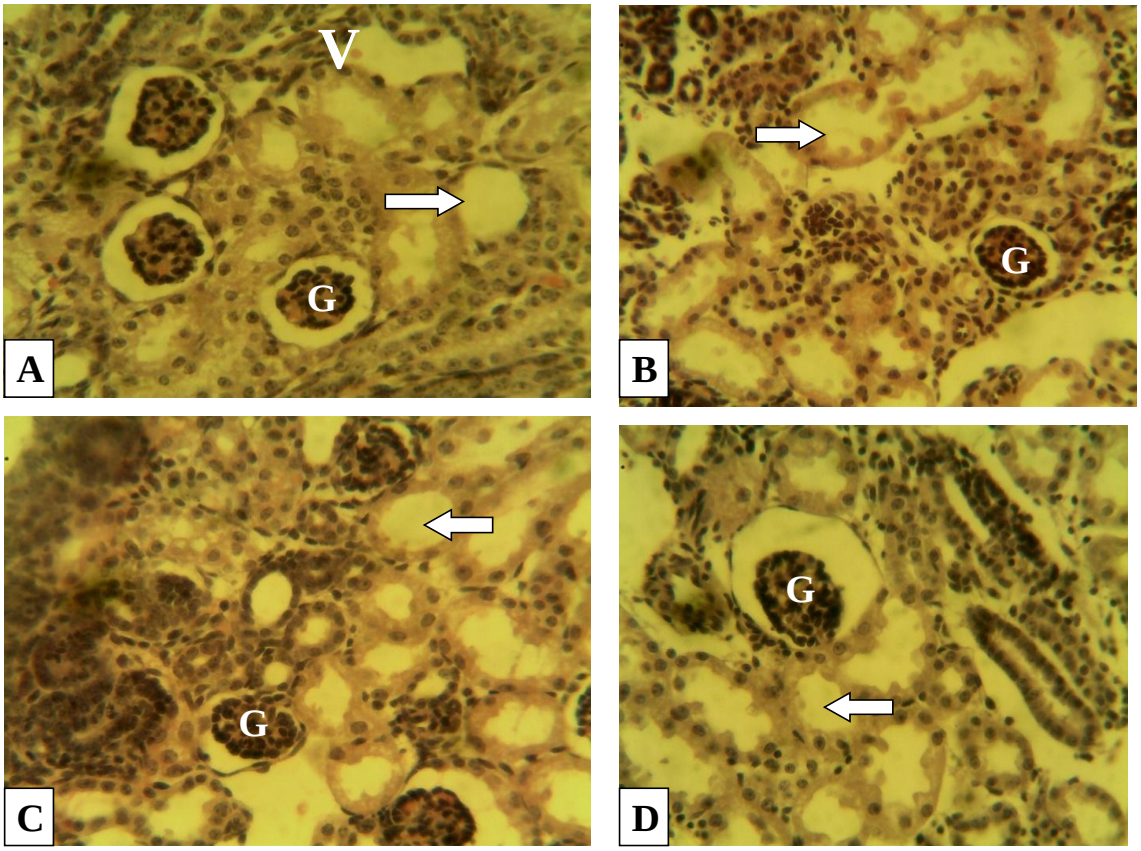

***Figure 3**. Photomicrographs of pups' kidney sections. H and E x 400.*
*Control (**A**), low dose (**B**), medium dose (**C**) and high dose (**D**) groups showing the maturing glomerulus (G) and renal tubules (arrows).There is no observable adverse reaction or lesion in all the groups. H and E x 400.*

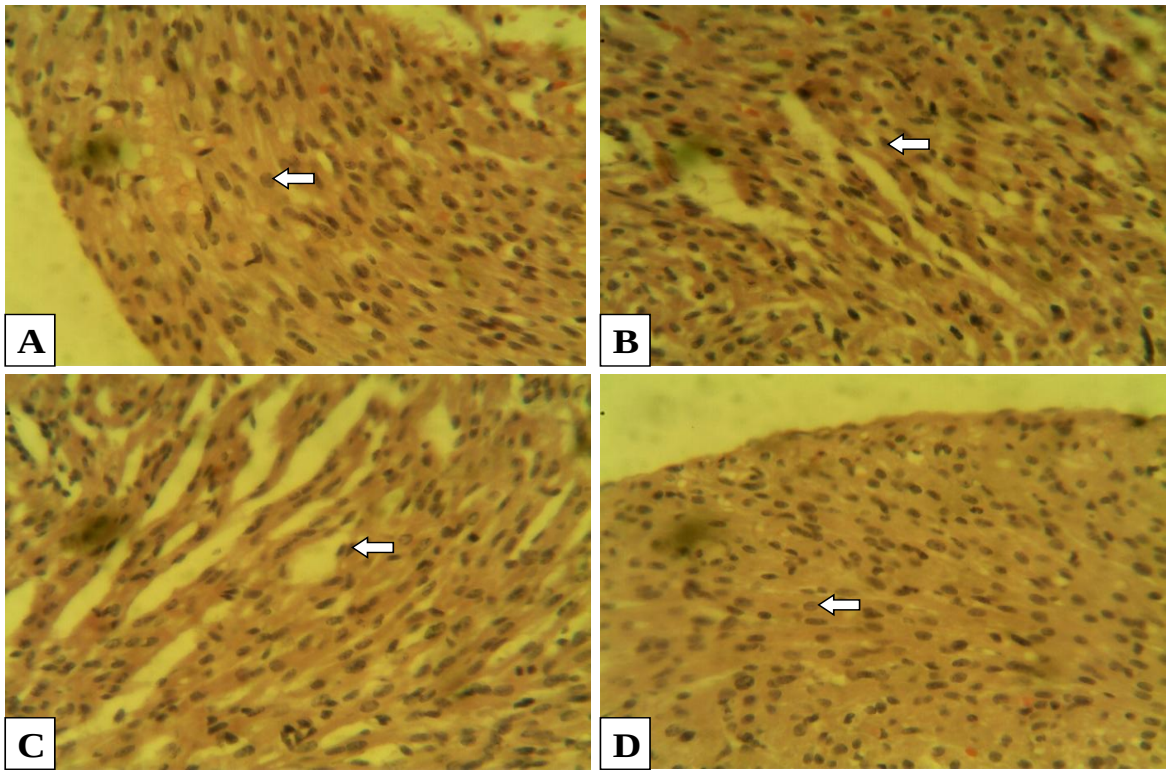

***Figure 4**. Photomicrographs of the pups' heart sections. Control (**A**), low dose (**B**), medium dose (**C**) and high dose (**D**). Groups showing poorly separated muscle fibres (arrows). There is no observable adverse reaction or lesion in all the groups. H and E x 400.*

2018 Algerian Journal of Natural Products (Online ISSN: 2353-0391)

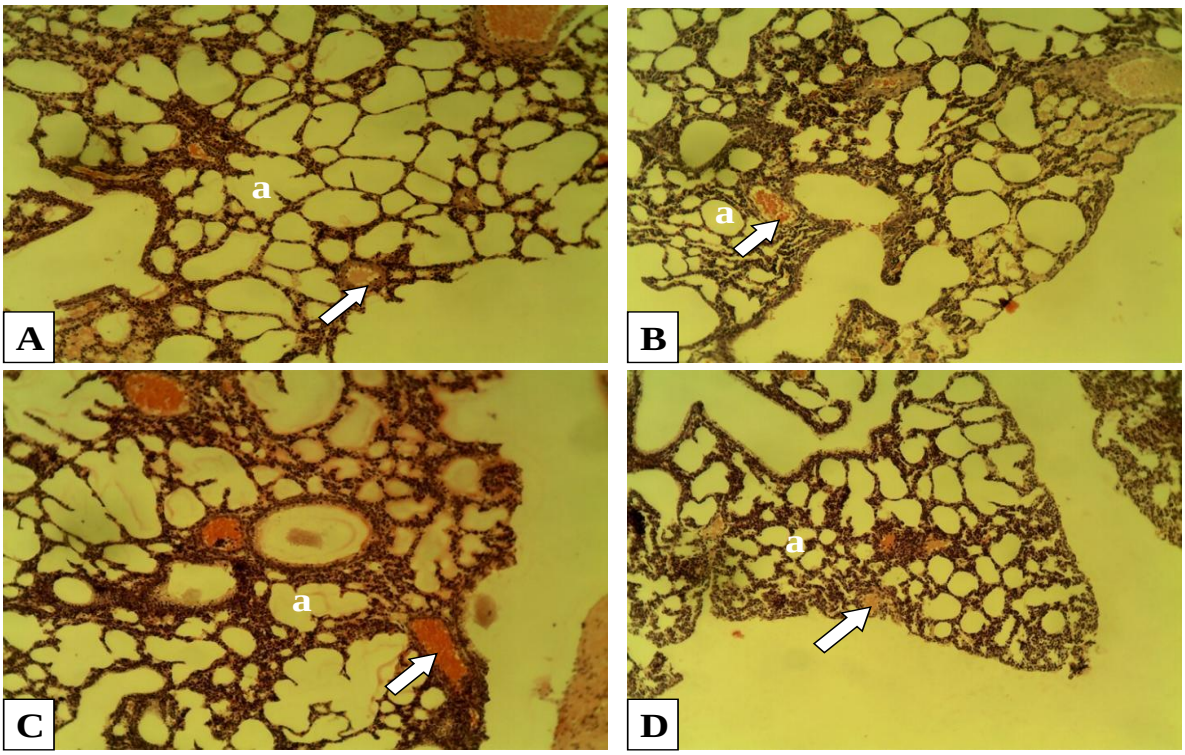

***Figure 5**. Potomicrographs of the pups' lungs section*
*control (**A**), low dose (**B**), medium dose (**C**) and high dose (**D**) groups showing the maturing alveoli (a) and pulmonary blood vessels (arrows).There is no observable adverse reaction or lesion in all the groups. H and E x 400.*

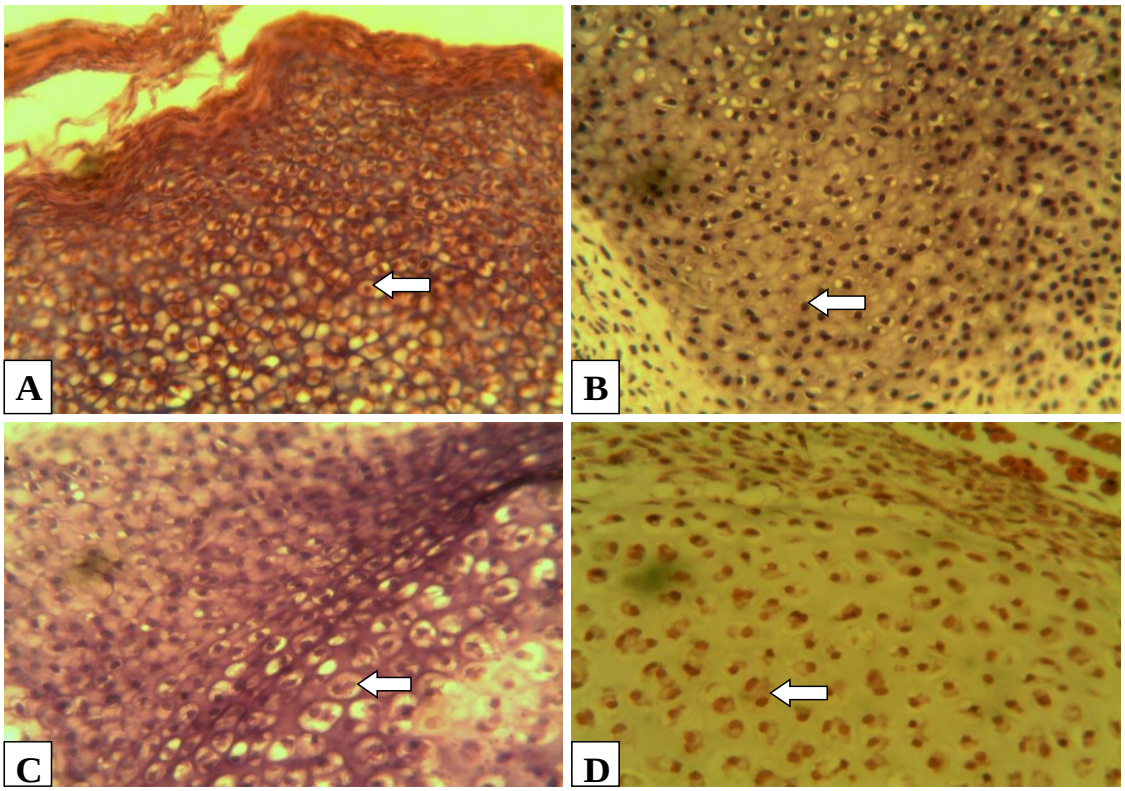

***Figure 6:** Photomicrographs of pups' femur sections.*
*Conrol (**A**), low dose (**B**), medium dose (**C**) and high dose (**D**) groups showing actively proliferating and mineralising cartilages (arrows).Note that there is poor mineralisation in high dose group (less bluish staining, which means less calcium depositions). H and E x 400.*

2018 Algerian Journal of Natural Products (Online ISSN: 2353-0391)

IV Discussion

The present study evaluated the teratogenic properties of *Dryopteris filix-mas* leaf extract in order to validate its safety in pregnancy. Acute toxicity and phytochemical screening tests were also carried out.

Absence of toxicity and death in animals dosed up to 5000 mg/kg in acute toxicity test suggests that the leaf extract of *D. filix-mas* is practically non-toxic. It had been established that LD_{50} of test substance above, 5000 mg/kg is considered safe [22].

Presence of tannins, flavonoids, saponins, steroids, alkaloids, terpenoids, reducing sugars and cardiac glycosides in the extract from the phytochemical screening results suggests that the leaf extract of *Dryopteris filix mas* could be of medicinal usefulness [17]. In support of this finding, U*wumarongie and co-workers* in the study of the phytochemical constituents of *Dryopteris filix mas* leaf also reported the presence of glycosides, tannins, flavonoids, steroids and other nutrients [11].

Progressive increase in body weights of pregnant mice could be as a result of organogenesis which resulted in body weight gain. This is substantiated by reduced body weights which occurred after parturition in all groups. Saleem and co-workers [9] revealed that body weight increase progressively during the period of organogenesis. Non-significant difference in body weight of mice in treatment groups compared to the control group suggests the extract may not contain anti-nutritive constituents which can contribute to nutrient malabsorption, loss of appetite and body weight reduction in pregnancy.

Non-significant change in number of littered pups, body weight, tail length as well as crown rump length of pups in control and the treatment groups suggests that the extract did not have deleterious effect on the development of functional parts of these organs. This is corroborated by absence of middle ear disease, polydactyl limbs, open eyes and normal general appearance observed in control and treated groups.

Absence of deformity in liver, kidney, heart and lung architectures suggests that normal development (organogenesis) of these organs in pups were not adversly affected by the leaf extract.

During fetal development, long bone/skeletal formation is known to start as proliferation of cartilaginous scaffold that is progressively resorbed and replaced by new bone in the epiphyseal areas, thereby undergoing mineralization to form primary new bone [23]. From the histological results, photomicrograph of the femurs from all the groups except high dose were actively proliferating and had mineralising cartilages. Poor mineralisation recorded only in high dose group (1000 mg/kg) suggests that high doses of the extract may lead to less calcium depositions thereby causing reduction in ossification rate.

Interaction of phytochemicals had been reported to be associated with some adverse effects [24]. Some reports had revealed that phytochemicals such as flavonoids could act as agonists and antagonists of the human estrogen receptors thereby causing poor fetal bone development or bone retardation [25-26]. Also, high level of flavonoids had been reported to posses several biological properties such as antiapoptosis, anti-inflammatory, antioxidant, protection and improvement of endothelial function, antiaging, anticarcinogen, as well as protection of vital organs against damage by toxicants [17]**.**

Based on this study, we could not categorically state that high dose of the extract could be associated with poor bone formation because no morphological deformity was recorded even at high dose of 1000 mg/kg.

V. Conclusion

Teratogenicity study revealed that the ethanol leaf extract of *Dryopteris filix-mas* may be teratogenic to the femur at 1000 mg/kg. It is hereby recommended that caution should be excercised by pregnant women who use high doses of the extract for long term treatment of various diseases.

VI. References

1. Biljana BP., Historical review of plant usage, Pharmacognosy Reviews, 6: 11 (2012) 1–5.
2. Narayanaswamy T., Thirunavukkarasu T., Prabakar S., Ernest D., A review on some poisonous plants and their medicinal values, *Journal of Acute Disease*, 3: 2(2014) 85-89.
3. Lozano R., Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study, *Lancet*, 380(2012): 2095-2128.
4. Lisha JJ., Nisha S., Herbal medicines use during pregnancy: A review from the Middle East, *Oman Medical Journal*, 30:4(2015): 229–236.
5. Tamuno I., Omole-Ohonsi A., Fadare J., Use of Herbal Medicine Among Pregnant Women Attending A Tertiary Hospital In Northern Nigeria, *Internet Journal of Gynecology and Obstetrics,* 15:2 (2010) 1-8.
6. Chukwuma BD., Kenechi AU., Nnebue CC., Ikechukwu IM., Kevin CD., Chuka CA., Anthony CI., Irene AM., Socio-demographic determinants of herbal medicines use in pregnancy among Nigerian women attending clinics in a tertiary hospital in Imo State, South-East, Nigeria". *American Journal of Medicine Studies*. 4:1 (2016) 1-10.
7. Ray G., Niall S., Mark JR., The History and Implications of Testing Thalidomide on Animals, *The Journal of Philosophy, Science and Law*,11 (2011) 1-32.
8. Saganuwan SA., Toxicity study of drugs and chemicals in animals: An overview, *Bulgarian Journal of Veterinary Medicine*. 2016 online first. 2016, DOI: 10.15547/bjvm.983.
9. Saleem U., Ahmad B., Hussain K., Bukhari NI, Anjum AA, Teratogenic and embryotoxic effects of latex and leaves of methanol extract of *Euphorbia helioscopia L*. in mice and chicken, *The Journal of plant and animal sciences*, 24: 2 (2014) 450-454.
10. Sekendar MA., Kawsarul M., Obayed MR., Khalilur MR., Aslam MH., Shah MA., Antioxidant and Cytotoxic activities of Methanol extract of *Dryopteris filix*-mas (L.) Schott Leaves, *Internationa*l *Journal of Drug Development and Research,* 4:2 (2012) 223-229.
11. Uwumarongie HO., Enike MA., Bafor EE., Pharmacognostic evaluation and gastrointestinal activity of *D.filix-mas*, *Ewemen Journal of herbal chemistry and pharmacology research*, 2:1 (2016) 19-25.
12. Tagarelli G., Tagarelli A., Piro A., Folk medicine used to heal malaria in Calabria (southern Italy), *Journal of Ethnobiology and Ethnomedicine*, 6:27 (2010) 1-16.
13. Beyrouthy EM., Arnold N., Delelis-Dusollier A., Dupont F., Plants used as remedies antirheumatic and antineuralgic in the traditional medicine of Lebanon, *Journal of Ethnopharmacology*, 120:3 (2008) 315–334.
14. Mandal A., Kumar-Mondal A., Studies on antimicrobial activities of some selected ferns and lycophytes in Eastern India with special emphasis on ethno-medicinal uses, *African Journal of Plant Science,* 5:7 (2011) 412-420.
15. Hamiduddin AM., Sofi G., Wadud A., Use of traditional drugs in pregnant and nursing mothers, A review of associated adverse drug reactions, *Journal of Pharmaceutical Scientific Innovation*, 5:1 (2016) 2277-4572.
16. Anosike CA., Obidoa O., Anti-inflammatory and Anti-ulcerogenic effect of ethanol extract of Coconut (*Cocos Nucifera*) on experimental rats, *African Journal of Food, Agriculture, Nutrition and Development,* 10:10 (2010) 4286-4300.
17. Yadav RNS., Agarwala M., Phytochemical analysis of some medicinal plants, *Journal of Phytology*, 3:12 (2011) 10-14.
18. Randhawa MA., Calculation of LD_{50} value from the method of Miller and Tainter of Ayub Medical College A bbottabad, *Journal of Ayub Medical college Abbottabad*, 21:3 (2009) 1-3.
19. Golalipour MJ., Ghafari S., Maleki A., Kiani M., Asadi E., Farsi M., Study of Embryotoxicity of *Mentha piperita* L. During Organogenesis in Balb/c Mice, *International. Journal of Morphology,* 29: 3 (2011) 862-867.
20. Behringer R, Gertsenstein M, Nagy KV, Nagy A. Selecting female mice in estrus and cheking plugs, *Cold Spring Harb Protoc*, (2016) 729-731.
21. Bancroft JD., Gamble M., Theory and Practice of Histological Techniques. Edition Benkroft. Churchill Livingstone, Edinburgh. (2002) 16-64.

22. Ahmed M., Acute Toxicity (Lethal Dose 50 Calculation) of Herbal Drug Somina in Rats and Mice, *Pharmacology and Pharmacy,* 6 (2015) 185-189.
23. Kovacs CS., Bone development in the fetus and neonate: role of the calciotropic hormones. *Current Osteoporosis Report*, 9:4 (2011) 274-283.
24. Hassan SW., Ladan MJ., Dogondaji RA., Umar RA., Bilbis LS., Hassan LG., Ebbo AA., Matazu IK., Phytochemical and Toxicological studies of aqueous leaves extracts of *Erythrophyleum africanum, Pakistan Journal of Biological Science,* 10: 21 (2007) 3815-3821.
25. Collins-Burow BM., Antoon JW., Frigo DE., Elliott S., Weldon CB., Boue SM., Beckman BS., Curie TJ., Alam J., McLachlan JA., Burow ME., Antiestrogenic Activity of Flavonoid Phytochemicals Mediated via the c-Jun N-terminal Protein Kinase Pathway: Cell-type specific regulation of estrogen receptor alpha, *Journal of Steroid Biochemistry and Molecular Biology*, 132 (2012) 186–193.
26. Nurcahyani N., Wirasti Y., Jamsari F., Tjong DH., Kanedi M. Methanol plant extract of Rumput Teki (*Cyperus rotundus L.*) causing fetal skeletal retardation in mice, *European Journal of Biomedical and Pharmaceutical Sciences*, 4:6 (2017) 128-131.

Cite this paper as:

Earnest Oghenesuvwe Erhirhie, Oluchi Nzubechukwu Ezemokwe and Emmanuel Emeka Ilodigwe, Teratogenic Effects of Ethanol Leaf Extract of *Dryopteris filix –mas* (L.) Schott, ***Algerian J. Nat. Products***,6:1(2018) 573-583