UNIVERSITI PUTRA MALAYSIA

IMPROVED REPRODUCTIVE PERFORMANCE THROUGH EDIBLE BIRD'S NEST AND ITS AMELIORATING PROPERTIES IN LEAD ACETATE TOXICITY OF REPRODUCTIVE SYSTEM IN FEMALE RATS

ABDULLA AAID HADI ALBISHTUE

FPV 2018 17

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By

ABDULLA AAID HADI ALBISHTUE

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia in Fulfillment of the requirements for the Degree of Doctor of Philosophy

May 2018

DEDICATION

This thesis is dedicated to my beloved parents; Aaid Hadi and Hameedah Sabr, my wife Hala Abdulrazzaq and my children; Morsaleen, Baqer and Sajjad.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

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Chairman : Nurhusien Yimer Degu, PhD
Faculty : Veterinary Medicine

Edible Bird's Nest (EBN) is an animal product from the salivary secretion of male swiftlet birds (*Aerodramus fuciphagus and Aerodramus maximus*). It is traditionally consumed Asians for its nutritional and medicinal values. Although enhancing reproductive functions is among the traditionally claimed benefits of consuming EBN there is a dearth of scientific evidence in this regard. The aims of this study were to determine the effects of EBN supplement on the reproductive functions of cycling female rats, on pregnant female rats, and subsequently to evaluate the ameliorating effect of EBN supplement against toxic effect of lead acetate (LA) to the female reproductive system and pituitary gland.

To address the first objective of this study (evaluation of the effects of EBN supplement on the ovarian, uterine and pituitary gland activities of cycling female rats), histomorphometric analysis and assessment of expressions of epidermal growth factor (EGF), its receptor (REGF), proliferating cell nuclear antigen (PCNA), vascular endothelial growth factor (VEGF), steroid receptors on ovaries and uteri as well as measurement of steroid hormones, prolactin (P) and growth hormone (GH) from plasma, were employed. Twenty four Sprague Dawley rats were divided into 4 equal groups (n=6): G1 as control group while G2, G3 and G4 were treated groups with EBN at graded concentrations of 30, 60 and 120 mg/kg of body weight per day respectively for 8 weeks. The EBN was administered orally using gavage tube. At the proestrus stage all rats were sacrificed to remove ovaries, uteri, pituitary glands and liver for histological and immunohistochemical analyses. Results showed significant ovarian structural and histological changes such as numbers of interstitial cells and growing follicles in EBN treated groups, with significant increase in endocrine cells and vascularization of pars distalis of the pituitary glands as well as increased uterine

epithelium and number of uterine glands. There was no histomorphological change of liver among groups. Samples from G3 and G4 demonstrated significant expressions of EGF on ovarian surface epithelium, interstitial cells, uterine surface epithelium and uterine stromal cells as well as higher expressions of PCNA and VEGF, and estrogen receptor (E_2R) compared with G1 and G2. No staining for progesterone receptor (P_4R) was observed in the treated groups. In addition, immunohistochemistry of the uterus showed significantly higher expressions of EGF, REGF, PCNA, E_2R and P_4R ($p < 0.05$) in G4. The plasma levels of estrogen (E_2) (ng/mL) and progesterone (P_4) (ng/mL) in G4 (18000±1786; 168±17) were significantly higher than G3 (11000±3670; 84.04±9.56), G2 (6300±1566; 63.66±9.06), and G1 (1100±143; 50.03±4.18). Moreover, concentrations of prolactin P and GH were observed to be significantly higher ($p < 0.05$) in G4. These findings suggest that EBN supplement enhances ovarian follicular growth, uterine structures, expressions of E_2R, P_4R EGF, REGF, VEGF, and PCNA and subsequent rise in plasma E_2, P_4, P and GH levels. These imply the strong enhancing effect of EBN on the reproductive system of cycling female rats.

In order to determine effect of EBN supplement on embryo implantation rate and associated changes in the uterus, plasma steroids and oxidative stress biomarkers (2^{nd} objective), a total 24 female adult rats underwent similar treatment for 8 weeks. In the last week of treatment, however, intact fertile male rats were introduced into each group (three per group) with proestrous stage overnight for mating. On day 7 post-mating (expected days of implantation; peri- and post-implantation), the animals were sacrificed for assessment of implantation rate, histological and electron microscopic examination of the uterus, oxidative stress biomarkers (OSB) and antioxidant (AO) assay, GH, P, steroid hormones analysis, and expressions of steroid receptors, EGF, REGF, PCNA, and VEGF on the uterus. Results showed that as the concentrations of EBN increases, the pregnancy rate, embryonic implantations rate and development of microvilli with pinopodes in uterine epithelium were also increased. There was an increased level of superoxide dismutase (SOD) and total antioxidant capacity (TAC) ($p < 0.05$) in the G4, with lower ($p < 0.05$) concentrations of thiobarbituric acid reactive substance (TBARS) compared to control. All results of the hormones assay and immunohistochemistry showed significantly higher concentrations and expressions of steroid receptors, EGF and REGF, PCNA, and VEGF ($p < 0.05$) in G4 compared to the other groups. These findings imply that almost all the factors important for embryo implantation and development are enhanced in concentrations and expressions with EBN supplement in a dose dependant manner subsequently resulting in increased embryo-implantation and pregnancy rate.

The last objective in the present study was to evaluate the protective effect of EBN supplement to the reproductive system (ovaries and uteri) and pituitary glands of female rats against lead acetate (LA) toxicity. LA is a toxic compound that has harmful effects on the female reproductive system such as altered uterine and ovarian histology, size and function, and low oestrogen production. There were five treatment groups: Group 1 - control (C) was given normal saline, group 2 (T0) was administered with LA (10 mg/kg bwt), while groups 3 (T1), 4 (T2) and 5 (T3) were given LA (10

mg/kg bwt) and graded concentrations of 30, 60, and 120 mg/kg bwt of EBN, respectively. Rats were euthanized at day 30 for collection of blood plasma, ovary and uterus. Organ tissues were fixed in 10 % buffered formalin and subjected to histological analyses and immunohistochemistry for expression of steroid receptors, EGF and REGF, PCNA, and VEGF on the ovary and uterus. Plasma was used to determine concentrations of E2, oxidative stress biomarker (OSB) and antioxidant (AO). Results showed that the level of E_2 was lower ($p < 0.05$) in the T0 group while the T3 group had the highest E2 concentration. There was a decreased level of SOD and TAC ($p < 0.05$) in the T0 group and an increased SOD and TAC level in the T3 group, while T0 had higher ($p < 0.05$) concentrations of TBARS compared to treated groups, indicating oxidative stress. There was a reduced number of primordial follicles and increased numbers of atretic follicles in the ovary as well as significant damage in the uterus as evidenced by reduction in uterine glands and decrease in height of columnar cells in the T0 group compared with the treatment groups. Moreover, histological examination of pituitary gland of LA exposed rats without EBN supplement showed degenerative changes in endocrine cells of pars distalis such as non-uniform arrangement of the cells and decrease in cell number and size. Interestingly, histological examination of pituitary glands, ovaries and uteri of EBN treated groups showed significant protection as evidenced by a significant increase in endocrine cells of pars distalis, growing follicles and CL, but decrease in number of atretic follicles on ovaries as well as increase in uterine glands and height of columnar cells. All results of immunohistochemistry showed significantly higher expression of steroid receptors, EGF, PCNA, and VEGF ($p < 0.05$) in T3 compared to other groups. This part of the experiment reaffirmed the detrimental effects of LA on the reproductive system and revealed novel findings on the ameliorating effect of the oral supplementation of EBN against LA toxicity damage to the reproductive system, achieved best at 120mg/kg body weight.

In general, this study suggests that EBN supplement enhances functions of the pituitary gland, ovary, uterus, expression of steroid receptors, EGF, REGF, VEGF, and PCNA on ovaries and uteri along with a rise in serum E_2, P_4, P and GH levels. Moreover, EBN has showed a promoting effect on fertility indexes by increasing pregnancy and embryo implantation rates. Furthermore, the present study revealed that EBN supplement at oral dose of 60 – 120mg/kg body weight is capable of protecting and preventing alterations in the pituitary gland and the reproductive system due to lead toxicity through an integrated mechanism of maintaining antioxidant – reactive oxygen species (ROS) balance. Overall findings of the present study provide scientific evidence in support of the traditional claim of EBN's benefit to reproduction and being one of the reasons for consumption among humans.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PRESTASI PEMBIAKAN TERTINGKAT MELALUI PENGGUNAAN SANGKAR BURUNG BOLEH MAKAN DAN CIRI PEMBAIKANNYA DALAM KETOKSIKAN PLUMBUM ASETAT SISTEM PEMBIAKAN TIKUS BETINA

Oleh

ABDULLA AAID HADI ALBISHTUE

Mei 2018

Pengerusi : Nurhusien Yimer Degu, PhD
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Sarang burung yang boleh dimakan (EBN) merupakan produk haiwan dari rembesan air liur burung walit jantan (*Aerodramus fuciphagus* dan *Aerodramus maximus*). Ianya secara tradisi dimakan oleh orang Asia kerana nilai pemakanan dan perubatannya. Walaupun meningkatkan fungsi pembiakan adalah antara dakwaan manfaat tradisional memakan EBN, terdapat kekurangan bukti saintifik di dalam hal ini. Tujuan kajian ini adalah untuk menentukan kesan penambahan EBN ke atas fungsi pembiakan tikus betina dalam kitaran, tikus betina hamil, dan seterusnya menilai kesan pembaikan EBN terhadap kerosakan sistem pembiakan betina dan kelenjar pituitari yang disebabkan oleh toksik plumbum asetat (LA).

Bagi mencapai objektif pertama kajian ini (i.e penilaian kesan penambahan EBN ke atas aktiviti ovari, uterus dan kelenjar pituitari tikus betina dalam kitaran), analisis histomorfometri dan penilaian ekspresi faktor pertumbuhan epidermis (EGF), reseptornya (REGF), antigen nuklear sel membiak (PCNA), faktor pertumbuhan endotelium vaskular (VEGF), reseptor steroid pada ovari dan uterus serta pengukuran hormon steroid, prolaktin (P) dan hormon pertumbuhan (GH) dari plasma telah dijalankan. Dua puluh empat ekor tikus Sprague Dawley telah dibahagikan kepada 4 kumpulan (n=5): G1 adalah kumpulan kawalan yang tidak dirawat, manakala G2, G3 dan G4 adalah kumpulan yang dirawat dengan EBN pada kadar kepekatan yang berbeza masing-masing sebanyak 30, 60 dan 120 mg/kg berat badan setiap hari selama 8 minggu. Pemberian EBN adalah melalui mulut degan menggunakan tiub gavaj. Pada peringkat proestrus, semua tikus telah dikorbankan untuk mengeluarkan ovari, uterus, kelenjar pituitari dan hati untuk analisis histologi dan imunohistokimia. Hasil kajian menunjukkan perubahan struktur dan histologi ovari yang signifikan seperti jumlah

sel celahan dan folikel bertumbuhan dalam kumpulan yang dirawat dengan EBN, ditambah pula dengan peningkatan yang ketara bagi sel gonadotrof dan vaskularisasi kelenjar pituitari serta peningkatan epitelium uterus dan bilangan kelenjar uterus. Tiada perubahan histomorfologi bagi hati dalam semua kumpulan. Sampel dari G3 dan G4 menunjukkan ekspresi EGF yang ketara pada epitelium permukaan ovari, sel-sel celahan, epitelium permukaan uterus dan sel-sel stroma uterus serta ekspresi PCNA dan VEGF dan reseptor estrogen (E2R) yang lebih tinggi berbanding dengan G1 dan G2. Tiada pewarnaan untuk reseptor progesteron (P4R) diperhatikan dalam kumpulan yang dirawat kecuali pewarnaan minimum bagi epitelium ovari dalam G3 dan G4. Di samping itu, kajian imunohistokimia uterus menunjukkan ekspresi EGF, REGF, PCNA, E2R dan P4R yang lebih tinggi ($p < 0.05$) di dalam G4. Kadar plasma estrogen (E2) (ng/mL) dan progesteron (P4) (ng/mL) di dalam G4 (18000±1786; 168±17) lebih tinggi ($p < 0.05$) daripada G3 (11000±3670; 84.04±9.56), G2 (6300±1566; 63.66±9.06), dan G1 (1100±143; 50.03±4.18). Selain itu, kepekatan prolaktin P dan GH juga lebih tinggi ($p < 0.05$) dalam G4. Hasil kajian ini mencadangkan bahawa penambahan EBN meningkatkan pertumbuhan folikel ovari, struktur uterus, ekspresi ER, EGF, REGF, VEGF dan PCNA dan seterusnya kenaikan paras plasma E2, P4, P dan GH. Ini menunjukkan EBN mempunyai kesan peningkatan yang kuat ke atas sistem pembiakan tikus betina yang mengalami kitaran

Untuk menentukan kesan EBN ke atas kadar implantasi embrio dan perubahan yang berkaitan di dalam uterus, steroid plasma dan biomarker tekanan oksidatif (objektif ke 2), sejumlah 24 ekor tikus betina dewasa menjalani rawatan yang sama untuk 8 minggu. Walaubagaimanapun, pada minggu terakhir rawatan, tikus jantan yang subur telah dimasukkan ke dalam setiap kumpulan (tiga ekor setiap kumpulan) di peringkat proestrus semalaman untuk mengawan. Pada hari ke 6 dan 7 selepas mengawan (hari yang dijangka berlaku implantasi; semasa- dan pasca-implantasi), haiwan-haiwan tersebut dikorbankan untuk penilaian kadar implantasi, pemeriksaan histologi dan mikroskop elektron pada uterus, biomarker tekanan oksidatif (OSB) dan cerakin antioksidan (AO), GH, PR, analisis hormon steroid, dan ekspresi reseptor steroid, EGF, REGF, PCNA dan VEGF pada uterus. Hasil kajian menunjukkan apabila kepekatan EBN meningkat, kadar kehamilan, kadar implantatasi embrio dan pembangunan mikrovilus dengan pinopod dalam epitelium uterus juga meningkat. Terdapat peningkatan paras superoksida dismutase (SOD) dan jumlah kapasiti antioksidan (TAC) ($p < 0.05$) di dalam G4, dan lebih rendah ($p < 0.05$) kepekatan bahan reaktif asid tiobarbiturik (TBARS) berbanding dengan kawalan. Semua keputusan cerakin hormon dan imunohistokimia menunjukkan kepekatan dan ekspresi reseptor steroid EGF dan REGF, PCNA dan VEGF yang lebih tinggi ($p < 0.05$) dalam G4 berbanding dengan kumpulan lain. Keputusan ini memberi implikasi bahawa hampir semua faktor yang penting untuk implantasi dan pembangunan embrio telah dipertingkatkan dalam kepekatan dan ekspresi dengan penambahan EBN yang seterusnya akan menyebabkan peningkatan implantasi-embrio dan kadar kehamilan.
Objektif terakhir di dalam kajian ini adalah untuk menilai kesan perlindungan penambahan EBN ke atas sistem pembiakan (ovari dan uterus) dan kelenjar pituitari tikus betina terhadap ketoksikan LA. Plumbum asetat adalah sebatian toksik yang mempunyai kesan buruk terhadap sistem pembiakan betina seperti perubahan histologi uterus dan ovari, saiz dan fungsi, dan pengeluaran estrogen yang rendah.

Terdapat 5 kumpulan rawatan: Kumpulan 1 - kawalan (C) diberikan salina normal, kumpulan 2 (T0) telah diberi LA (10 mg/kg bwt), manakala kumpulan 3 (T1), 4 (T2) dan 5 (T3) diberikan LA (10mg/kg bwt) dan kepekatan EBN yang berbeza masing-masing sebanyak 30, 60, dan 120 mg/kg bwt. Semua tikus telah dimatikan pada hari ke 30 untuk pengambilan plasma darah, ovari dan uterus. Tisu organ telah diawetkan didalam 10% formalin berpenimbal untuk analisis histologi dan imunohistokimia bagi memeriksa ekspresi reseptor steroid, EGF dan REGF, PCNA dan VEGF pada ovari dan uterus. Plasma darah digunakan untuk menentukan kepekatan E2, OSB dan AO. Hasil kajian menunjukkan bahawa tahap E2 adalah lebih rendah ($p < 0.05$) dalam kumpulan T0 manakala kumpulan T3 mempunyai kepekatan E2 tertinggi. Terdapat penununrun tahap SOD dan TAC ($p < 0.05$) dalam kumpulan T0 dan peningkatan tahap TAC dalam kumpulan T3, manakala T0 mempunyai kepekatan TBARS lebih tinggi ($p < 0.05$) berbanding kumpulan dirawat, menunjukkan tekanan oksidatif. Terdapat pengurangan jumlah folikel primordium dan peningkatan bilangan folikel beratresia di dalam ovari serta kerosakan ketara di dalam uterus seperti yang dibuktikan oleh pengurangan kelenjar uterus dan pengurangan ketinggian sel turus di dalam kumpulan T0 berbanding dengan kumpulan rawatan. Selain itu, pemeriksaan histologi kelenjar pituitari tikus yang terdedah kepada LA tanpa penambahan EBN menunjukkan perubahan degeneratif di dalam sel endokrin pars distalis. Menariknya, pemeriksaan histologi kelenjar pituitari, ovari dan uterus kumpulan dirawat dengan EBN menunjukkan perlindungan yang signifikan seperti yang dibuktikan oleh peningkatan ketara sel gonadotrof, folikel yang membesar dan CL, tetapi bilangan folikel beratresia pada ovari serta peningkatan dalam kelenjar uterus dan ketinggian sel-sel turus adalah menurun. Semua keputusan imunohistokimia menunjukkan ekspresi yang lebih tinggi ($p < 0.05$) bagi reseptor steroid, EGF, PCNA dan VEGF dalam T3 berbanding kumpulan lain. Eksperimen ini mengesahkan kesan buruk LA ke atas sistem pembiakan dan mendedahkan penemuan baru kesan peningkatan penambahan EBN melalui mulut terhadap kerosakan yang disebabkan oleh ketoksikan LA kepada sistem pembiakan, dimana pencapaian terbaik adalah pada kadar 120mg/kg berat badan.

Secara umum, kajian ini menunjukkan bahawa penambahan EBN meningkatkan fungsi kelenhar pituitary, ovari, uterus, ekspresi reseptor steroid, EGF, REGF, VEGF dan PCNA ke atas ovari dan uterus bersama dengan peningkatan tahap serum E2, P4, P dan GH. Tambahan lagi, EBN telah menunjukkan kesan penggalakan pada indeks kesuburan dengan meningkatkan kadar kehamilan dan implantasi embrio. Juga, kajian ini menunjukkan bahawa penambahan EBN pada dos mulut 60 - 120mg/kg berat badan mampu melindungi dan mencegah perubahan dalam kelenjar pituitari dan sistem pembiakan akibat ketoksikan plumbum melalui suatu mekanisme bersepadu yang mengekalkan keseimbangan antioksidan-spesies oksigen reaktif (ROS). Dapatan keseluruhannya kajian ini menyediakan bukti saintifik yang menyokong tuntutan tradisional tentang manfaat EBN terhadap pembiakan yang menjadi salah satu sebab penggunaannya di kalangan manusia.

ACKNOWLEDGEMENTS

First of all, I want to thank the God Almighty for his grace and divine enablement to complete this work. Secondly, I wish to express my sincere gratitude to the following people without whom this study would not have become a reality:

My utmost gratitude goes to my supervisor Dr. Nurhusien Yimer for his generous advice and ongoing assistance and encouragement throughout the duration of this work. May God bless you richly.

The members of my supervisory committee, Professor Dr. Abd Wahid Haron, Professor. Dr. Md. Zuki Bin Abu Bakar and the late Associate Professor Dr. Rosnina Bt Hj. Yusoff for all their guidance and support during this study. Truly, they have been my guardian angels!

My father, mother, brothers and sisters, thank you all for the support that gave me throughtout this journey. Special thanks goes to my family: wife and children, you stand by me with all you have got in all situations 'under the rain and in the sun' giving me hope and motivations.may Allah reward you abundantly.

The Ministry of Higher Education and Scientific Research, Iraq for selecting me as a scholarly candidate and funding my study here in Malaysia. Acknowledgement also goes to Department of Anatomy and Histology, Faculty of Veterinary Medicine, University of Kufa, Najaf, Iraq for granting me leave during the tenure of my study.
I would also like to express my appreciation to the academic, technical staff who contributed immensely to the success of this great accomplishment: Dr. Bahaa Almahanawi, Dr. Adamu Abdul Abubakar, Dr. Kareem Hendol, Mr. Jamil, Mrs. Jimilah and Mrs. Latifah.

Lastly, I am not forgetting, Professor Dr. Abdul Salam Babji for providing edible bird's nest to us during experimental period. Almighty God rewards you abundantly.

I certify that a Thesis Examination Committee has met on 7 May 2018 to conduct the final examination of Abdulla Aaid Hadi Albishtue on his thesis entitled "Improved Reproductive Performance Through Edible Bird's Nest and its Ameliorating Properties in Lead Acetate Toxicity of Reproductive System in Female Rats" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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Date: 30 July 2018

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirements for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Declaration by graduate student

I hereby confirm that:

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This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) were adhered to.

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µg	micro gram
µl	Microliter
µm	Micrometer
µmol	Micromole
AF	Atretic follicle
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANOVA	Analysis of variance
AO	Antioxidant
AR	Amphiregulin
AST	Asparate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
bFGF	Basic fibroblast growth factor
BW	Body weight
Caco-2 cells	Human colonic adenocarcinoma cell line
CFTR	Cystic fibrosis transmembrane conductance regulator
CL	Corpus luteum
CO_2	Carbon dioxide
cpm	Counts per minute
CREA	Creatinine
DAB	3,3-diaminobenzidine
DNA	Deoxyribonucleic acid
E_2	Estrogen
E_2R	Receptor of estrogen

EBN	Edible bird's nest
EGF	Epidermal growth factor
EIS	Embryonic implantation sites
ENaC	Epithelial Na+ channel
ETP	Economic Transformation Programme
F	Follicular unit
FGFS	Fibroblast growth factors
FSH	Follicle-stimulating hormone
FSH	Follicular stimulating hormone
GE	Glandular epithelium
GH	Growth hormone
GHRH	Growth hormone releasing hormone
GSH	Glutathione
H and E	Using hematoxylin and eosin
H_2O_2	Hydrogen peroxide
hADSCs	Human adipose-derived stem cells
HB-EGF	Heparin-binding epidermal growth factor
HGF	Hepatocyte growth factor
IC	Interstitial cell
ICM	Inner cell mass
IGF	Insulin-like growth factor
LA	Lead acetate
LE	The luminal epithelium
LH	Luteinizing hormone
MDA	malondialdehyde

min	Minute
ml	Milliliter
mmol	Millimole
MSCs	Placenta-derived multi potent mesenchymal stem cells
NC	Control stain without antibody
NF	Antral follicle
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitrogen oxides
NOS	Nitrogen oxide species
O_2 -	Superoxide
OBWR	Ovarian body weight ratio
ºC	degree Celsius
OD	optical density
OS	Oxidative stress
OSB	Oxidative stress biomarkers
OSE	Ovarian surface epithelium
P	Prolactin
P_4	Progesterone
P_4R	Receptor of Progesterone
Pb	Lead
PCNA	Proliferating cell nuclear antigen
REGF	Receptor of epidermal growth factor
ROS	Reactive oxygen species
S	Stromal cells
SA	Sialic acid

SE	Standard error
SEM	Scanning electron microscope
SOD	Superoxide dismutase
T	Testosterone
TAC	Total antioxidant capacity
TBARS	Thiobarbituric acid reactive substance
TNF-α	Tumour necrosis factor-alpha
UBWR	Uterine body weight ratio
UE	Uterine endothelium
un	Number of uterine glands in endothelium
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

There has been an increase in interest towards natural substances and their bioactive components in the last two decades. One of the primary motives was hormone replacement therapy that showed their dangerous side effects over time, whereas natural substances have been used for centuries without side effects (Hanafy and Hatem, 1991). Edible bird's nest (EBN) is a natural product of the salivary secretion of two male distinct swiftlets; *Aerodramus fucifagus* and *Aerodramus maximus*. Swiftlet's are insectivorous birds naturally found inhabiting mainly limestone caves in Asian countries, such as Malaysia, Indonesia, Thailand, Vietnam, Philippines and China (Marcone, 2005). Indonesia is the major resource, while the Malaysian Borneo provinces of Sarawak and Sabah (East Malaysia) being the second major sources (Hobbs, 2004). Edible bird's nest is traditionally considered as effective medicine by the Chinese community for centuries and has been used to alleviate many ailments.

Research on various aspects of EBN, including its nutritional and health benefit, has gained momentum recently and scientific explanations are being provided mainly supporting the traditional beliefs. Enhancement of reproductive performance and behaviours such as libido are among the traditionally believed benefits of EBN which are yet to be explained and proven scientifically. Emerging research findings on EBN in areas other than reproduction have shown that EBN possesses many biological properties, including the ability to stimulate growth and proliferation of stem cells, epidermal growth factor (EGF) – like activity, enhance production of reproductive hormones like estrogen and act as an antioxidant. Bioactive compounds reported to be found in EBN include sialic acid, glycoproteins, hormones, minerals and vitamins (Ma and Liu, 2012b). Thus, it is understood that all these biological properties of EBN would have a potential influence on the process of reproduction. According to Spencer (2013) pregnancy rates from a single insemination per animal is known as fertility, which is considered high in sheep, moderate in beef cattle and low in dairy and humans. Therefore, infertility and sub fertility are major problems in humans. Early pregnancy losses, endometria are responsible for about two- third (Ledee-Bataille *et al.*, 2002). Successful implantation requires regulation of maternal hormones such as ovarian estrogen and progesterone and their receptors in endometrium that lead to production of signaling molecules which include proliferating cell nuclear antigen (PCNA) and growth factors such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and receptor of epidermal growth factor (REGF) (Dey *et al*., 2004). Looking for strategies to enhance reproductive success, which is a multifactorial issue, has been an active research area. Considering all the potential bioactive ingredients and functions of EBN reviewed above, we hypothesized that EBN would also confer enhancing effect to reproduction as well as be able to ameliorate toxic damages caused by exposure toxic heavy materials like Lead (pb) among major growing environmental pollutants that affect body organs through exposure from air, water and food sources .Band lead acetate(LA) was one of the

mainly environmental pollutants environmental levels of lead have increased more than 1000-fold over the past three centuries as result of human activity and due to increasing worldwide use of leaded gasoline(Agency for Toxic Substances and Disease Registry - ATSDR, 2007). Several studies showed the adverse effect of Pb toxicity on the liver, pituitary gland and reproduction associated with damage to surviving ovarian follicles and the reproductive system including the ovary and uterus and ovarian follicles. One of the important mechanisms underlying LA toxicity is the induction of oxidative stress as a result of production of reactive oxygen species, depletion of the antioxidant defense system and LA crosses the biomembranes to reach the soft tissue cells, and thus precipitates in the ovary, and placenta (Flora *et al*.,2011). Although EBN has been praised as a potent antioxidant (Yida *et al*., 2015a), its role in mitigating the effect of LA toxicity on the reproductive system is unknown.

Therefore, the objectives of the study were:

1. To determine effects of EBN supplementation on cycling female rats with expect to its reproductive and pituitary gland histomorphology, hormones and expressions of their receprters, proliferating cell nuclear antigen (PCNA) and growth factors such as EGF, REGF, and VEGF as well as on oxidative stress biomarkers (OSB) and antioxidants (AO).
2. To determine effects of EBN supplementation on rat's uterine histomorphology and ultrastructure, embryo implantation, endometrial expression of P_4R and E_2R, PCNA and growth factors as well as levels of steroid hormones, OSB and AOs.
3. To evaluate ameliorating effect of EBN supplementation on LA toxicity effect on the reproductive system of female rats through assessment of histopathology of ovary, uterus, pituitary gland, ovarian and endometrial expression of E_2R, P_4R and PCNA and growth factors as well as plasma steroid hormones, OSB and AOs.

From the above objectives it is hypothesized that EBN supplement improves fertility of female rats through enhancing the functions of uterus, ovary and pituitary gland as well as minimizing oxidative stress without causing toxic effect on liver. In addition, EBN plays a prophylactic role in protecting the reproductive functions of rats from toxic effect of lead acetate.

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