UNIVERSITI PUTRA MALAYSIA

EFFECTS OF *ANDROGRAPHIS PANICULATA*, *CARICA PAPAYA* AND *CASSIA ALATA* EXTRACTS ON THE REPRODUCTIVE SYSTEMS OF MICE

AZMAHANI ABDULLAH

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By

AZMAHANI ABDULLAH

Thesis Submitted to the School of Graduates Studies, Universiti Putra Malaysia, In Fulfillment of the Requirement for the Degree of Master of Science

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DEDICATION

"Dedicated to my supervisor Associate Professor Dr. Mohd Nazrul Hakim Abdullah, my father (Abdullah), my mom (Azizah) and my brothers and sisters (Arzura, Azlinda, Al-Fatihah, Adibah, Al-Fadilah, Mohd. Asyraf, Alia Shazwani and Aiman Adli & Friends"

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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Chairman : Associate Professor Mohammad Nazrul Hakim bin Abdullah, Ph. D.

Faculty : Medicine and Health Sciences

In facing the high rise of population especially in developing countries, a continuing need is felt for oral and non-surgical methods of contraception. Plants extracts have been used widely in traditional medical practice especially as an anti-fertility agent. The *Andrographis paniculata, Cassia alata* and *Carica papaya* extracts have been reported to poses multifunctional properties. In the present studies, the effects of 20 mg/kg body weight ethanol extract of *Andrographis paniculata*, *Carica papaya* and *Cassia alata* on the reproductive systems was studied after 30 days and 90 days of treatment in female and male mice. Clomiphene citrate, given daily at 50 mg/kg body weight, was used for the purposed comparison. Results obtained showed that the female genital organs (ovaries and uteri) weight was reduced significantly after treatment with *Carica papaya* and *Andrographis paniculata* respectively. All females groups showed changes in fertility and reduction in litter number. However, after treatment with the same extracts,

the litter number for *Cassia alata* treatment was found to increase as compared to control group. A significant decrease in the number of Graffian follicles and corpora lutea with significant increase in number of atretic follicles in all treatment groups was observed except in the group treated with *Cassia alata.* There were no changes in the weight of the body, epididymides and seminal vesicles. A reduction in epididymal sperm count, sperm motility, number of fertile males, litter number, and serum testosterone levels were also observed after manipulation of all extracts duration of treatment except *Cassia alata.* Testis histology study revealed spermatogenetic arrest at the spermatocyte level. In mice treated with clomiphene citrate, the body weight, testis, epididymis, and seminal vesicle weight, sperm counts, and sperm motility were found to reduce. Sperm morphology revealed abnormalities of the head, neck and tail. Progressive regress of the seminiferous tubules with most tubules devoid of spermatozoa and spermatid were also seen. However, these effects were reversible upon cessation of treatment. The findings therefore suggest that *Carica papaya* and *Andrographis paniculata* have mild inhibitory effects on male and female reproductive systems as compared to control group (clomiphene citrate). However, *Cassia alata* extracts aid in promoting fertility by improving male and female reproductive functions.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KESAN EKSTRAK *ANDROGRAPHIS PANICULATA, CARICA PAPAYA* DAN *CASSIA ALATA* KE ATAS SISTEM PEMBIAKAN MENCIT

Oleh

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Dengan meningkatnya populasi penduduk terutama di negara membangun, kaedah perancang keluarga tanpa pembedahan yang berterusan diperlukan. Ekstrak tumbuhan telah digunakan dengan meluas dalam perubatan tradisional terutama sebagai agen anti-kesuburan. Ekstrak *Andrographis paniculata, Carica papaya* dan *Cassia alata* telah dilaporkan mempunyai pelbagai kegunaannya. Dalam kajian ini, kesan 20 mg/kg berat badan ekstrak etanol *Andrographis paniculata, Carica papaya* dan *Cassia alata* dikaji pada sistem pembiakan mencit betina dan jantan selepas 30 dan 90 hari rawatan. Clomiphene sitrat, di beri setiap hari pada 50 mg/kg berat badan digunakan untuk tujuan perbandingan. Keputusan kajian mendapati berat alat kelamin betina (ovari dan uteri) telah menurun secara bererti selepas rawatan *Carica papaya* dan *Andrographis paniculata*. Kesemua kumpulan betina menunjukkan perubahan dalam kesuburan dan penurunan dalam bilangan anak. Walaubagaimanapun, bilangan anak bagi rawatan *Cassia alata* didapati bertambah berbanding kumpulan kawalan. Penurunan bererti pada

bilangan folikel Graffian dan corpora lutea dan peningkatan bererti pada bilangan folikel atretik pada semua rawatan melainkan ekstrak *Cassia alata*. Berat badan dan berat epididimis dan vesikel seminal tidak menunjukkan sebarang perubahan. Pengurangan dalam bilangan sperma epididimis, pergerakan sperma, bilangan jantan yang subur, bilangan anak dan aras testosterone serum juga dilihat selepas manipulasi jangka masa rawatan kesemua ekstrak kecuali *Cassia alata*. Kajian histologi pada testis menunjukkan terhentinya proses spermatogenesis pada peringkat spermatosit. Dalam mencit yang dirawatan dengan clomiphene sitrate, berat badan, berat testis, epididimis, dan vesikel seminal, serta bilangan dan pergerakan sperma didapati berkurangan. Morfologi sperma menunjukkan kecacatan pada bahagian kepala, leher dan ekor. Dari kajian histologi testis pula menunjukkan tanda-tanda regrasi pada tubul seminiferous dengan ketidakhadiran spermatozoa dan spermatid pada kebanyakan tubul. Namun, kesan ini hilang selepas rawatan dihentikan. Dengan itu, penemuan ini mencadangkan bahawa ekstrak *Andrographis paniculata* dan *Carica papaya* memberi sedikit kesan perencatan pada sistem pembiakan betina dan jantan berbanding kumpulan kawalan (clomiphene citrate). Sebaliknya ekstrak *Cassia alata* membantu menambah kesuburan dengan meningkatkan fungsi sistem pembiakan mencit jantan dan betina.

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LIST OF ABBREVIATIONS

b.w.	body weight
^{0} C	Degress Celcius
g	gram
M	molar
mg	miligram
mm	millimeter
ml	mililiters
µl	microliters
µm	micrometer
µg	microgram
mw	miliwolt
s.e.m	standard error of mean
pH	$-\log_{10}[H^+]$
rpm	rotation per minute
ng	nanogram
p	probability of an event due to chance alone
ELISA	enzyme-linked immunosorbent assay
Min	minute
G.I.	Gastrointestinal
FSH	follicle-stimulating hormone

CHAPTER 1

INTRODUCTION

1.1 Population Explosion

The single outstanding fact about world population during the past two hundred years has been the rapidity of its growth. Since 1750, there has been a rapid and accelerating expansion in population and more recently termed 'population explosion'. Currently, according to the World Health Organization (WHO), 3.7 human beings are born every second: the net increment works out to be at 222 per minute, 13 260 per hour, 318 240 per day, or nearly 2.25 million per week (Robinson, 1981).

The limits to growth have been analysed recently by a team of scientists led by Professor Dennis Meadows from the Massachussets Institute of Technology, with the help of models and computers. These models were constructed to investigate 'the five major trends of global concern – accelerating industrialization, rapid population growth, widespread malnutrition, depletion of non-renewable resources, and a deteriorating environment' (Llewellyn-Jones, 1975). The recent and unprecedented population explosion is of concern not only to the demographer but to the politician, economist, geographer, sociologist, and medical scientist among many others, all of whom are very much concerned with ensuring that the sheer quantity of human beings will not diminish the quality of human life (Robinson, 1981).

Global search of anti-fertility agents is going to tackle the problem of 'Population Explosion'. Many hormonal drugs are available for the purpose but they are not free from side effects. Hence, the search for a suitable product from indigenous medicinal plants is proposed which could be effectively used in place of the synthetic or hormonal (Hoffman, 1990).

1.2 Contraceptive

There are several methods of contraception today. However, an ideal contraceptive that is safe, inexpensive, totally effective, easily reversible and without side effects has yet to be develop. Oral contraceptives, intrauterine devices, male and female sterilizations, barrier contraceptives, medical termination of pregnancy, rhythm and symptothermal methods and *coitus interruptus* are presently being used to control births (Salunkhe *et al*., 1989).

1.2.1 Contraceptive Methods for Women

The pill is a very simple and easy to use method of birth control. The female sexual partner simply swallows one pill each day for 20 or 21 days. During that month she will not get pregnant. The pill works by keeping the woman's ovaries from releasing an egg as long as she is taking the pills according to the prescribed regimen. The pill contains the female hormones estrogen and progesterone which a woman's body produces when she is pregnant. These hormones keep her body from releasing eggs for as long as she takes birth control pills. The eggs simply do not mature and thus are not released by the ovaries. For a few women, the pills sometimes produce temporary and mildly unpleasant

side effects. Some women experience mild nausea or stomach upsets when taking the first few pills. This goes away after the pills have been used for a month or so (Zawacki, 1971). Other problems that need further study to establish their association with the pill are an increased risk of urinary tract infections, gall bladder disease, liver disease and tumors, and birth defects if pill use is continued into pregnancy. Prolonged infertility is also possible after the pill is discontinued, but whether it is caused by the pill itself or masked by the artificial menses during use is unclear. Evidence so far shows pill users to have a lower risk of benign breast disease, fewer ovarian cysts, and unchanged risk of cervical cancer (Hauser, 1979).

Chemical impregnated intra-vaginal plugs have been used for contraceptive purpose by many primitive tribes. Currently, there are over 50 suppositories, pessaries, gels, or foams available. The solid vaginal suppositories contain spermicide in a base of soap, gelatin or cocoa-butter which is designed to melt at body temperature. The vagitory is inserted just prior to coitus. The gels which are made up in a water-soluble gelatinous base disperse easily in the vagina, and usually serve as an additional protection if the male uses a condom, or in conjunction with a vaginal diaphragm. The gel or cream is usually introduced high into the vagina through a plastic plunger applicator which is provided in the package. The foams are either in foaming tablet form or in containers from which the appropriate amount can be introduced into the vagina (Llewellyn-Jones, 1975). Disadvantages are the leakage of fluid from the vagina, the need to wait while the content of the vaginal suppositories melts, and poor effectiveness, usually due to poor quality, inadequate quantity, or disregard for the required waiting period (Hauser, 1979).

1.2.2 Contraceptive Methods for Men

Apart from abortion and infanticide, coitus interruptus is probably the oldest method of birth control (Llewellyn-Jones, 1975). The method requires no supplies, expense, preparation, or assistance from physicians. On the other hand, it demands practice, male-control, and considerable motivation. It may be reliable in highly motivated couples. Failures can result from the escape of semen before ejaculation, from semen deposited externally near the vagina, or from simple delay in withdrawal (Hauser, 1979). Its greatest disadvantage is that it is difficult to practice because it interrupts the act of sex just at a point when human nature desires no interruption (Zawacki, 1971).

A cylindrical sheath that envelops the penis, the condom has the advantage of being cheap, simple to use and can be obtained without prescription from a physician. However, it has the disadvantages of being distracting and dulling sensation. Moreover in some cultures, it is associated with prostitution because of its prophylactic role in venereal diseases. It is effective if properly used and carefully manufactured. Rubber condoms deteriorate with time, particularly in sunlight and heat, and therefore have a limited shelf life, especially in tropical countries (Hauser, 1979). Male sterilization (called vasectomy) is quite a simple operation that can be done in a doctor's office or a clinic. The man merely goes home and rests for a few of days. The procedure involves the removal of a small section of the two tubes that carry the male sperm to the penis. This procedure will not change in his nature or his sexual desire (Zawacki, 1971).

1.3 Herbs, Fertility and Contraception

Several approaches are being used in different parts of the world to control human fertility. Most of the currently used methods of birth control are associated with certain risks and side effects. As such, an ideal contraceptive has yet to be developed. Many plants have been used in traditional medicine as contraceptive agents.

New and improved methods of contraception are being developed. For example, long-acting injectable preparations, postcoital drugs, low-dose oral contraceptives, biphasic and triphasic pills, paper pills, sperm and ova pills. The currently used methods of contraception are associated with risks and side effects. For example, the use of oral contraceptives is associated with some circulatory system diseases including thromboembolism, myocardial infarction and hypertension. Endometrial bleeding, pelvic infections, pelvic inflammatory disease and ectopic pregnancy are frequently observed with use of the intrauterine device (IUD) (Stephen *et al.*, 1994).

Great attention is being given to plants with potential anti-fertility properties. These may act through effects on sperm motility and viability, implantation of the fertilized egg or a rejection effect within the uterus. The biochemistry of these pathways is complex, and the study of plants having such effects is revealing new mechanisms all the time. The planetary crisis that is upon us has the population explosion as a major component, and the World Health Organization has put great emphasis on the search for a safe, cheap and socially acceptable form of contraception (Hoffman, 1990).