INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

EXAMINING THE EFFECTS OF IKMO (*PIPER BETLE* LINN.) ON THE THYROXINE LEVEL OF FEMALE ALBINO RATS AND ITS RELATIONSHIP TO INFERTILITY AND HYPERPROLACTINEMIA

Louie Ian B. Mariano *, Renato B. Boquiron Jr., Eloisa P. Rementilla
College of Liberal Arts and Sciences, Colegio de San Juan de Letran, Manila
*Corresponding Author Email: louieian.mariano@letran.edu.ph

Article Received on: 18/06/17 Approved for publication: 02/08/17

DOI: 10.7897/2230-8407.087132

ABSTRACT

The use of plants as a natural contraceptive is now a trend in populous countries. One of the most popular natural contraceptive today is the *Piper betle*. Thyroid glands and hormones play a significant role in the development and function of the reproductive system. There are reports stating that thyroxine level is inversely correlated with the level of prolactin. Similarly, estrogen level is positively correlated with the level of prolactin which is linked with a condition characterized by the deficiency or excess of the hormone: prolactin. The aim of this study is to evaluate the effects of *Piper betle* as a natural contraceptive on the level of thyroxine of rats. For this purpose, nine female albino rats were divided into three groups; control samples that were administered with standard commercial pellet and water; experimental group 1 that was administered with 0.5ml of *Piper betle* extract and experimental group 2 that was administered with 1 ml of *Piper betle* extract for two weeks. Results showed that thyroxine level varies among groups and no statistical differences were reported. These findings supported other studies showing the correlation among thyroxine, prolactin, and estrogen. It also suggests that *Piper betle* is an effective and a safe natural contraceptive. In addition, the development of possible side effects is minimal.

Keywords: *Piper betle*, contraceptive, Thyroxine, Prolactin, Infertility

INTRODUCTION

The Philippines is among the most populous countries in the world. The Philippine Statistics Authority (PSA) quantified the year 2010 Philippine population with a total of 92.34 million. In 2013, according to United Nations, Philippines ranks as the twelfth most populous country in the world with a total of 98.39 million. The Philippine Statistics Authority projected that the population would reach 101.6 million last year (2015). In fact, the Philippine population reached 100 million last July 2014. For more than three decades, the country implements family planning programs to manage the increasing population in relation to the developmental needs of the Philippines[1].

One factor of reproductive health that holds importance and interest is fertility regulation comprising contraception[2]. According to the Family Health Survey, the pill, an artificial contraceptive was the leading method with 19.8 % of married women using it followed by female sterilization (8.6%) and withdrawal (8.2%) (Philippine Statistics Authority, 2013). A study[1] concluded that older women tend to choose permanent methods such as sterilization while younger women tend to prefer reversible methods such as the pills. In addition, intrauterine device and male condoms are also being used. Also, Laguna et.al.[1] stated that Catholic women tend to prefer the intrauterine device and reject the use of injectable and other traditional methods than non-Catholic women. In the said study, it was mentioned that both modern and traditional contraceptive method utilization is superior in urban than in rural areas and that working women who belong to wealthier households are more likely to prefer modern contraceptive methods. By region, use of condoms and female sterilization is highest in the National Capital Region (NCR) while in Mindanao, on the other hand, the use of the pill, intrauterine device, and injectable are more preferred[1]. The various preferences of methods in different regions may suggest differences in the accessibility as well as the difference of cultural and religious practices of the people. Since most contraceptives, especially artificial ones, are said to have side effects that can cause great harm to the users, there is a need for contraceptive agents of natural and safer qualities. There are several medicinal plants linked with infertility activities and contraceptive properties. In addition, one of these is associated with common activities of some Philippine indigenous tribes.

Pagnganganga or betel quid chewing is one of the important traditional customary, integrated into social and cultural practices and ceremonies[3], of some Philippine indigenous tribes such as the Mangyans and Igorots. According to the Flora et. al[3], it is also practiced in other Asian countries such as Pakistan, Sri Lanka, Bangladesh, Thailand, China, Taiwan and other Pacific Islands. The four main ingredients of the betel quid are the ikmo or *Piper betle* L. which is the leaf of the tree *P. betel* that symbolizes life, bunga or the betel nut symbolizes success for its abundance, apog, on the other hand, is the white shell powder prepared from seashells or quarried limestone also known as slaked lime (calcium hydroxide)[3], which symbolizes purity, and tobacco which symbolizes the preservation of customs and traditions. The betel nut, apog, and tobacco are placed inside the betel leaf which is rolled before upon being chewed[4]. Other substances such as spices are added to the betel quid according to preference[5]. The betel quid can be obtained for a cheaper price which suggests affordability to the least advantaged members of the society where it is usually being practiced. Since it is cheap and integrated into social practices, it is the fourth most commonly consumed psychoactive substance after

caffeine, alcohol, and nicotine[3]. In addition, according to the study, betel quid chewing is more often observed in the older age groups and among blue collar workers and that it is more prevalent in rural areas. Flora et. al[3]suggests that betel quid consumption is inversely correlated with education and income.

Among the four primary ingredients of betel quid that holds importance in this study is the betel leaf. The betel leaf (*Piper betel L.*), also known as betel pepper, or locally as Ikmo, is an evergreen, perennial vine that thrives in humid forest conditions and in deep and well-drained soils. It is cultivated in most South-Asian countries[6] including the Philippines. The leaf is shiny and is heart-shaped in appearance. The leaves were alternate and have a color of yellowish green to bright green[7]. The leaf has carminative properties that prevent the formation of gas in the gastrointestinal tract, aphrodisiac properties that stimulate excitement, tonic properties that strengthen well-being, laxative properties that are helpful for bowel movements and appetite-improving properties[8]. In addition according to Indian folkloric medicine, it also has antiseptic properties[9], applied on wounds to reduce infection. It has chemical constituents such as water, proteins, carbohydrates, minerals, fats, fiber, tannin, alkaloid, specifically arakene, vitamins A and C, amino acids, nicotinic acid, and thiamine[10]. According to Pradhan et.al.[10], phenolic content enhances the quality of the *Piper betle* leaf.

Some traditional uses of the leaves are for the cure for inflammatory swelling, sore throat, indigestion, wounds, and boils. In addition, advantages to pulmonary infection are also mentioned as modern medicinal uses in addition to the traditional uses[11]. Although positive effects of piper betel leaves were investigated, there are studies suggesting that its stalk has negative effects. According to tostudies[2,12], the piper betel leaf stalk extract decreased the level of testosterone, sperm count, spermatozoa motility, and the pH or acidity of the seminal plasma of male rats which suggests that the ingredients of betel quid have harmful effects on the consumer, especially on the reproductive system. This is mainly because of the presence of arakene, an alkaloid, which is said to have the same effect as cocaine. Estrogen increases and progesterone decreases in rats that were administered with cocaine which in turn illustrated the importance of female gonadal hormones in drug-seeking behavior and possible effects to female hormonal level[13].

Betel quid is not only consumed by men, women are not excluded in the practice of betel quid chewing. It is not uncommon for women to consume betel quid even after pregnancy. This raises concerns about the possible effects of betel quid to the health of a woman and her child, especially during pregnancy. The use of piper betel as natural contraceptive also raised concerns about its possible negative effects on the body especially to the level of estrogen, prolactin, and thyroid, specifically thyroxine, on non-pregnant and non-breastfeeding woman.

Prolactin (PRL), a polypeptide, is one of the several hormones that are produced by the anterior pituitary gland[14]. In men, prolactin affects the sperm production; high levels can cause to decreased testosterone levels or abnormal sperm. In non-pregnant women, prolactin helps the regulation of menstrual cycle. In pregnant women, the hormone prolactin is required for mammary development and milk protein gene expression[15]. One of the prolactin's most important role to the body is to stimulate milk production in women after delivery of a baby. Its levels increase during pregnancy and it causes the enlargement of mammary glands for breastfeeding preparation and secretion of colostrums closely after the delivery.

Hyperprolactinemia and hypoprolactinemia are two prolactin conditions that raise issues nowadays. Hyperprolactinemia pertains to the excessive increase of prolactin levels in the blood that is usually caused by prolactinoma, a benign tumor on the pituitary gland. It can also be caused by hyperestrogenemia[16], the disruption of prolactin levels caused by prescription drugs, medicinal herbs, and heavy metals. It may cause galactorrhea, disruption of the normal menstrual period in women, and hypogonadism and infertility in men. Hypoprolactenemia, on the other hand, is characterized by prolactin deficiency that usually results from hypopituitarism[17],hypothyroidism[18], deficiency of growth hormone, autoimmune disease, and excessive levels of dopamine, a neurotransmitter that can inhibit prolactin secretion from the anterior pituitary gland.

Thyroid gland and thyroid hormones also play an important role in reproductive system development and function. The two principal thyroid hormones are thyroxine (T4 or L-3,5,30,50-tetraiodothyronine) and triiodothyronine (T3 or L-3,5,30-triiodothyronine)[19]. T3 is identified as the biologically active hormone. Its primary function is to regulate protein and carbohydrate in all cells. Changes in its level can have a profound effect on the cardiovascular, nervous, immune and reproductive systems of the body. On the other hand, T4, which is secreted from the thyroid gland is the major thyroid hormone. It is considered as a precursor or prohormone[19].

Abnormalities in the thyroid glands and level of thyroid hormones, specifically hyperthyroidism, and hypothyroidism, also raised concern about its effect on reproduction. Hypothyroidism occurs when the thyroid gland produces thyroid hormone that is below the normal level. The main causes of hypothyroidism are the inadequate production of TH, the resistance of hormone and the inadequate conversion of T4-T3[19]. Hence, the thyroid is underactive which means the thyroid does not produce enough thyroid hormone that keeps the body function normally[20]. According to a study[21], hypothyroidism and hyperprolactinemia have a positive correlation. In addition, a high prevalence of hyperprolactinemia occurs to infertile women[21]. Furthermore, infertile women are subjected to a greater vulnerability for thyroid disorder than fertile women[22].Several animal studies and reviews reported that hypothyroidism can cause infertility. One study[23]reported that thyroid disease negatively affects spermatogenesis and consequently may cause male infertility. Decreased libido or impotence is also present in hypothyroidism[24].

Because of this, the researchers conducted this study to determine the negative effects of piper betel as an alternative contraceptive. Specifically, it aims to determine if there is an alteration in the level of free thyroxine, that is one of the determinants of hypothyroidism, in non-breastfeeding rats. This study will be helpful to people who practice betel quid chewing especially to women and in the advancement of the use plants in population control. In addition, the study will be of helpful information to individuals who use *Piper betle* as a natural contraceptive. This study will not include the determination of the level of the hormone estrogen, prolactin, TSH and T3 of female rats.

MATERIALS AND METHODS

Collection of the Plant Sample

Piper betel samples were purchased from Quiapo, Manila. A plant sample specimen was deposited to and identified and authenticated by the professionals of the Botany Department, National Museum of the Philippines.

Preparation of Plant Extract

The collected plant samples were extracted with the aid of the professionals from Department of Science and Technology (DOST), Philippines. Piper betel leaves were blended and soaked in 2.0L of 95% ethanol for 48 hours. The mixture was filtered and the filtrate obtained was concentrated using rotary evaporator at 60ºC under vacuum for 2 hours. The concentrated extract was further evaporated using water bath at 60ºC to obtain a semi-solid extract.

Phytochemical Analysis

Piper betel leaves were submitted to the professionals of the Department of Science and Technology (DOST) for phytochemical analysis to determine the various plant constituents.

Experimental Animals

Nine adult female albino rats, weighing 130 – 160 grams were purchased from the Food and Drug Administration in Muntinlupa City, Philippines. The rats were placed in an individual cage lined with husk which was renewed every day. Each rat has access to commercial pellet and water. The animals were housed in a controlled environment with a lighting condition of 12 hours light and 12 hours darkness at room temperature.

Acclimatization

To ensure good health, the rats were acclimatized for one week before starting the experimentation. The laboratory animals were given the standard food during the process.

Administration of *Piper Betel L.* Extract

Animal samples were divided into three groups, each group is composed of three rats. The first group of mice was controlled mice that were administered with commercial pellet and has access to distilled water. The first group of experimental animals, which was the second group, were administered with piper betel extract of 0.5mL mixed with the commercial pellet and had access to distilled water. The second group of experimental animals, which was the third group, were administered with piper betel extract of 1mL mixed with the commercial pellet and had access to distilled water. The administration lasted for seven days. Experimental animals were administered with 10 ml/kg volume selection. The dosage was according to the standard of OECD's (Organization for Economic Corporation and Development) guidelines[25] in which low dose of crude extract was administered. This was calculated by dividing the weight of the animal sample by 1000 grams multiplied by 10 ml.

Experimental Design

After the completion of each respective days of treatment, blood samples were collected from each rat. One mL of blood samples were deposited to Hi-Precision Diagnostics International, Manila, the Philippines for plasma blood test, specifically FT4 (Free thyroxine) blood test. The Free thyroxine test is used to evaluate the thyroid function as well as to diagnose thyroid diseases such as hyperthyroidism and hypothyroidism.

Statistical Analysis

Data obtained after the experimentation was treated statistically using Two-Way ANOVA in order to determine whether there is a statistical difference among the means of the samples.

RESULTS

Table 1. Phytochemical Analysis of Piper Betel

Components	Level of Components
Alkaloids	(+)
Flavonoids	(+)
Triterpenes	(+)
Sterols	(+)
Glycosides	(+)
Tannins	(+)
Saponins	(+)(+)

(+) – traces (+)(+) – abundance

Table 1 shows the results of the phytochemical analysis of the Piper betel plant. According to the results, traces of alkaloids, flavonoids, triterpenes, sterols, glycosides, and tannins were detected. In addition, the presence of a chemical with antibacterial, antioxidant anticancer, antidiabetic, and anti-obesity properties[26], saponins, is moderately greater than the amount of the other chemicals mentioned.

Many alkaloids are poisonous while others are addictive[27]. This is a natural chemical compound that contains nitrogen bases mostly used as medical and recreational drugs such as local anesthetic, morphine, nicotine, and cocaine[28]. Flavonoids, on the other hand, is helpful for hepatic and cardiovascular protection and has pharmacological uses such as anticancer, antioxidant, antibacterial, antifungal, antiviral properties[29]. Triterpenes are of low toxicity, it is pharmacologically useful for it has wound-healing, anti-inflammatory, antibacterial, antiviral, antitumor, and hepatoprotective properties[30]. Sterols, a chemical compound that cannot be synthesized by humans, are concentrated in plant food especially those with high lipid content[31]. In addition, the study[31]suggested that sterols reduce cardiovascular disease risk. Tannin, a chemical compound abundant in plants, has a bitter and astringent taste and anti-inflammatory properties that give remedy to bowel disorders and other gastrointestinal problems[32].

Table 2: Blood Thyroid Hormone Level of Animal Samples

Animal Sample	Thyroid Level (Pre-test)	Thyroid Level (Post-test)	Change in Level(+/-)
A (Control 1)	18.96	18.24	- 0.72
H (Control 2)	16.05	21.75	+5.7
I (Control 3)	19.12	25.90	+6.78
B (Exp.1 1)	26.75	16.79	-9.96
C (Exp.1 2)	26.79	25.92	-0.87
D (Exp.1 3)	24.64	23.88	-0.76
E (Exp.2 1)	23.80	24.74	+0.94
F (Exp.2 2)	19.99	16.49	-3.5
G (Exp.2 3)	15.12	18.56	+3.44

Table 2 shows the Free Thyroxin (FTS) level of each animal sample before and after the administration of *Piper betle* extract. As shown above, FT4 levels were altered after the administration of extract. Controlled animals H and I's FT4 levels increased by + 5.7 and +6.78, respectively while sample A decreased by 0.72. On the other hand, all experimental animals that were administered by .5 ml of piper betel extract saw a decrease in their free thyroxine level. Experimental animals B, C and D's FT4 level decreased by 9.96, 0.87 and 0.76 respectively. Free thyroxine levels of experimental animals that were administered by 1 ml of piper betel extract vary. There is a 0.94 and 3.44 increase in both samples E and G respectively and a decrease in sample F, which is by 3.5.

Table 3: Statistical Analysis: Summary Table

SUMMARY	Count	Sum	Average	Variance
Row 1	2	37.2	18.6	0.2592
Row 2	2	37.8	18.9	16.245
Row 3	2	45.02	22.51	22.9842
Row 4	2	43.54	21.77	49.6008
Row 5	2	52.71	26.355	0.37845
Row 6	2	48.52	24.26	0.2888
Row 7	2	48.54	24.27	0.4418
Row 8	2	36.48	18.24	6.125
Row 9	2	33.68	16.84	5.9168
Column 1	9	191.22	21.24667	19.3652
Column 2	9	192.27	21.36333	15.18852

Table 4. Statistical Analysis: ANOVA Summary Table

ANOVA						
Source of Variation	**SS**	**df**	**MS**	**F**	**P-value**	**F crit**
Rows	174.3	8	21.7814	1.705354	0.233439	3.438101
Columns	0.061	1	0.06125	0.004796	0.946491	5.317655
Error	102.2	8	12.7724			
Total	276.5	17				

P-value >0.05 indicates that there is significant difference

Tables 3 and 4 show the statistical analysis of the gathered data. As shown in table 5, there is no statistical difference between the thyroid levels in the three groups of samples and the thyroid levels of each sample before and after the administration of *Piper betle* since the value of P is greater than 0.05.

DISCUSSION

The use of natural contraceptive is now a trend to control population boom of populous countries particularly the Philippines. With the abundance of Philippine plants in the country, natural contraceptives are also abundant. One of this plants is ikmo or *Piper betle*. This plant is the main ingredient in the betel quid, which indigenous Filipino family still practice. The plant contains several chemicals that have the antifertility effect. This chemical plant contains an alkaloid, specifically arakene. Arakene is said to have same effects like the drug cocaine. Because of the popular use of this plant and its chemical components, the need to assess the effects of it to our body must be addressed.

The present study aims to determine if the piper betel extract as natural contraceptive alters the level of thyroxine which is responsible for the development of thyroid problems, specifically hyperthyroidism and hypothyroidism, and the development of prolactinemia.

Prolactin is a hormone that is present both in males and in females. It regulates the menstrual cycle in female and is important in the secretion of milk in pregnant women. Similarly, thyroid gland and thyroid hormones also play an important role in the reproductive system. Changes in the normal level of the principal thyroid hormones, T3 and T4, may cause a debilitating effect on a person's health.

In the present study, the level of thyroxine varies among the groups. The results suggest that there is no significant difference between the thyroid levels in the three groups of samples and the thyroid levels of each sample before and after the administration of *Piper betle*. Some subjects, even after the administration of the extract, had an increase and some had a decrease in the thyroxine levels. This suggests that *Piper betle* does not significantly affect the thyroxine levels, and hence the prolactin levels as well of female albino rats. This might be due to the experimental samples reactivity to the *Piper betle* extract.

The present study did not determine the estrogen and prolactin level of each sample. Because of this, no quantitative value of estrogen and prolactin can be compared to the level of thyroxine that will further support the claim. Although lacking quantitative data, the result suggests that a positive relationship is still present since according to some studies, *Piper betle* extract decreases the level of estrogen in the body, thus making it a good natural contraceptive.

Hypothyroidism and hyperprolactinemia have a positive correlation[21]. Hence, there is an inverse relationship between the level of prolactin and level of thyroxine and if the level of thyroxine is low, the prolactin level is high. A high prevalence of hyperprolactinemia occurs to infertile women[21]. Furthermore, infertile women are subjected to a greater vulnerability for thyroid disorder than fertile women[22]. Several animal studies and reviews reported that hypothyroidism can cause infertility.

CONCLUSION

In conclusion, *Piper betle* extracts have been proven to be a safe, natural contraceptive with no alteration in the level of thyroxine which is responsible for the development of hypothyroidism and hyperprolactinemia. Since there are

established studies showing the different relationships among estrogen, prolactin, and thyroxine, it is suggested that that piper betel extract is a safe and effective natural contraceptive. But its effectivity and safeness rely on the subject's reactivity to the extract and the amount that will be consumed by the subject. In addition, the researchers concluded that the plant material can be used as an alternative and cheaper way of controlling population boom among developing countries.

RECOMMENDATIONS

The following recommendations can help improve the future researchers for the development of this study: first, future researchers should also assess the levels of estrogen, testosterone, TSH, T3, and prolactin in order to have a quantitative data that will further support the study. Unfortunately, the researchers were not able to include this because of financial constraint; second it is suggested that the level of arakene should be tested in order to determine if it is really the one responsible for the altered level; third, the future researchers should also conduct a comparative study regarding its effect on both sexes in order to develop a product that is more effective and safe. The present study would also like to recommend the use of *Piper betle* extract in developing a safer and cheaper alternative contraceptive with little to no side effects.

ACKNOWLEDGEMENT

This research was carried out with the financial support from Letran Research Center. We also like to extend our gratitude to Kathleen Magno and Johnsen Timbreza for their contribution in conducting the experiment.

REFERENCES

1. Laguna EP, Po. AL. C., Perez, A. E., and Kantner, A.. Contraceptive use dynamics in the Philippines: Determinants of contraceptive method choice and discontinuation. 2000. Calverton, Maryland: ORC Macro.
2. Vengaiah V, Govardhan NA, Changamma C.Aspects on the antifertility property of piper betel linn. leaf stalk extract: Effect of gravimetric analysis and cauda epididymal sperm parameters. World of Journal of Pharmaceutical Research2014; Vol. 3, No. 6, pp. 626-636.
3. Flora M, Mascie-Taylor C, Rahman M. 2012.Betel quid chewing and its risks factors in Bangladeshi adults. World Health Organization South-East Asia Journal of Public Health, Vol. 1, No. 2, pp. 169-181.
4. Ubaldo, LR. 2011.Buyo, buyung at bae: Betel chewing in Philippine epics. Malay, Vol. 23, No. 2, pp. 137-158.
5. Sripradha S. 2014.Betel leaf: The green gold. Journal of Pharmaceutical Sciences and Research, Vol. 6, No. 1, pp. 36-37.
6. Al-Adhroey A, Nor Z, Al-Mekhalafi H, Amran A, Mahmud R. 2011. Antimalarial activity of methanolic leaf extract of *Piper betle* L., Molecules, p. 16.
7. Arambewela L, Arawwala M, Rajapaksa D. 2006. *Piper betle*: A potential natural oxidant. International Journal of Food Science and Technology, Vol. 41, No. 1, pp. 10-14.
8. Ghosh K, Bhattacharya T. 2005. Chemical constituents of *Piper betle* linn. (piperaceae) roots. Molecules, Vol. 10, pp. 798-802.
9. Datta A, Ghoshdastidar S, Singh M. 3, 2011. Antimicrobial property of *Piper betle* leaf against clinical isolates of bacteria. International Journal of Pharmaceutical Sciences and Research, Vol. 2, No. 3, pp. 104-109.
10. Pradhan D, Suri KA, Pradhan DK, Biswasroy P. 2013. Golden heart of the nature: *Piper betle* L. Journal of Pharmacognosy and Phytochemistry, Vol. 1, No. 6, pp. 147-167.
11. Dwivedi V, Tripathi S. 2014. Review study on potential activity of *Piper betle*. Journal of Pharmacognosy and Phytochemistry, Vol. 3, No. 4, pp. 93-98.
12. Verma A, Hembrom A, Pragya S, Singh V. 2015. Antifertility effect of aqueous extract of piper betel leaf stalk on seminal quality of Swiss albino male mice. International Journal of Pharmaceutical Sciences Review and Research, Vol. 31, No. 2, pp. 116-118.
13. Larson EB, Anker JJ, Gliddon LA, Fons KS, Carroll ME. 2007. Effects of estrogen and progesterone on the escalation of cocaine self-administration in female rats during extended access. Experimental and Clinical Psychopharmacology, Vol. 15, No. 5, pp. 461-471.
14. Orbach H, Shoenfeld Y. 2006. Hyperprolactinemia and autoimmune diseases. Autoimmunity Reviews, Elsevier, Vol. 6, No. 8, pp. 537-542.
15. Kelly PA, Bachelot A, Kedzia C, Hennighausen L, Ormandy CJ, Kopchick JJ, Binart N. 2002. The role of prolactin and growth hormone in mammary gland development. Molecular and Cellular Endocrinology, Vol. 197, No. 1 – 2, pp. 127-131.
16. Law B. Jr. 2005. Evaluation and management of hyperprolactinemia. Revista de Endocronologia y Nutricion, Vol. 13, No. 3, pp. S56-S59.
17. Strauss JF III, Barbieri RL.2014. Yen & Jaffe's Reproductive Endocrinology. 7th. Elsevier Health Sciences, ISBN: 978-1-4557-2758-2.
18. Davis A.2010. Handbook of Pediatric Neuropsychology. Springer Publishing Company, p. 1134.
19. Choksi NY, Jahnke GD, Hilaire C, Shelby M. 2003. Role of thyroid hormones in human and laboratory animal reproductive health. Birth Defects Research Part B, Vol. 68, pp. 479-491.
20. Association, American Thyroid. American Thyroid Association. [Online] 2013. https://www.thyroid.org/hypothyroidism.
21. Avasthi K, Kaur J, Gupta S, Narang PA. 2006. Hyperprolactinemia and its correlation with hypothyroidism in infertile women. The Journal of Obstetrics and Gynecology of India, Vol. 56, No. 1, pp. 68-71.
22. Goswami B, Patel S, Chatterjee M, Koner BC, Saxena A. 2009. Correlation of prolactin and thyroid hormone concentration with menstrual patterns in infertile women. Journal of Reproduction and Infertility, Vol. 10, No. 3.
23. Rajender S, Monica MG, Walter L, Agarwal A. 2011. Thyroid, spermatogenesis, and male infertility. Frontiers in Bioscience (Elite Edition), Vol. 1, No. 3, pp. 843-855.
24. Aiceles V, Ramos C. 2016. A link between hypothyroidism, obesity and male reproduction. Hormone Molecular Biology and Clinical Investigation, Vol. 25, No. 1.
25. Oghenesuvwe EE, Ekene NE, Ajaghaku DL. 2014. Guidelines on dosage calculation and stock solution preparation in experimental animals' studies. Journal of Natural Sciences Research, Vol. 4, No. 18.
26. Cheok C, Salman H, Sulaiman R. 2014. Extraction and quantification of saponins: A review. Food Research International. Vol. 59, pp. 16-40.
27. Woolley JG.2001. Plant alkaloids. Encyclopedia of Life Sciences. Nature Publishing Group.
28. Kakhia TI.Alkaloids and alkaloids plants. Adana University - Industry Joint Research Center. n. d.
29. Mohammed H. 2009. Natural and synthetic flavonoid derivatives with potential antioxidant and anticancer activities.

30. Jager S, Trojan H, Kopp T, Laszczyk M, Scheffler A. 2009. PentacyclicTriterpene distribution in various plants – rich sources for a new group of multi-potent plant extracts. Molecules, Vol. 14, pp. 2016-2031.
31. Grattan B Jr. 2013. Plant sterols as anticancer nutrients: Evidence for their role in breast cancer. Nutrients, Vol. 5, pp. 359-387.
32. Ashok P, Upadhyaya K. 2012. Tannins are astringent. Journal of Pharmacognosy and Phytochemistry, Vol. 41, No. 1, pp. 45-50.

Cite this article as:

Louie Ian B. Mariano *et al*. Examining the effects of Ikmo (*Piper betle* Linn.) on the thyroxine level of female albino rats and its relationship to infertility and hyperprolactinemia. Int. Res. J. Pharm. 2017;8(7):137-142 http://dx.doi.org/10.7897/2230-8407.087132

Source of support: Letran Research Center, Conflict of interest: None Declared

Disclaimer: IRJP is solely owned by Moksha Publishing House - A non-profit publishing house, dedicated to publish quality research, while every effort has been taken to verify the accuracy of the content published in our Journal. IRJP cannot accept any responsibility or liability for the site content and articles published. The views expressed in articles by our contributing authors are not necessarily those of IRJP editor or editorial board members.