R

E

S

Ε

A

R

С

Н

Α

R

Т

П

С

L

F

J

Ρ

Α

R

2

0

1

8

# Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

# Comparative effects of *Cosmos caudatus* and *Piper* sarmentosum aqueous extracts on estrous cycle and fertility in female mice

Dzulsuhaimi Daud<sup>1,2\*</sup>, Adriana Azahar<sup>1</sup>, SitiSolehahFatinahZainal Abidin<sup>1</sup>, Alene Tawang<sup>3</sup>, Ernie Eileen Rizlan Ross<sup>1</sup>, Nooraain Hashim<sup>1</sup>

<sup>1</sup>Faculty of Applied Sciences, UniversitiTeknologi MARA, 40450 Shah Alam, Selangor, Malaysia.

<sup>2</sup>Faculty of Applied Sciences, UniversitiTeknologi MARA, Perak Branch Tapah Campus, 35400 Tapah Road, Perak, Malaysia.

<sup>3</sup>Faculty of Science and Mathematics, UniversitiPendidikan Sultan Idris, 35900 TanjongMalim, Perak, Malaysia.

Received: 23.09.2018

Revised: 27.09.2018

Accepted: 28.09.2018

Published: 30.09.2018

**ABSTRACT:** Background: The use of medicinal plants and their products for fertility regulation in Malaysia and other countries in Asia is still continuing. **Aim:** This study was conducted to compare the fertility of female mice supplemented with *Cosmos caudatus* or *Piper sarmentosum* aqueous extracts. **Methodology:** Eighteen female mice were randomly divided into three groups and fed with maintenance diets (5 g/head/day of rodent pellets and water *ad-libitum*). Group 1 (n=6) served as a control and treated with 2 ml/kg bwt of distilled water. Group 2 (n=6) was supplemented with 500 mg/kg bwt of *C. caudatus* and group 3 was supplemented with 500 mg/kg bwt of *P. sarmentosum* aqueous extracts.All treatments were conducted for the duration of 28 days. The stage of estrous cycle was identified on a daily basis and the bodyweight was measured on day 1, 7, 14, 21 and 28 of treatments. At the end of the treatments, all female mice were mated with proven fertile male and the numbers of implantation sites were counted. **Results:** Our data revealed that female fertility was not affected by *C. caudatus* consumption but *P. sarmentosum* significantly reduced the fertility in female mice. In addition, no physical signs of toxicity were observed and bodyweight was not affected by *C. caudatus* or *P. sarmentosum* aqueous extracts. **Conclusion:** It could be concluded that the *P. sarmentosum* exhibited anti-fertility effect in female mice but not *C. caudatus*.

# Corresponding author\*

Dzulsuhaimi Daud Faculty of Applied Sciences, UniversitiTeknologi MARA, 40450 Shah Alam, Selangor, Malaysia. Email ID: dzuls990@gmail.com Tel: +603-5543 8433

**Keywords:** Ethno-medicine, Herbs, *In-vivo* fertilization, Ovarian cycle.

## **INTRODUCTIONS:**

Plants and their products have been used for the regulation of fertility since ancient times <sup>[1]</sup>. It is well established that plants action on ovarian-uterine axis are able to provoke changes in the pattern of reproductive cycle. Plants with estrogenic properties can directly influence action by peripheral modulation of Luteinizing Hormone (LH) and Follicle Stimulating Hormone

(FSH), decreasing the secretion of these hormones and blocking ovulation <sup>[2]</sup>. In addition, previous study has shown that women who consumed high amounts of isoflavones (estrogenic property) from soy had a decrease in serum estrogen <sup>[3]</sup>. On the other hand, plants with anti-estrogenic activities intercept the process of ovum and endometrium development <sup>[4-5]</sup>.

Cosmos caudatus is a potential medicinal plant belong to the family of Asteraceae and are found in tropical areas including Malaysia, Thailand, Central and South America. This plant has been gaining attention in many countries because of the medicinal and nutritional benefits provided by their potential natural antioxidants. In Malaysia, C. caudatus is often consumed raw as a salad due to its unique, appealing smell and aroma, which add diversity and taste to food <sup>[6]</sup>. Meanwhile, Piper sarmentosum belong to the family of Piperaceae is locally known as kaduk in Malaysia and menkadak in Indonesia<sup>[7]</sup>. Traditionally, in Malaysia it was used as a remedy to relieve toothache, cough, flu and dysentery <sup>[8]</sup>. In Thailand, P. sarmentosum was used traditionally to relieve asthma, refreshing the throat and enhancing appetite<sup>[9]</sup>.

The effects of *C. caudatus* and *P. sarmentosum* leaves aqueous extracts on male mice sperm quality and fertility has been documented <sup>[10]</sup>. However, there is a lack of data concerning the effects of both plants on female reproductive system. Here, we report the effects of *C. caudatus* and *P. sarmentosum* leaves aqueous extracts on female mice fertility, specifically on estrous cycle and capability to produce offspring. In addition, we also report the effects of aqueous extract of both plants on animal body growth and physical signs of toxicity.

## **MATERIALS AND METHODS:**

### Plants material and aqueous extract preparation:

Leaves of *C. caudatus* were purchased from a local market in Shah Alam, Selangor and leaves of wild *P. sarmentosum* were collected from a rural area of Kota Bharu, Kelantan. Both plants were authenticated by qualified taxonomist (Herbarium of the National University of Malaysia). A voucher specimens, UKMB40335-Raja and UKMB40316-Kaduk were deposited in Biology Laboratory, UniversitiTeknologi MARA, Shah Alam, Selangor. The leaves of both plants were washed under running water, air dried under low intensity of sunlight for 48 h and later in hot air oven for one week. Dried leaves were crushed for size reduction

to a coarse powder using an electrical blender (Pensonic PB-3203L, Malaysia). Aqueous extract was prepared as previously described <sup>[11]</sup> with slight modification. Briefly, dried plant materials were soaked in distilled water at a ratio of 1:10 w/v for three days. Then, the mixture was filtered with filter paper (Whatman No. 1, Sigma-Aldrich, Germany) and evaporated using rotary evaporator (Buchi Rotavapor R-210, Germany). The harvested dried extract was kept at 4 °C for later use.

# Animals and treatments:

Animals were purchased from commercial supplier (Chenur Supplier Sdn Bhd, Malaysia) and maintained under supervision of Research Committee of the Ethical Use of Animals in Research, UniversitiTeknologi MARA (UiTM Care 111/2015). The mice were approximately 6 to 8 weeks olds and ranged from 27 to 30 g in weight. Eighteen female mice were randomly distributed into three groups with six females each. Group 1 served as a control and orally gavaged with 2 ml/kg bwt of distilled water. Group 2 was orally gavaged with 500 mg/kg bwt of C. caudatus aqueous extract and group 3 was orally gavaged with 500 mg/kg of body weight (BW) of P. sarmentosum aqueous extract. All animals also received rodent pellets (Golden Coin, Malaysia) and water ad libitum as a maintenance diet. The treatment was conducted on a daily basis and lasted for 28 days. Bodyweight was recorded on day 1, 7, 14, 21 and 28 in order to monitor growth performance. Physical signs of illness and toxicity (piloerection, lethargy, hair loss, dark urine, diarrhoea, paleness of skin, locomotor activity and mortality) were monitored, twice daily at 7 am and 5 pm as previously described [12-13].

# The effects of *C. caudatus* and *P. sarmentosum* aqueous extracts on mice estrous cyclicity:

Prior to the test, vaginal smear was monitored daily for three cycles to select females with regular estrous cycle. Those with regular estrous cycle were randomly divided into three groups and treated as previously described (in section Animals and Treatments). Vaginal cytology methods as previously described by Byers and coworkers<sup>[14]</sup> was utilised to determine the stage of estrous cycle in female mouse. A wet cotton tipped swab was inserted into the vagina of the restrained mouse. The swab was gently turned and rolled against the vaginal wall. Then the cells were transferred to glass slide and air dried. Later, the slide was fixed with absolute methanol (Kollin Chemicals, USA) for five second and

#### J Pharm Adv Res, 2018; 1(7): 346-351.

air dried again before flooded with Giemsa stain for 30 min. After 30 min, the slide was gently rinsed under running water, fixed with DPX Mountant (Sigma-Aldrich, Germany) and observed under light microscope (Olympus CX22, Japan). The phase of estrous cycle was determined based on the presence or absence of leukocytes, cornified epithelial and nucleated epithelial cells <sup>[15-16]</sup>. Smears containing nucleated and cornified epithelial cells were defined as representing the proestrus and estrus phases, respectively. Smear containing cornified epithelial cells and leukocytes was defined as representing the metestrus phase. Meanwhile smear containing primarily leukocytes was defined as representing the diestrus phase. The estrous cycle was observed for seven cycles.

# The effects of *C. caudatus* and *P. sarmentosum* aqueous extracts on *in-vivo* fertilization in female mice:

After 28 days with the respective treatments as previously described, each female was caged with a proven fertile male to allow copulation. The day on which sperm was detected in vaginal smear was considered as a day one of gestation. After successful copulation, the male was removed from the cage and the female was fed with maintenance diets only. On day 15 of gestation, female was killed by cervical dislocation. Uterus was collected and the numbers of implantation sites were counted as previously described by Amano and co-workers<sup>[16]</sup>.

# Statistical analysis:

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) Version 11 for Windows. Values are given as mean  $\pm$  standard error of mean, if not otherwise indicated. Differences were regarded as significant when the p<0.05.

# **RESULTS AND DISCUSSION:**

# Bodyweight and physical signs of illness:

Oral feeding of the aqueous extracts of *C. caudatus* and *P. sarmentosum* for 28 days had no negative effect on the bodyweights of experimental mice compared to the control group (Fig 1). After 28 days of experimental period, bodyweight of mice was increased by 10.9 % in the control group, 12.2 % in the group treated *C. caudatus* aqueous extract with 500 mg/kg BW and by 8.8 % in the group treated with *P. sarmentosum* aqueous extract with 500 mg/kg bwt. This data indicates that the

general body growth of mice treated with *C. caudatus* and *P. sarmentosum* were normal.

There is an increasing body of evidence that underweight or overweight can negatively affect reproductive health especially in mammals <sup>[17]</sup>. According to Jokela and colleagues <sup>[18]</sup>, lower fertility is associated with underweight as well as obesity. Previous authors documented that C. caudatus might be useful in the prevention and treatment of obesity by limiting dietary fat digestion, absorption and accumulation in adipose tissue <sup>[19]</sup>. Quercetin, rutin and chlorogenic acid in C. caudatus are known to take significant part in regulation of body weight <sup>[19-22]</sup>. Meanwhile, in folk medicine, P. sarmentosum are said to be able to enhance appetite <sup>[23]</sup>. On the other hand, Ugusman, et al. <sup>[24]</sup> reported that *P. sarmentosum* is rich with rutin, which would be helpful in body growth and bodyweight management.

Table 1. Physical signs of illnes among the mice treated with distilled water (2 ml/kg BW), *C. caudatus* (CC) and *P. sarmentosum* (PS) aqueous extract (500 mg/kg BW).

Physical sign	Control (dH <sub>2</sub> O)	CC	PS
Piloerection	-	-	-
Lethargy	-	-	-
Hair loss	-	-	-
Dark urine	-	-	-
Diarrhea	-	-	-
Paleness of skin	-	-	-
Locomotor activity	А	А	А
Mortality	-	-	-

Note: + (presence of sign of illness), - (absence of sign of illness). A - Active

In addition, daily administration of *C. caudatus* and *P. sarmentosum* aqueous extracts were well tolerated and no visible physical signs of illness were observed (Table 1). No significant variation in behaviours, health condition and zero mortality were basic evidences indicating the non-toxic nature of both extracts. Previous authors demonstrated that no deaths or signs of toxicity in the rats that received up to 5000 mg/kg *C. caudatus* ethanolic extract <sup>[25]</sup>. Meanwhile, Zainudin and coworkers <sup>[26]</sup> reported that Sprague Dawley rats received *P. sarmentosum* aqueous extract up to 2000 mg/kg BW did not show any signs of toxicity.

### Estrous cycle and *in-vivo* fertilization:

The order of appearance of various phases and the duration of the estrous cycle did not significantly different in mice treated with 500 mg/kg BW of *C. caudatus* aqueous extract compared to control (Table 2). However, *P. sarmentosum* aqueous extract at a dose of 500 mg/kg BW prolonged the length of the estrous cycle with significant decreased (p<0.05) in the duration of estrus phase and significant increased (p<0.05) in the duration of diestrus phase. These findings associated with the signs of fertility decrement in females treated with 500 mg/kg BW *P. sarmentosum* aqueous extract, as demonstrated in Table 3. Estrus improves fertility and decreases pregnancy losses <sup>[27]</sup>. Any alteration to estrous cycle especially estrus phase will affect female fertility.

Consumption of 500 mg/kg BW of P. sarmentosum aqueous extract for 28 days decreased the percentage of pregnant female compared to the control and mice treated with 500 mg/kg BW of C. caudatus (Table 3). The percentage of pregnancy was decreased by 17 % in group treated with 500 mg/kg BW of P. sarmentosum. However, the difference was not statistically significant (p>0.05). Interestingly, average number of implantation sites per mating was decreased significantly (p<0.05) in mice treated with 500 mg/kg BW of P. sarmentosum compared to the control and mice treated with 500 mg/kg BW of C. caudatus. Meanwhile the number of implantation sites was increased in mice treated with 500 mg/kg BW of C. caudatus compared to the control, but the difference was not statistically significant (p>0.05).

Table 2. Estrous phase of mice after 28 days of treatment with distilled water (control, 2 ml/kg BW), *C. caudatus* (CC) and *P. sarmentosum* (*PS*) aqueous extract (500 mg/kg BW).

Estrous	Control	CC	PS
phase	( <b>dH</b> <sub>2</sub> <b>O</b> )		
Proestrus	$0.88 \pm 0.04^{a}$	$0.87 \pm 0.07^{a}$	$0.86 \pm 0.09^{a}$
Estrus	0.90±0.12 <sup>a</sup>	$0.95 \pm 0.05^{a}$	$0.69 \pm 0.04^{b}$
Metestrus	0.83±0.09 <sup>a</sup>	$0.81 \pm 0.04^{a}$	$0.81{\pm}0.07^{a}$
Diestrus	$1.38 \pm 0.07^{a}$	$1.36 \pm 0.06^{a}$	$1.64 \pm 0.09^{b}$

Values are presented as mean $\pm$ standard error of mean (n=6). Values with different superscript letters within the same row shows significant difference at p<0.05 (n=6).

Anti-fertility effect of *Piperaceae* family has been well established. Sharma and co-workers <sup>[28]</sup> documented that female mice treated with *Piper betle* demonstrated a

reduction in plasma estrogen levels and number of litters. Previous author reported that *Piper nigram* significantly decreased the number of ovarian follicles and altered plasma levels of estrogen and progesterone <sup>[29]</sup>. The pituitary-gonadal axis is important for the maintenance of the reproductive system; hence, any distortion to this can be deleterious <sup>[30]</sup>. In the current study, no attempt was made to investigate hormonal changes and to ascertain the mechanism of observed anti-fertility activity. The exact cause of the anti-fertility effect in mice treated with *P. sarmentosum* should be explored in the future experiments.

Table 3. The percentage of pregnancy and the number of implantation sites in mice treated with distilled water (control, 2 ml/kg BW), *C. caudatus* (CC) and *P. sarmentosum* (*PS*) aqueous extract (500 mg/kg BW).

Para- meters	Control (dH <sub>2</sub> O)	CC	PS
Pregnancy (%)	100 (6/6) <sup>a</sup>	100 (6/6) <sup>a</sup>	83 (5/6) <sup>a</sup>
Implantation sites (n)	7.8±0.7 <sup>a</sup>	$8.5 \pm 0.5^{a}$	4.5±1.2 <sup>b</sup>

Values are presented as mean $\pm$ standard error of mean (n=6). Values with different superscript letters within the same row shows significant difference at p<0.05 (n=6).

On the other hand, *C. caudatus* which exerts high antioxidant properties <sup>[31]</sup>, may has a positive effect on female reproductive system. In female, several animal and *in-vitro* studies suggest that oxidative stress may affect female fertility <sup>[32]</sup>. Oxidative stress in female reproductive system occurs when the generation of reactive oxygen species (ROS) and other radical species exceeds the scavenging capacity by antioxidants due to excessive production of ROS and/or inadequate intake of antioxidants. Therefore, it is rational to assume that consumption of *C. caudatus* protects female mice in the current experiment from ROS. However, further investigation is needed to reveal the mechanism of action by *C. Caudatus* in maintaining female fertility.

# **CONCLUSION:**

In conclusion, there are no negative effects on female mice fertility imposed by *C. caudatus* aqueous extract. In contrast, *P. sarmentosum* aqueous extract exhibited anti-fertility activity.

# **ACKNOWLEDGEMENTS:**

All authors are greatly indebted to the Faculty of Applied Sciences and the Institute of Research



Fig 1. Body weight data of mice treated with distilled water (control, 2 ml/kg BW), *C. caudatus* and *P. sarmentosum* aqueous extract (500 mg/kg BW). Values are presented as mean  $\pm$  standard error of mean (n=6).

Management and Innovation (IRMI), UniversitiTeknologi MARA for providing all research facilities and administrative support to accomplish this research.

# **REFERENCES:**

- Rao MV, Alice KM. Contraceptive effects of *Phyllanthusamarus* in female mice. Phytother Res, 2001; 15: 265-267.
- Brinker F. Inhibition of endocrine function by botanical agents, antigonadotropic activity. Br J Phytother, 1997; 4: 123-145.
- Nagata C, Takatsuka N, Inaba S, Kawakami N, Shimizu H. Effect of soymilk consumption on serum estrogen concentration in pre-menopausal Japanese women. J Natl Cancer Inst, 1998; 90: 1830-1835.
- Shibeshi W, Makonnen E, Zerihun L, Debella A. Effect of *AchyranthesasperaL*. on fetal abortion, uterine and pituitary weights, serum lipids and hormones. Afr Health Sci, 2006; 6: 108-112.
- Junaimuang T, Luangpirom A, Somsapt P. Antifertility properties of *Cissampelospareira* Linn. leaf gel in male and female mice. Intl J Phytomedicine, 2015; 7: 112-118.
- Mediani A, Abas F, Khatib A, Tan CP. *Cosmos caudatus* as a potential source of polyphenolic compounds: Optimisation of oven drying conditions and characterisation of its functional properties. Molecules, 2013; 18: 10452-10464.
- 7. Atiax E, Ahmad F, Sirat HM, Arbain D. Antibacterial activity and cytotoxicity screening of

Sumatran Kaduk (*Piper sarmentosum* Roxb.). Iranian J Pharm Ther, 2011; 10: 1-5.

- Hussain K, Ismail Z, Sadikun A and Ibrahim P. Analysis of proteins, polysaccharides, glycosaponins contents of *Piper sarmentosum* Roxb., and anti-TB evaluation for bio-enhancing/interaction effects of leaf extracts with Isoniazid (INH). Nat Prod Radiance, 2008; 7: 402-408.
- Ridtitid W, Ruangsang P, Reanmongkol W, Wongnawa M. Studies of the anti-inflammatory and antipyretic activities of the methanolic extract of *Piper sarmentosum*Roxb leaves in rats. Songklanakarin J Sci Tech, 2007; 29: 1519-1526.
- Daud D, Azahar A, Zainal-Abidin SSF, Tawang A. The effects of *Cosmos caudatus* and *Piper sarmentosum* aqueous extracts on male mice fertility. Intl J Pharm Pharm Sci, 2015; 7: 296-298.
- 11. Alo MN, Anyim C, Igwe JC, ElomM, Uchenna DS. Antibacterial activity of water, ethanol and methanol extracts of *Ocimum gratissimum*, *Vernonia amygdalina* and *Aframomum melegueta*. Adv Appl Sci Res, 2012; 3: 844-848.
- Basir R, Chan KL, Yam MF, Abdullah WO, Moklas MAM, Rahim ASA, Ismail IS, *et al.* Antimalarial activity of selected Malaysian medicinal plants. Phytopharmacol, 2012; 3: 82-92.
- 13. Goncalves ES, Silva JR, Gomes CL, Nery MBL, Navarro DMAF, Santos GKN, *et al.* Effects of the oral treatment with *Copaifera multijuga* oil on reproductive performance of male Wistar rats. Rev Bras Farmacogn, 2014; 24: 355-362.
- 14. Byers SL, Wiles MV, Dunn SL, Taft RA. Mouse estrous cycle identification tool and images. PLoS ONE, 2012; 7: e35538.
- Felicio LS, Nelson JF, Finch CE. Longitudinal studies of estrouscyclicity in aging C57BL/6J mice: II. Cessation of cyclicity and the duration of persistant vaginal cornification. Bio Reprod, 1984; 31: 446-453.
- 16. Amano T, Anzai M, Matsumoto K. The clock mutation reduces reproductive performance of mice by affecting the implantation capacity: Maternal clock mutation is not the only factor affecting implantation. Theriogenology, 2016; 86: 1670-1684.
- 17. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility

treatments: A review. Hum Reprod Update, 2007; 13: 209-223.

- Jokela M, Elovainio M, Kivimaki M. Lower fertility associated with obesity and underweight: the US National Longitudinal Survey of Youth. Am J Clin Nutr, 2008; 88: 886-893.
- 19. Rahman HA, Sahib NG, Saari N, Abas F, Ismail A, Mumtaz MW, Hamid AA. Anti-obesity effect of ethanolic extract from *Cosmos caudatus* Kunth leaf in lean rats fed a high fat diet. BMC Complement Altern Med, 2017; 1-17.
- 20. Seo MJ, Lee YJ, Hwang JH, Kim KJ, Lee BY. The inhibitory effects of quercetin on obesity and obesity-induced inflammation by regulation of MAPK signalling. J Nutr Biochem, 2015; 26: 1308-1316.
- 21. Hsu CL, Wu CH, Huang SL, Yen GC. Phenolic compounds rutin and o-coumaric acid ameliorate obesity induced by high-fat diet in rats. J Agric Food Chem, 2009; 57: 425-431.
- 22. Meng S, Cao J, Feng Q, Peng J, Hu Y. Roles of chlorogenic acid on regulating glucose and lipids metabolism: A review. Evid Based Complement Alternat Med, 2013; 1-11.
- 23. A. Apisariyakul. Investigation of fractions isolated from Thai medicinal plants affecting isolated rat ileum. Proceedings of the 10<sup>th</sup> Conference of Science, and Technology of Thailand, pp. 450-451, 1984.
- 24. Ugusman A, Zakaria Z, Hui CK, Nordin NAMM, Mahdy ZA. Flavonoids of *Piper sarmentosum* and its cyto-protective effects against oxidative stress. EXCLI J, 2012; 11: 705-714.
- 25. Amna OF, Nooraain H, Noriham A, Azizah AH, Husna RN. Acute and oral subacute toxicity study of ethanolic extract of *Cosmos caudatus* leaf in Sprague Dawley rats. Int J Biosci Biochem Bioinforma, 2013; 3: 301-305.
- 26. Zainudin MM, Zakaria Z, Nordin NAMM, Othman F. Does oral ingestion of *Piper sarmentosum* cause toxicity in experimental animals? Evid Based Complement Alternat Med, 2013; 1-9.
- 27. Pereira MH, Wiltbank MC, Vasconcelos JL. Expression of estrus improves fertility and decreases pregnancy losses in lactating dairy cows that receive artificial insemination or embryo transfer. J Dairy Sci, 2016; 99: 2237-2247.

- 28. Sharma JD, Sharma L, Yadav P. Antifertility efficacy of *Piper betle* Linn. on female albino rats. Asian J Exp Sci, 2007; 21: 145-150.
- 29. Nirala PK, Dwivedi SC. Antifertility effect of alcoholic *P. nigram* fruit extract on adult female Wistar rat models. Int J New Tech Res, 2015; 1: 73-75.
- 30. Amah CI, Yama OE, Noronha CC. Infecund evaluation of cycling female Sprague Dawley rats: an aftermath treatment with *Momordica charantia* seed extract. Middle East Fertil Soc J, 2012; 17: 37-41.
- 31. Mustafa RA, Abdul Hamid A, Mohamed S, Bakar FA. Total phenolic compounds, flavonoids and radical scavenging activity of 21 selected tropical plants. J Food Sci, 2010; 75: C28-C35.
- 32. Ruder EH, Hartman TJ, Goldman MB. Impact of oxidative stress on female fertility. Curr Opin Obstet Gynecol, 2009; 21: 219-222.

# **Conflict of Interest:** None **Source of Funding:** Nil

**Paper Citation:** Daud D, Azahar A, Abidin SSFZ, Tawang A, Ross EER, Hashim N. Comparative effects of *Cosmos caudatus* and *Piper sarmentosum* aqueous extracts on estrous cycle and fertility in female mice. J Pharm Adv Res, 2018; 1(7): 346-351.