Original Article

Pueraria mirifica can modulate the ovarian activity of crossbred-Thai native does

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Abstract

To evaluate the effect of *P. mirifica* supplementation on ovarian activity in crossbred Thai native does, a study was carried out for three consecutive estrus cycle periods: 1) D0-D21(pre-treatment), 2) D21-D42 (treatment) and 3) D42-D63 (post-treatment); D0, D21 and D42 were the days of expected estrus. *P. mirifica* was orally fed at 1000 mg/kg BW/d for 21 days in supplemented groups. Twenty-one does were equally divided into three groups: 1) CON – control, no supplementation and 2) supplemented groups included 2.1) FEC – start feeding at early-cycle (D21-D42), and 2.2) FMC – start feeding at mid-cycle (D32-D53). Estrus behavior was determined by observation, ovarian activity was monitored by transrectal ultrasonography and fecal progesterone concentration (FPC) was analyzed by EIA. The results showed that CON had lower (P<0.05) receptive behavior and shorter (P<0.05) estrous duration than those of FEC and FMC at treatment and post-treatment periods. FEC had a lesser number of developed follicles (P<0.05) and a greater number of undeveloped follicles than others at treatment period. FMC had a higher (P<0.05) number of undeveloped follicles at post-treatment period. Moreover, FEC and FMC had a higher (P<0.05) number of anovulatory follicles than that of CON, while only FMC had a lower (P<0.05) number of CLs along with a greater (P<0.05) number of early CL regression at the post-treatment period. FPC of FEC and FMC was lower than that of CON during administration. In conclusion, the *P. mirifica* dosage used in this study enhanced estrus behavior but suppressed ovarian activity in the consequent cycle when fed either at early or mid-cycle. Feeding over ovulation might have more adverse effects concerning CL function.

Keywords: *P. mirifica*, phytoestrogens, ovary, estrus cycle, does

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Introduction

Pueraria mirifica (*P. mirifica*) is an indigenous Thai herb in the family *Leguminosae,* subfamily *Papilinoideae* (Kashemsanta *et al*., 1952). The useful part of *P. mirifica* comes from tuberous roots which play an important role in the accumulation of phytoestrogen substances including chromene (miroestrol, deoxymiroestrol) isoflavones (daidzein, genistein), isoflavone glycoside (daidzin, genistin, mirificin, puerarin) and coumestan (coumestrol, mirificoumestan) (Cherdshewasart *et al*., 2008). Currently, due to the mechanism of action being similar to estrogen, *P. mirifica* is being used in various forms of powder as an animal feed additive or cream as a rejuvenating drug and pills for estrogen replacement in humans (Muangman and Cherdshewasart, 2001).

Isoflavone genistein has more affinity on estrogen receptor β than estrogen receptor α (Nynca *et al*., 2013), which is directly related to the reproductive system. Using *P. mirifica* focused on the reproductive system has found that the effect depends on the level and duration of consumption. Continuous administration of *P. mirifica* in high dosage (1000 mg/kg BW/day) can affect reproductive organs, gonads and gonadotropin, e.g., increase uterus weight and vagina cornification, prolong estrus, reduce peripheral FSH and LH, increase high atretic follicles and inhibit ovulation as demonstrated in rats (Malaivijitnond *et al*., 2004; Trisomboon *et al*., 2005). However, these effects have not been observed when employed at a low dosage (≤ 100 mg/kg BW/day).

Phytoestrogens can both promote and interfere with reproductive processes as reviewed by Sirotkin and Harrath (2014). Thus, it is of interest to study the effect of *P. mirifica* on cyclic farm animals for reproductive manipulation, as previously mentioned by Adams (1995) as 'effects of low concentrations of phytoestrogens on reproductive function in ruminants are likely to receive increasing attention'. In addition, some phytoestrogens could be involved in the improvement of reproductive performance in goats (Keskin *et al*., 2004; Al-Hamedawi *et al*., 2015). To our knowledge, there has been no report concerning the effect of *P. mirifica* in goats. Therefore, the scope of this study was to evaluate the effect of *P. mirifica* on estrus behavior, ovarian activity and the progesterone profile in crossbred Thai native does.

Materials and Methods

Ethics approval: This study was conducted at the small ruminant research center, Kasetsart University, Nakhon Pathom, Thailand. Animal usage was approved by the Animal Usage and Ethics Committee, Kasetsart University (ACKU61-VET-015)

Experimental design: The study was carried out for three consecutive estrus cycle periods: 1) D0-D21(pre-treatment), 2) D21-D42 (treatment) and 3) D42-D63 (post-treatment); D0, D21 and D42 were the days of expected estrus, as shown in Figure 1. *P. mirifica* was used in the form of a crude powder containing 25.10±2.43 µg/g miroestrol and 9.06±0.71 µg/g deoxymiroestrol, which was obtained from the Animal Science Research Center, Kasetsart University, Kamphaeng Saen Campus, Nakhon Pathom, Thailand. *P. mirifica* crude powder was suspended in distilled water (1000 mg/ml) and orally fed at 1000 mg/kg BW/d (40-60 ml/doe) for 21 days in supplemented groups. Twenty-one does were equally divided into three groups: 1) CON – control, no supplementation, and 2) supplemented groups included 2.1) FEC – starting feeding at early-cycle (D21-D42), and 2.2) FMC – starting feeding at mid-cycle (D32-D53).

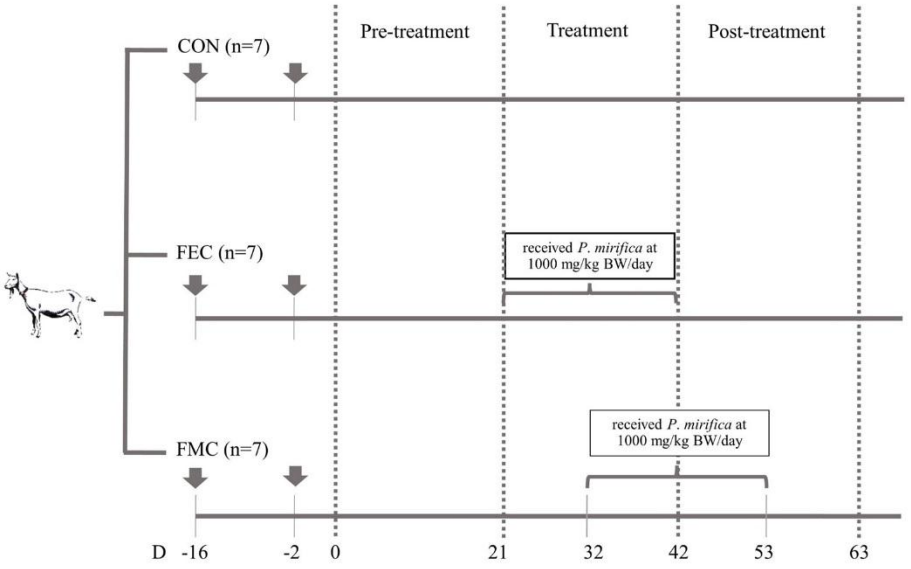

Figure 1

Estrus synchronization and behavioral determination: All does had synchronized estrus by two injections of $PGF_{2\alpha}$ (250 µg of Cloprostenol, Estrumate®, Intervet) 14 days apart, starting on day -16. Estrus behavior was determined by observation, which could be classified as proceptive and receptive behavior (Okada *et al*., 1996). Proceptivity phase: the does expressed a clear mucous coupled with redness and swelling of the vulva, tail switching, frequent urination and constant vocalization. Receptivity phase: the does expressed immobilization, mounting and standing heat.

Transrectal ultrasonography: Ovarian structure was examined by transrectal ultrasonography two days at a time following Medan *et al*. (2004). The position, size and number of individual follicles (≥ 3 mm in diameter), as well as corpus luteum (CL), were recorded.

The parameters included: a) DEC: Estrous cycle duration (number of days between one estrus to the next); b) DLP: duration of luteal phase (mean number of the days that CL remained); c) DFP: duration of follicular phase (mean number of days from CL regression to ovulation); d) NFW: number of follicular waves (mean number of follicular waves per cycle); e) NDF: number of developed follicles (mean number of follicles with normal growth and regression); f) NUF: number of undeveloped follicles (mean number of follicles that with no more than 3.5 mm in diameter); g) NFC: total number of follicles per cycle (mean number of follicles comprised of developed and undeveloped follicles over the entire estrus cycle); h) NFO: number of follicles in ovulatory wave; i) NOF: number of ovulatory follicles > 5mm; j) OFS: ovulatory follicular sizes (mm); k) TCL: total CLs/doe (mean number of CL per cycle per doe); l) NPF: number of persistent follicle/doe: (mean number of persistent follicles per doe with characteristics as shown in Figure 2 (B)); m) ECL: number of early CL regression/doe (mean number of CLs that had 3-7 days of age and suddenly regressed accompanied with undetectable progesterone since Day 7 of the cycle); and n) OVR: ovulation rate (ratio of total CL in the next divided by number of ovulatory follicles > 5mm)

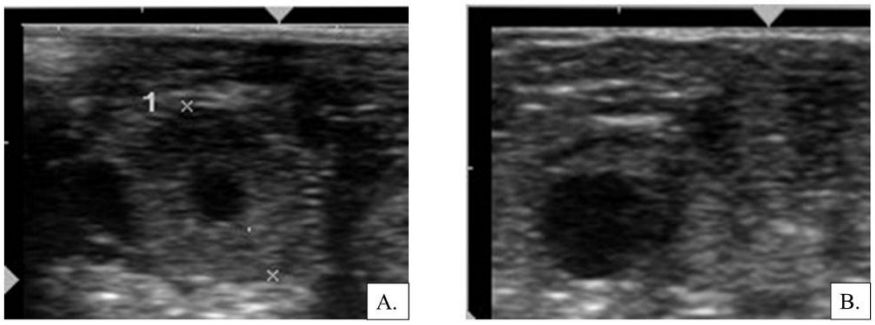

Figure 2

Fecal collection, steroid extraction and metabolite analysis: Fecal samples were collected before performing transrectal ultrasonography (every 2 days) and kept at -20°C until extraction. Fecal extraction was done by a boiling method (Brown *et al*., 2005). Briefly, wet samples were dried in a conventional oven at 60 ° C for 24 h, 0.1 g (±0.01) of dry powdered feces were extracted twice in 90% ethanol in distilled water by boiling in a water bath (96 ° C) for 20 minutes. Samples were centrifuged at 1500 x g for 20 mins and the supernatants were air-dried in a 96 ° C water bath. Dried extracts were reconstituted in methanol and stored at -20 ° C. Progesterone (P4) concentrations were determined by a double-antibody enzyme EIA with a monoclonal goat anti-mouse progesterone antibody (Brown *et al*., 2005). Assay sensitivity (based on 90% binding) was 0.14 ng/ml (0.014 ng/g). Samples were analyzed in duplicate; intra-and inter-assay CVs were < 10% and < 15%, respectively. Fecal P4 concentrations were expressed as ng/g of dried feces.

Statistical analysis: Results were expressed as mean ±SE, which was analyzed using a one-way analysis of variance. LSD was used to determine significant differences between groups. Chi-square was used to compare the percentage of each estrus behavior expression and ovulation rate. All parameters were performed using SPSS 19 statistical software (SPSS, Inc., Chicago IL, USA) at a significance level of $P<0.05$ and tendency was considered as a P-value=0.05-0.15.

Results

Effect of P. mirifica on behavior and duration of estrus: The effect of *P. mirifica* on estrus behavior and the ovarian cycle is shown in Table 1. FEC and FMC had a longer (P=0.048 and P=0.029) estrus duration than that of CON during the treatment and post-treatment periods, respectively. Both supplemented groups had significantly higher (P=0.030) receptivity than CON in the post-treatment period. However, FMC tended to have a shorter (P=0.10) DLP than that of CON and FEC during the post-treatment period.

Effect of P. mirifica on follicular dynamic: The effect of *P. mirifica* on follicular dynamics is shown in Table 2. The number of follicular waves was similar among groups in all experimental periods. However, FEC had a significantly lower (P=0.027) NDF and significantly higher (P=0.012) NUF than those of CON and FMC during the treatment period. In addition, CON tended to have a higher (P=0.15) NDF during the post-treatment period. Moreover, FMC had a significantly higher (P=0.011) NUF than those of CON and FEC during the post-treatment period.

Effect of P. mirifica on the number of ovulatory follicles and CLs: The effect of *P. mirifica* on ovulatory follicles and CLs is shown in Table 3. The number of follicles in the ovulatory wave, number of follicles > 5 mm in the ovulatory wave and ovulatory follicular sizes showed no significant difference among groups in all periods (P>0.05). The ovulation rate of CON tended to be higher (P=0.125) than that of FMC at treatment periods. Moreover, FMC tended to have a lower (P=0.13) number of CLs and tended to have more ECL (P=0.11) than CON at the post-treatment period. There was also significantly higher (P=0.04) NPF of FEC and FMC than that of CON at the post-treatment period.

Table 1 Effect of *P. mirifica* on estrus behavior and ovarian cycle in the does

	Pre-treatment (Day 0-21)			Treatment (Day 21-42)			Post-treatment (Day 42-63)		
	CON	FEC	FMC	CON	FEC	FMC	CON	FEC	FMC
Estrous behavior									
- Proceptivity (%)	2/7 (28.6)	1/7 (14.3)	3/7 (42.9)	1/7 (14.3)	0/7 (0)	0/7 (0)	3/7 (42.9)	0/7 (0)	0/7 (0)
- Receptivity (%)	5/7 (81.4)	6/7 (85.7)	4/7 (57.1)	6/7 (85.7)	7/7 (100)	7/7 (100)	4/7 (57.1)	7/7 (100)	7/7 (100)
Estrous duration (h)	33.6±4.4	42.8±2.4	36.0±3.7	40.8±7.2^{b}	68.5±5.6^{a}	65.1±8.6^{a}	24.0±0.0^{b}	48.0±7.4^{a}	37.7±7.4^{ab}
DLP (days)	15.5±2.6	14.5±0.7	16.8±0.4	14.8±1.0	16.2±0.5	14.5±1.0	16.0±0.0^{a}	15.3±0.8^{a}	12.8±1.3^{b}
DFP (days)	6.0±1.4	6.5±0.7	7.6±2.2	6.8±0.4	6.0±0.7	6.8±0.9	6.5±0.5	6.3±0.3	7.6±1.1
DEC (days)	21.2±1.2	21.1±0.7	23.1±1.6	21.6±0.9	22.2±0.6	21.4±0.8	21.6±0.9	21.1±0.7	20.5±0.3

^{a,b} Showed significant difference between treatments. CON: control, no supplementation, and supplemented groups FEC - start feeding at early-cycle, and FMC: start feeding at mid-cycle. DLP: duration of luteal phase; DFP: duration of follicular phase; DEC: estrous cycle duration.

Table 2 Effect of *P.mirifica* on characteristics of follicles in does

	Pre-treatment (Day 0-21)			Treatment (Day 21-42)			Post-treatment (Day 42-63)		
	CON	FEC	FMC	CON	FEC	FMC	CON	FEC	FMC
NFW	3.40±0.24	3.43±0.20	3.14±0.14	3.60±0.24	3.43±0.20	3.71±0.18	3.60±0.40	3.71±0.18	3.43±0.20
NDF	10.00±0.94	11.00±1.36	10.29±0.91	11.60±0.74^{a}	8.86±0.50^{b}	12.57±1.27^{a}	11.60±1.47	9.86±1.03	8.43±0.71
NUF	0.20±0.20	0.00±0.00	0.14±0.14	1.00±0.62^{b}	7.00±1.52^{a}	3.29±1.07^{b}	0.60±0.40^{b}	1.71±4.00^{b}	4.00±0.61^{a}
NFC	10.20±0.97	11.00±1.36	10.43±0.81	12.60±0.92	15.86±1.93	15.86±1.89	12.20±1.59	11.57±0.89	12.43±0.99

^{a,b} Showed significant difference between treatments.
CON: control, no supplementation, and supplemented groups FEC - start feeding at early-cycle, and FMC: start feeding at mid-cycle. NFW: number of follicular wave; NDF: number of developed follicles; NUF: number of undeveloped follicles; NFC: total number of follicles per cycle

Table 3 Effect of *P.mirifica* on ovarian activity in does.

	Pre-treatment (Day 0-21)			Treatment (Day 21-42)			Post-treatment (Day 42-63)		
	CON	FEC	FMC	CON	FEC	FMC	CON	FEC	FMC
NFO	4.20±0.67	5.00±0.81	4.57±0.43	3.40±0.75	3.43±0.48	4.43±0.72	4.40±0.40	4.43±0.53	3.14±0.40
NOF	2.80±0.49	3.00±0.38	2.71±0.42	2.20±0.37	3.00±0.31	1.85±0.40	2.80±0.25	2.14±0.56	2.29±0.28
OFS	7.09±0.35	6.58±0.31	6.98±0.46	6.16±0.22	5.73±0.45	6.54±0.44	6.01±0.21	6.11±0.22	6.13±0.26
TCL	1.00±0.48	1.14±0.34	1.57±0.48	2.20±0.20	1.86±0.14	1.86±0.14	1.80±0.49^{a}	1.43±0.37^{ab}	1.00±0.31^{b}
NPF	0	0.14±0.14	0.43±0.30	0	0	0.29±0.14	0^{b}	0.86±0.34^{a}	0.86±0.14^{a}
ECL	0	0	0.29±0.29	0	0.14±0.14	0.29±0.18	0^{b}	0.14±0.14^{ab}	0.71±0.42^{a}
OVR	78.60	61.9	56.5	69.2	47.6	33.3	50	68.4	38.1

^{a,b} Show significant difference between treatments. CON: control, no supplementation, and supplemented groups FEC - start feeding at early-cycle, and FMC: start feeding at mid-cycle. NFO: number of follicles in ovulatory wave, NOF: number of ovulatory follicles > 5mm, OFS: ovulatory follicular sizes (mm), TCL: total CLs/doe, NPF: number of persistent follicle/doe, ECL: number of early CL regression/doe, OVR: ovulation rate (%)

Effect of P. mirifica on CLs diameter and fecal P4 concentration: Mean CLs diameters are shown in Figure 3. The initial sizes started on day 2 at 6.65-8 mm, then increased to the largest at 9-12 mm on day 8-10 and gradually reduced to 6-7.5 mm on day 18 until disappearing on day 20. The tendency was to be smaller in CL diameter on Day 54 (P=0.08) and Day 56 (P=0.10) and significantly lower on Day 60 (P=0.01) of FMC than those of CON and FEC, respectively.

Fecal P4 concentrations corresponded with CL size. Nadir stage valued at 500 ng/g feces on Day 2 and started increasing to 8000-9000 ng/g feces on Day 12-14 of the cycle, then the concentration decreased gradually to the baseline level on Day 22. There was a higher fecal P4 concentration in the CON group than that of the FEC group on Day 38 (P=0.038) and this tended to be higher than that of the FMC on Day 58 (P=0.148). In addition, there was a high correlation between two day-delayed fecal P4 concentration and CL diameters in all groups (CON: r=0.644; FEC: r=0.735; FMC: r=0.804, P<0.001).

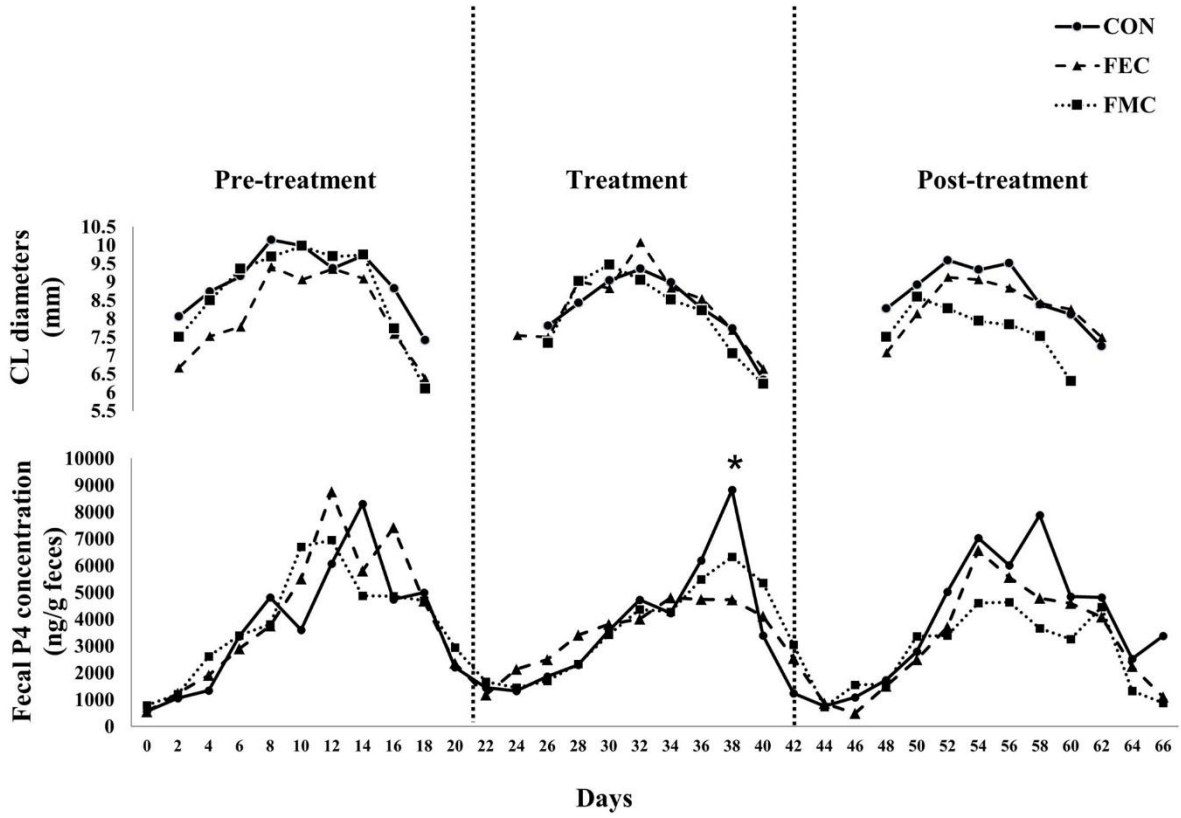

Figure 3

Discussion

The results showed that supplementation of *P. mirifica* at 1000 mg/kg BW for 21 days affected the doe reproductive system. These effects included enhancing estrus behavior during treatment and suppression of ovarian activity in the post-treatment period, either fed at early or mid-cycle of the previous cycle. Mid-cycle feeding had more detrimental effects in terms of CL function.

Doe estrus expression was stronger and longer during treatment and post-treatment periods when fed with *P. mirifica* at either early or mid-cycle. Since *P. mirifica* contained some amounts of miroestrol and coumestrol, which could enhance estrogen receptors (ER), both ERα- and ERβ-mediated transactivation and the mode of action were similar to estradiol-17β (Chindewa *et al*., 2008; Okamura *et al*., 2008). The correlation between estradiol-17β level and visual estrus symptoms during the estrus period was significantly observed in cattle (Lyimo *et al*., 2000; Mondal *et al*., 2006). Although the estradiol-17β level was not measured in this study, it can be assumed that the high receptive behavior during treatment and post-treatment periods in FEC and FMC was due to the influence of *P. mirifica* metabolites via activated ERα at the preoptic area and mediobasal hypothalamus (Blache *et al*., 1991; Fabre-Nys and Gelez, 2007), which is the region that promotes receptive behavior in ewes, rather than of the presence of large follicles. Other phytoestrogens have also given similar results of prolonging estrus duration, e.g., sheep fed with bean sprouts (Hans Ririmasse and Bachruddin, 2015) or rats fed with soybean (Kouki *et al*., 2003).

Unlike the effect of prolonging the menstrual cycle of *P. mirifica* found in monkeys (Trisomboon *et al*., 2004), the duration of estrus cycle in this study was unchanged. In this study, the luteal phase of FMC was shorter than other groups during the post-treatment period, indicating *P. mirifica*'s might have an effect on CL structure. However, it could not change the cycle duration from a normal range.

The total number of follicles per cycle decreased during the post-treatment period when either of the does received *P. mirifica* early or in the mid-estrus cycle. Moreover, supplementation at an early-estrus cycle contributed to the high number of undeveloped follicles along with a low number of developed follicles during the treatment period (Table 2). The development of ovarian follicles is commonly exhibited as a wave-like pattern, which is associated with FSH levels (Medan *et al*., 2005). However, FSH secretion was inhibited by ovarian feedback through the concentration of inhibin A and the synergistic effect between estradiol-17β and progesterone (Medan *et al*., 2005; Scaramuzzi *et al*., 2011). Similar to natural estrogen, metabolites of *P. mirifica* could signal to ERs in the hypothalamus, resulting in a decline of FSH and LH production (Malaivijitnond *et al*., 2004; Wójcik-Gładysz *et al*., 2005; Jaroenporn *et al*., 2007), Therefore, the number of developed and undeveloped follicles can be affected by *P. mirifica* metabolites. The effects were similar to genistein, another phytoestrogen (Tanaka *et al*., 2007; Zin *et al*., 2013; Talsness *et al*., 2015).

Due to the disrupted secretion of LH at the end of the estrus cycle, ovulatory follicles were unable to ovulate (Hettle and Kitts, 1983; Murthy *et al*., 1997; Trisomboon *et al*., 2005; Malaivijitnond, 2012). Consequently, C had a lower number of CLs per doe and a higher number of anovulatory follicles than those of other groups during the post-treatment period (Table 3). These results demonstrated that anovulatory follicles could occur at high rates when the does were continuously receiving *P. mirifica* throughout the ovulation and luteogenesis (FMC group). In other words, if the supplementation had been withdrawn at the end of the estrus cycle (FEC group), the ovulation rate would not be disrupted. The persistent follicles also produced inhibin A, which suppressed the growth of small follicles (Trisomboon *et al*., 2005). As a result, a higher number of anovulatory follicles (Table 3) along with a non-significantly lower number of developed follicles (Table 2) were observed in FMC during the post-treatment period.

Ovulation was inhibited via suppression of the release of gonadotropin, phytoestrogens and their metabolites, which can disturb the structure of CL. Modulation in the ratio of $PGF_{2\alpha}$ and PGE: the luteolytic and luteoprotective agents, respectively, might be involved. $PGF_{2\alpha}$ was significantly stimulated by the metabolites of phytoestrogen in the steroidogenic CL cells. The imbalance of $PGF_{2\alpha}$ and PGE ratio could lead to early CL regression (Woclawek-Potocka *et al*., 2005; Watzková *et al*., 2010). In addition, progesterone secreted from the steroidogenic cell of CL also acts as an anti-luteolytic agent against uterine $PGF_{2\alpha}$ synthesis. Inadequate P4 production coincident with sustained exogenous estrogen supplementation might cause $PGF_{2\alpha}$ synthesis, resulting in luteolysis at early CL formation (Bishop and Stormshak, 2006; Davis *et al*., 2010). For these reasons, continuously receiving *P. mirifica* throughout the ovulation period can result in a high number of early CL regression (Table 3), small CLs and low fecal P4 concentration (Figure 3), and finally, shorten the luteal phase in the post-treatment period (Table 1).

Continuously receiving *P. mirifica* also affected the function of CL, which in this study was observed in a decline of fecal P4 concentration when either supplemented at early or mid-estrus cycle (Figure 3). The influence of *P. mirifica* on P4 reduction might be similar to other phytoestrogens. Genistein could directly act on CNS in the hypothalamus and as a result, modulate GnRH and LH secretion (Wójcik-Gładysz *et al*., 2005). The reduction of LH was also observed in OVX rats and ovary-intact mice after long-term exposure to *P. mirifica* (Malaivijitnond *et al*., 2004; Jaroenporn *et al*., 2007). Instead, basal LH is necessary for luteal cell production of progesterone (Quintal-Franco *et al*., 1999), which thus disrupted LH secretion and caused a decrease in P4 production. In addition, genistein directly inhibited post-cAMP of 3β-hydroxysteroid dehydrogenase/isomerase, the key enzyme for P4 synthesis (Tiemann *et al*., 2007; Nynca *et al*., 2013), while equol and para-ethyl phenol, the metabolites of genistein and daidzein, reduced LH-stimulated P4 secretion in bovine luteal cells (Piotrowska *et al*., 2006; Woclawek-Potocka *et al*., 2006). Long-term supplementation with Berseem clover, with estrogenic roughage, resulted in a decline in P4 concentration along with higher estradiol level, where the imbalance of P4 to E2 led to a low conception rate (Hashem and Soltan, 2016). This result indicated that 1000 mg/kg BW/day of *P. mirifica*, especially during luteogenesis, caused impairments in both structure and functional CL.

In conclusion, *P. mirifica* affected reproductive performance in cyclic does in terms of estrus behavior and ovarian activity. Supplementation with *P. mirifica* at 1000 mg/kg BW/day through ovulation and luteogenesis had an adverse effect on CL function. The effect of lower dosage of *P. mirifica* might be recommended for further studies.

***Conflict of interest*:** The authors declare that they have no conflict of interest.

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