Effect of fermented concentrated potato protein on milk yield and fertility parameters in dairy cows in the prepartum and postpartum periods

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SUMMARY

This study aims to determine the effects of fermented concentrated potato protein (FCPP) which showed very high levels of indole acetic acid (IAA) on milk yield, fertility, and level of insulin-like growth factor 1 (IGF-1) parameters in pregnant dairy cows and pregnant heifers.
In total, sixty Holstein cattle were enrolled in the study. The animals were divided into three groups, as control group (n=20), 25 g FCPP group (n=20), and 50 g FCPP group (n=20). Besides, these main groups were also divided into two sub-groups, as primiparous (n=10) and multiparous cows (n=10). Oral administration of FCPP started two weeks (14±4 days) before expected parturition and continued until postpartum day 100. The affinity of IAA found in FCPP pellets to 5HT1 and JAK2 receptors, which is thought to be related to IGF-1 release, was determined by the molecular docking method that receptor affinities were found as -5.8637 kcal/mol and -4.3857 kcal/mol, respectively.
Blood IGF-1 profile was followed at 7 different time points throughout the study. It was detected that the IGF-1 concentrations have significant difference in terms of both time and groups ($P<0.05$). Furthermore, there was a significant difference in interaction of time and parity ($P<0.05$).
The results showed that average and total 100-day milk yield was not affected by FCCP supplementation ($P>0.05$). FCPP supplementation generally has improved the mathematical data of fertility parameters, but no statistical significance was detected except for calving-conception interval. It was found that calving-conception interval reduce by 16.8% in primiparous cows supplemented with 25 g FCPP. The pregnancy rates in control, 25 g and 50 g FCPP were found as 72.2 %, 78.9 % and 88.9 %, respectively ($P>0.05$).
This study has concluded that fermented concentrated potato protein (which has indole acetic acid-indole compounds) may improve the productivity of dairy cows supplemented in transition period and it has suggested that further research must be done for its usage and beneficial effects in dairy cows.

KEY WORDS

Cow, fermented concentrated potato protein, fertility parameters, indole acetic acid, molecular docking.

INTRODUCTION

Dairy cattle are a sub-branch of animal husbandry. In addition to providing a regular income with the milk obtained from dairy cattle, the calf obtained every year is also an added value. Milk yield and fertility are closely related to IGF-1 and is thought to be used as a genetic predictor. For this reason, studies on feed additives that support IGF-1 production, and thus increase fertility and milk yield, gain importance.
In high-yielding cows, plasma IGF-1 concentration decreases after parturition, however, upregulation of liver growth hormone (GH) receptors stimulates IGF-1 production and consequently increase IGF-1 levels in the blood[1]. There are cases in which the IGF-1 level cannot be increased due to various stress factors. It is essential not to prolong this situation[2-6], as IGF-1 affects follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which have an impact on ovarian follicles. The IGF-1 is active in the cows' genital system and is useful in the formation and continuation of pregnancy[7,8].
In most species, follicular granulosa cells synthesize IGF-1, but this is not seen in cows. In ruminants, IGF-1, which is in follicular fluid, comes from blood circulation. The concentration of IGF-1 varies with age, breed, and lactation period[9]. Consequently, there are studies regarding the increase the release of IGF-1 in animals. There are also studies regarding the increase of IGF-1 level in the blood by using fermented concentrated potato protein (FCPP), but these are few. There were no studies conducted on the active substance IAA[10-15].
Tryptophan derivatives are bioactive compounds found in FCPP

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that can stimulate tissue growth in both animals and plants[16]. Plant growth is stimulated with tryptophan derivatives (e.g., indole acetic acid). Growth and cell proliferation in animal tissues are stimulated by serotonin, tryptamine, and indole, whose molecular structures are similar. Indole also stimulates liver regeneration[16]. There is no study suggesting that indole acetic acid increases IGF-1 secretion in cows. However, Gillessen and Rebiere[17] in 2011 (Patent Issue 13/064,818,) reported that there was increased IGF-1 in catfish, piglet, and laying hens.
Therefore, the molecular docking method used in the study is an application that predicts the preferential orientation of a molecule to a second molecule when bound to form a stable compound[18]. In this study, molecular docking compatibility is discussed to elucidate the mechanism of interaction between ligand-receptor[19].
The present study aims to find the effect of FCPP (indole acetic acid-indole compounds) on IGF-1 release and its effect on milk yield and fertility parameters in dairy cattle.

MATERIALS AND METHODS

Animal Housing and Care

The study was conducted in a commercial enterprise in the central Anatolia Region (Bünyan, Kayseri, Türkiye). In this farm, approximately 600 dairy cows were bred and milking was performed twice a day with a rotating milking system. Animal health care and herd management were under veterinary supervision. The animals were housed in groups in free-stall barns bedded with plastic and equipped with overhead fans and a sprinkler system.

Experimental Design

The study was carried out with 60 Holstein Friesian cattle consisting of 30 pregnant cows (multiparous cows) and 30 pregnant heifers (primiparous cows), which were randomly assigned to one of the three groups. They were paired based on similarities; lactation number (parity), milking performance in the previous lactation and BCS (3.5) to provide three groups (10 in each group). Also, pregnant heifers (primiparous cows) were divided into three groups as pregnant heifers (10 in each group) with similar BCS values (3.5) and from the same father.
The FCPP (Lianol® Dairy) used in the study was obtained from ANC Animal Nutrition and Health Services Inc. Feed was in pellet and suitable for consuming by cattle. The recommended dose, according to product instructions, was 25 g daily per animal. The nutritional analysis of the product (label values of the product) was the following: calcium carbonate 46%, dicalcium phosphate 10%, fermented potato protein 15%, potato protein 10%, wheat (carrier) 13%, molasses (carrier) 4%, soybean oil (carrier) 2%. The nutrient content of FCPP (label values of the product) was: Crude Protein 13.60%, Crude Fat 2.80%, Ash 52.00%, Crude Cellulose 1.00%. The FCPP was administered once per day to each animal orally, mixed in equal parts with water under human supervision. The administration started about two weeks (14±4 days) before expected time of calving and continued until postpartum (pp) day 100. As far as the rest of animal nutrition is concerned, a vertical TMR mixer was used, which, twice a day (at 09:00 and 17:00), was distributing the rations mentioned in Table 1 in equal amounts.

Data Collection and Sample Analysis

The schematic diagram of the study is presented in Figure 1. Milk yield data of the cows were continuously obtained from the farm management software for the whole 100-day period and were recorded for each animal. The milking process was carried out in different milking systems for the first seven days in order to get used to milking the heifers after parturition. Subsequent data were recorded up to pp day 100 as in cows. Blood samples (~8 ml) were collected from each animal by venipuncture of the coccygeal vessel at the beginning of the experiment, at parturition, on Day pp 21, 45, 60, at first insemination time (AI[1st]) and on Day pp 100. Once the samples were collected, the serum was separated by centrifugation (Hettich Universal 320, Germany) at 3000 rpm for 10 min and then frozen at -80°C for subsequent analysis.

Insemination and Fertility Parameters

In the postpartum period, oestrus symptoms were detected by pedometers and experienced farm personnel. Routine gynae-

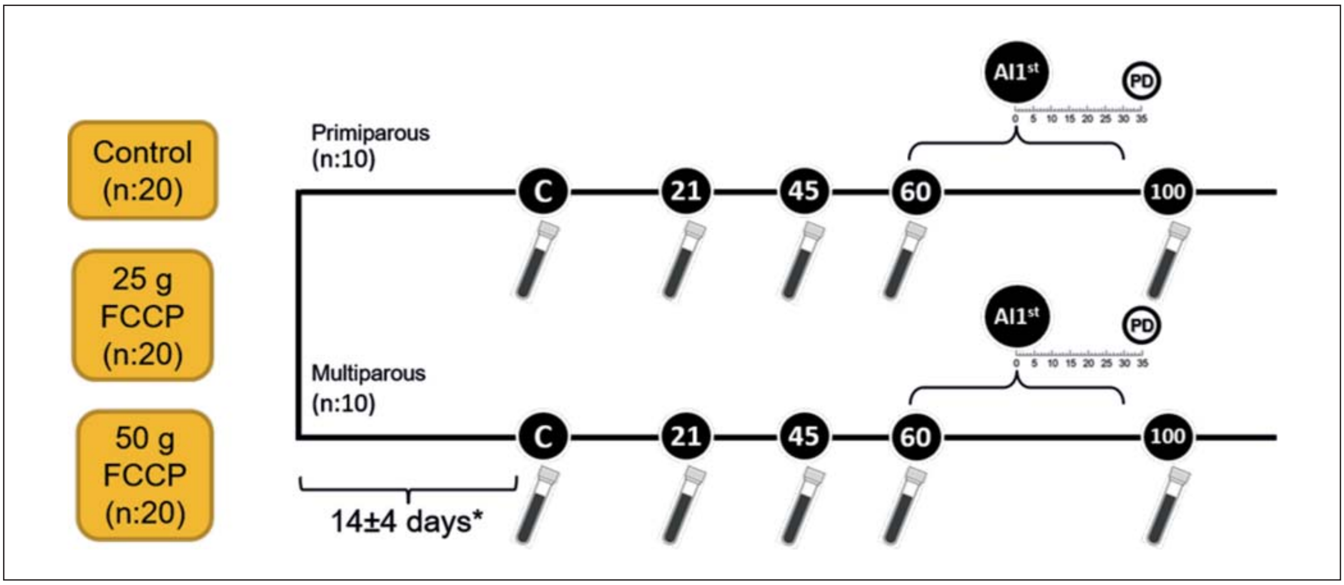

Figure 1 - The schematic diagram of the study.

Table 1 - The amount of raw material (kg) of TMR used in the farm.

PERIOD	Wheat straw	Alfalfa hay	Corn Silage	Concentrated Pellet Feed (21% HP) *	Concentrated Pellet Feed (19% HP)**	Corn grain	Magnesium	Sodium bicarbonate	Bypass fat
Close up	2.2	3.5	18.5	4.6	3.5	2	0.08	0.3	-
Early Lactation	1.5	5	23.5	13.5	-	2	0.08	0.3	0.2
Peak Lactation	1.5	5	23	4.6	2.5	2	0.08	0.3	-

* As fed basis (%): Razmol 21%, 46% HP soybean meal 20%, broken grain 20%, 28% HP sunflower meal 12.5%, rice bran 13%, corn 7.7%, molasses 2.6%, soybean oil 0.6%, marble powder 1.8%, salt 0.7%, vitamin-mineral mix 0,1%***
** As fed basis (%): Razmol 24%, 46% soybean meal 13.7%, broken grain 20%, 28% HP sunflower meal 12,5, 28% HP cotton seed meal 1.8%, rice bran 12.6%, corn 10.3%, molasses% 2.5, marble powder 1.8%, salt 0.7%, vitamin-mineral mix 0.1% ***
*** Each kilogram of vitamin-mineral mix; 13.000,000 IU of vitamin A, 3.500,000 IU of vitamin D, 40.000 mg of vitamin E, 50.000 mg of zinc, 50.000 mg of manganese, 50.000 mg of iron, 10.000 mg of copper, 150 mg of cobalt, 800 mg of iodine, 300 mg of selenium.

cological examinations were weekly performed to evaluate the healthy voluntary waiting period and to diagnose likely pp disease in the scope of the reproductive management procedure. Thus, it was confirmed that the genital tract of the animals to be included in the reproductive program were health. In addition, cows were followed up to the pp day 150 to evaluate the pregnancy rates obtained after the AI^{2nd} and AI^{3rd}. Artificial inseminations were performed by the same herd veterinarian. The animals were inseminated no more than three times during this study. Pregnancy diagnosis was performed with a portable ultrasound (MINDRAY DP-10 Vet, China) equipped with 5-8 MHz linear probe on Day 35 after AI.
The fertility parameters including calving to AI^{1st}; calving to conception interval; first oestrus; conception rate in AI^{1st}, AI^{2nd}, AI^{3rd} and total pregnancy rate were calculated as described by Ata[20] (2013) and Tekin and Daskin[21] (2016).

IGF-1 Analysis

The total serum IGF-1 concentration was determined by a commercial IGF-1 ELISA kit (Sunred Bio Bovine IGF-1 Elisa Kit). The absorbance values of the samples were determined by a 96-well microplate reader (µQuant, BIO-TEK) with a spectral waveband of 400-750 nm. The microplate was measured at 450 nm with this instrument.

Indole Acetic Acid (IAA) Analysis

The amount of IAA in FCPP pellet was analysed by AGILENT 1260 model high-pressure liquid chromatography (HPLC) with a DAD (Diode Array Detector) at Erciyes University Technology Research and Application Center (TAUM). Indole acetic acid, 87-51-4 CAS number, was used as a standard analyte in the analysis. The extracted samples were analysed by high-performance liquid chromatography (HPLC)[22].

Molecular Docking Method

The molecular docking method was used to determine the receptor-ligand relationship of IAA, which was contained in the FCPP pellet. The optimal molecular docking calculations were selected, based on Türkmenoğlu and Güzel[19] (2018).
In this study, the molecular docking process was applied to two different receptors, which were predicted to interact. Proteins acting on JAK2 and 5HT1 receptors from the protein data bank were examined, and the individual RMSD (square root of the standard deviation) value was calculated. The binding site between the most stable L-R was observed by finding the binding energies by the FlexX docking programme.
Molecular docking results were found from the protein databank (www.rcsb.org). In the molecular docking programme, IAA was used as ligand and interacted with two different proteins (PDB ID: 2XDG and 3UGC).

Statistical Analysis

The appropriateness of the data to the normal distribution was evaluated by the Q-Q plot, histogram, and Shapiro Wilk test. The homogeneity of the variances was examined by the Levene test. Descriptive statistics were shown as "Mean ± SEM," and percentages.
One-Way ANOVA and Kruskal Wallis were used to compare the importance between groups (Control, 25 g FCPP, and 50 g FCPP) in terms of milk yield and fertility parameters. Analyses of significant differences were performed using analysis of variance followed by the Tukey post hoc test.
The effect of the group on pregnancy rate was investigated by the Chi-Square test. The effect of groups, time, and lactation (primiparous-heifer and multiparous-cow) on the IGF-1 level was calculated with repeated measures ANOVA. Statistical analysis of the data was performed by the SPSS (version 20.0, SPSS Inc, USA) programme. The significance level was accepted as $P < 0.05$.

RESULTS

The interaction between the ligand-receptor shown in Figure 2a and 2b was found to be binding affinity G = -5.8637 kcal/mol using the FlexX docking programme. Between the ligand IAA and the amino acids, Asp 95 and Cys 96, there is a hydrogen bond. These bonds also indicate the interaction between the ligand and the receptor.
The interaction between the ligand-receptor shown in Figure 2 was found to be binding affinity G = -4.3857 kcal/mol using the FlexX docking programme. Between the ligand IAA and the amino acids, Ile 948 and His 950, there is a hydrogen bond. In this case, too, these bonds also indicate the interaction between the ligand and the receptor. Based on these results, it can be stated that IAA is theoretically active relative to the receptors. Results for IGF-1 levels, fertility parameters, milk yield are given in Table 2, Table 3 and Figure 3, respectively.
Five animals were removed from the farm against our will due to the farm's business policies at different times.

DISCUSSION

In literature, there are few studies showing the effect of FCCP on IGF-1 levels[23,24]. In these studies, it was observed that the

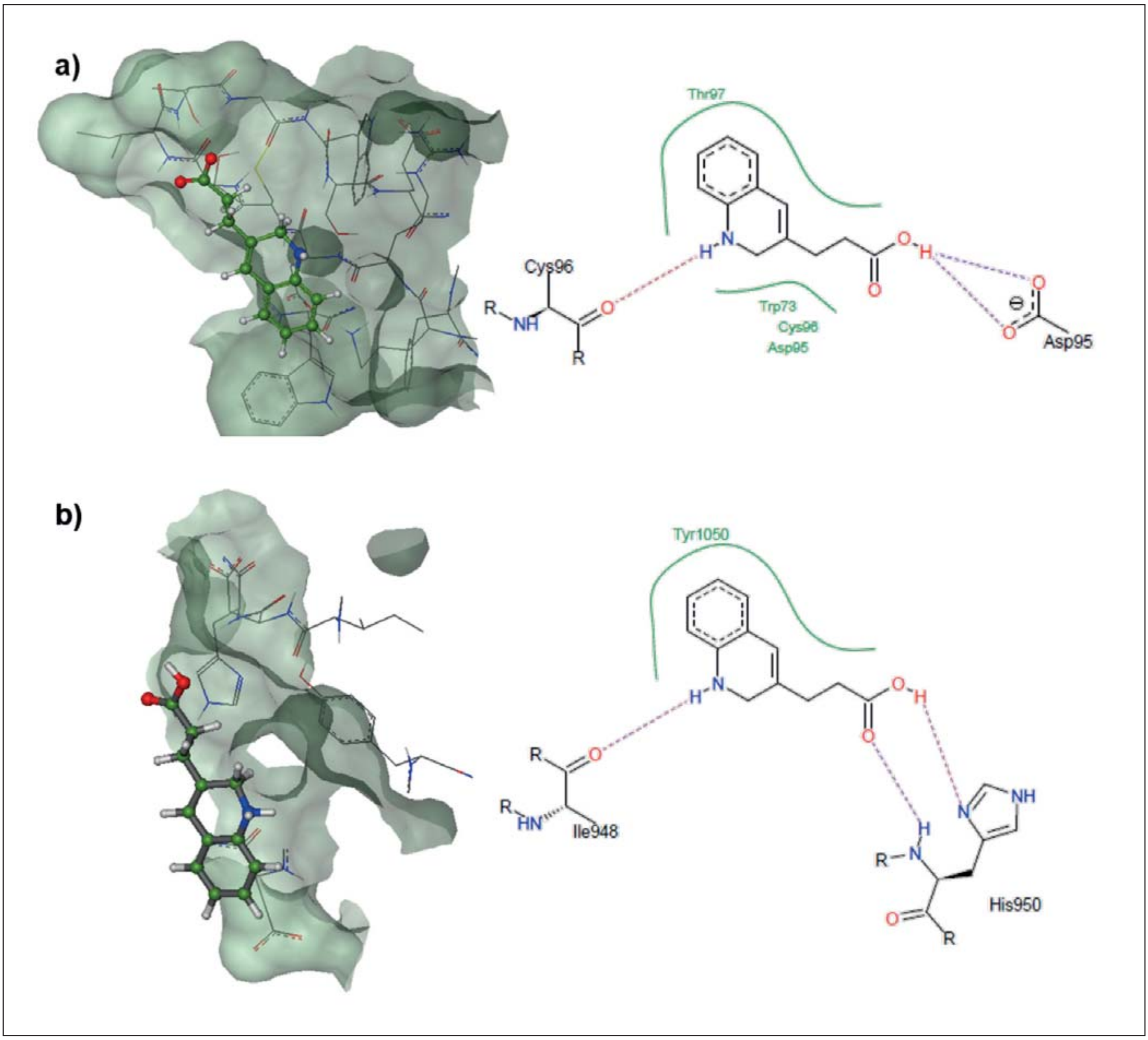

Figure 2 - **a)** Molecular docking between the receptor-ligand and the interaction diagram of the ligand inserted within the active site of the 5HT1 enzyme (PDB ID: 2XDG) of the GHRH receptor. **(b)** Molecular docking between receptor-ligand and the interaction diagram of the inserted ligand within the active site of the JAK2 receptor (PDB ID: 3UGC).

amount of IGF-1 was increased by the addition of FCCP to pigs as a feed additive. It has been reported that FCCP supplementation positively affected various yield parameters in those animals[23] and these effects of FCCP is associated with its tryptophan and derivatives ingredients[25,26]. However, indole derivatives (particularly IAA) are not mentioned in these studies. Indole derivatives are also known to be produced by various microorganisms in the intestine. These bioactive molecules also play a role in providing communication between intestinal microorganisms[27]. Currently, the intestinal flora is considered as the second brain of the body and the mechanisms of action of some bioactive substances produced by flora are still being studied. Indole derivatives, which are also bioactive substances (AhR ligand), are reported to stimulate the immune system[28,29]. It has been shown that different ligands such as 7,8-Tetrachlorodibenzo-p-dioxin (TCDD), flavonoids, carotenoids, and indoles can be bound to AhR[30]. Based on the previous studies, that different ligands can be bound to the same receptor, suggest that IAA may also be bound and activates a structure which triggers IGF-1 production. Furthermore, the molecular structure of the IAA included in FCPP was studied using the molecular docking method and computer-mediated examination, and showed that it can be bound to structures that can activate IGF-1 production.

In this study, it was determined that IGF-1 levels were significantly higher in the groups consuming 25 g and 50 g FCPP. Similarly, studies in pigs have shown that the use of FCPP significantly increases IGF-1 levels[10-13,15,23]. Similar results have been reported by Gillessen and Rebiere[17] (Patent Issue 13/064,818, 2011). In the early lactation period in dairy cattle, IGF-1 was in low concentration when GH levels were high[31,32]. In the third week after calving, IGF-1 concentration started to increase with the upregulation of liver GH receptors[1]. This finding is in line with the results of this study. Although there was a generally rapid increase of IGF-1 levels in all three groups within 100 days in milk, generally the higher IGF-1 levels were observed in the

Table 2 - The effects of FCCP on blood serum IGF-1 levels (ng / ml) in the prepartum and postpartum periods ($x \pm S_x$).

		Control	25 g FCPP	50 g FCPP		
Heifer	-14±4	200.00 ± 19.57^{CF}	219.46 ± 15.13^{DF}	211.36 ± 14.37^{CE}		P value
	Within 24 hours	124.48 ± 17.51^{DI}	154.63 ± 13.74^{EI}	155.20 ± 13.72^{DF}	Group	**0.031**
	21st day	208.94 ± 20.44^{CG}	227.18 ± 12.81^{CD}	225.33 ± 16.19^{C}		
	45th day	238.09 ± 10.14^{BM}	245.47 ± 36.38^{BG}	247.79 ± 16.76^{BH}	Lactation	0.106
	60th day	250.24 ± 26.27^{B}	241.86 ± 26.02^{BCM}	258.30 ± 27.53^{AB}		
	First Insemination Day	197.42 ± 7.61^{CN}	236.59 ± 16.12^{BCN}	267.79 ± 7.12^{AG}	Time	**<0.001**
	100th day	261.97 ± 12.44^{AP}	278.37 ± 23.30^{AP}	264.98 ± 5.69^{A}		
					Group * Lactation	0.641
Cow	-14±4	275.81 ± 19.07^{AF}	263.49 ± 19.63^{BF}	256.36 ± 33.51^{BE}		
	Within 24 hours	160.78 ± 13.59^{FI}	135.31 ± 14.70^{DI}	164.40 ± 17.48^{DF}	Time * Group	0.679
	21st day	169.27 ± 14.40^{aDG}	220.52 ± 28.51^{bC}	207.62 ± 15.48^{bC}		
	45th day	251.05 ± 27.98^{CM}	319.37 ± 35.60^{AG}	285.70 ± 22.93^{AH}	Time * Lactation	**0.035**
	60th day	217.35 ± 25.80^{B}	315.74 ± 44.87^{AM}	269.71 ± 20.51^{A}		
	First Insemination Day	183.14 ± 20.44^{EN}	245.87 ± 27.03^{CN}	239.00 ± 5.62^{BG}	Time * Group * Lactation	0.475
	100th day	265.36 ± 28.89^{BP}	280.04 ± 24.80^{BP}	287.68 ± 18.41^{A}		

a, b: Different letters on the same line show the difference between groups.
A, B, C, D, E, F, G, H, I, M, N, P: Different letters in the same column show the difference between groups.
(x): Arithmetic mean (S_x): Standard error

FCPP groups (except prepartum -14±4 and parturition day in cows; 60th day in heifers)
It is thought that the effect of FCCP on IGF-1 can be explained in two ways. First, IAA, which is found in the FCPP, acts like serotonin, affects the GHRH release. Indole acetic acid such as serotonin can be found in the central nervous system[33]. According to recent studies, it has been reported that similar molecules can activate the same receptor[30]. Docking method results showed that, like serotonin, IAA had been found to affect GHRH (Figure 2a). In this case, the GH level may increase and indirectly make it possible to increase IGF-1. A second possibility is that the affinity of the IAA to JAK2, as shown by the docking method, is likely to activate the signal in the liver (Figure 2b).
The effect of IGF-1 on body functions throughout the lifespan of the animal is significant[34]. Therefore, the insufficiency of IGF-1 may adversely affect growth and productivity. The IGF-1 also affects many parameters, such as milk yield and fertility[9,35]. In the study, there was no significant difference between average daily milk yields among groups. Although FCPP did not significantly affect milk yield, a mathematical increase was observed in both primiparous and multiparous cows. The fact that milk yield lev-

Table 3 - Postpartum fertility parameters of primiparous and multiparous cows in 25 g FCPP, 50 g FCPP and control groups.

Parameters	Parity	Control	25 g FCPP	50 g FCPP	P value
Service Period (Day) ($\bar{x} \pm S_{\bar{x}}$)	Heifer	80.60 ± 3.37	72.10 ± 4.05	76.75 ± 3.99	0.282
	Cow	81.87 ± 7.31	80.33 ± 3.54	75.80 ± 3.66	0.654
Calving-Conception Interval (Day) ($\bar{x} \pm S_{\bar{x}}$)	Heifer	116.00 ± 5.82^{a}	96.42 ± 6.20^{b}	111.42 ± 3.56^{ab}	**0.045**
	Cow	119.83 ± 8.12	117.37 ± 7.56	113.33 ± 8.31	0.853
First Oestrus (Day) ($\bar{x} \pm S_{\bar{x}}$)	Heifer	43.00 ± 3.20	45.50 ± 3.71	45.50 ± 1.75	0.792
	Cow	51.42 ± 5.25	41.75 ± 3.28	42.12 ± 1.27	0.119
Pregnancy Rate in AI1st (%)	Heifer	30.0	40.0	37.5	
	Cow	25.0	33.3	40.0	
	Total	27.8	36.8	38.9	0.756
Pregnancy Rate in AI2nd (%)	Heifer	57.1	50.0	60.0	
	Cow	33.3	50.0	33.3	
	Total	46.2	50.0	45.5	0.972
Pregnancy Rate in AI3rd (%)	Heifer	0.0	0.0	50.0	
	Cow	50.0	66.7	75.0	
	Total	28.6	33.3	66.7	0.333
Overall Pregnancy Rate (%)	Heifer	70.0	70.0	87.5	
	Cow	75.0	88.9	90.0	
	Total	72.2	78.9	88.9	0.453

a, b: The difference between the mean values of groups bearing different letters on the same line is significant ($P<0.05$).
($\bar{x}$): Arithmetic mean, **$S_{\bar{x}}$:** Standard error

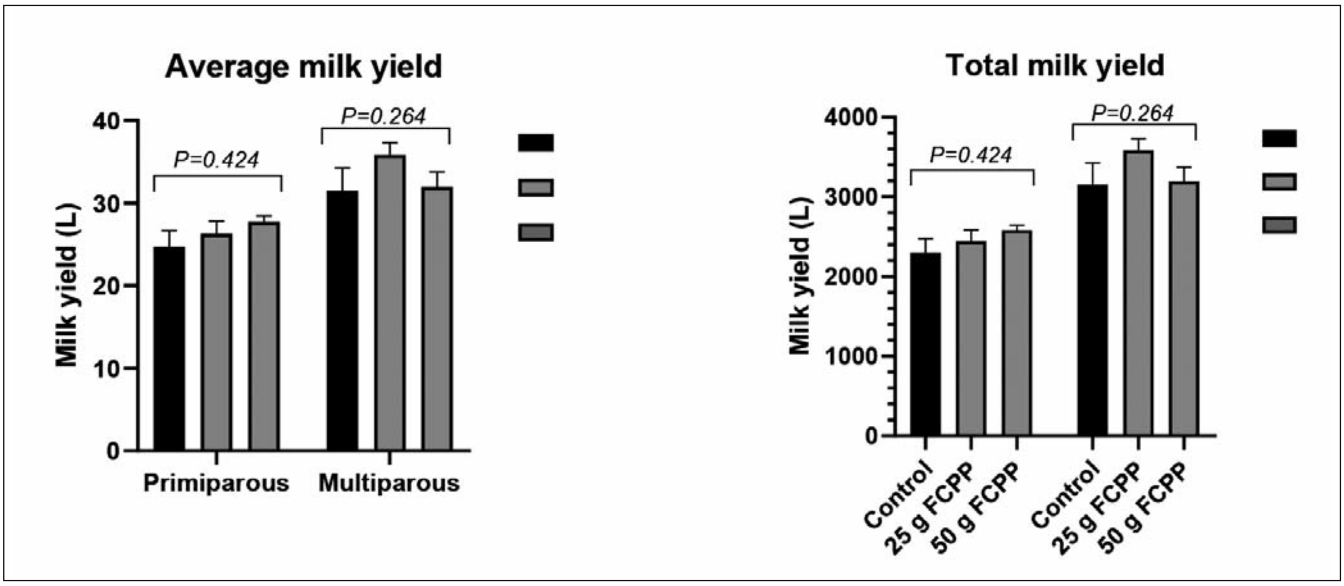

Figure 3 - The average (kg/day/animal) and total milk yields (kg/animal) of multiparous between 0-100 days and primiparous between 8-100 days.

els in primiparous cows are more homogeneous than in multiparous cows could be because the primiparous cows used in the study have the same father line. This may be one reason why standard deviations in primiparous cow groups are lower than in multiparous cow groups. In previous studies conducted in lactating goats infused with IGF-1 into the mammary artery, it was observed that blood flow was accelerated, and milk production was increased[36,37]. However, an increase in milk yield was not detected in sheep injected with growth hormone into the mammary artery[38]. Peel and Bauman[38] have reported that growth hormone might indirectly affect breast tissue with IGF-1.

When the fertility parameters were assessed, it was found that the first oestrus after calving observed earlier for multiparous cows, to which FCPP was administered, than in the control group. As far as the Calving-First Insemination Interval for both primiparous and multiparous cows in the 25 g and 50 g FCPP groups is concerned, although there was no statistically significant difference. This period was shorter, even for a lot of days, compared to the control group. In parallel, the Calving-Conception Interval was statistically shorter in primiparous cows. Although there is no statistically significant difference, the pregnancy rate of all animals in the 25 g and 50 g FCPP groups was found to be higher by 6.7% and 16.7%, respectively, when compared to the control group. Plasma IGF-1 level in dairy cattle during the periparturient period has a positive impact on insemination and has been stated to be a useful parameter for reproduction[39]. Likewise, it is considered as an essential indicator for the fertility management of dairy animals in the postpartum period[39]. IGF-1 is seen as an important factor for the resumption of the oestrus cycle in the early postpartum period[40]. Scaramuzzi et al.[35] showed that exogenous administration of IGF-1 in vivo is a potent stimulator of both follicle growth and estradiol secretion in sheep. However, Falkenberg et al.[41] argued that IGF-1 is not an essential factor.

The results of the study have shown that supplementation with FCPP increases the total pregnancy rate in primiparous and multiparous cows, shortens the service period in primiparous cows and increases the milk yield in primiparous cows. Based on the results obtained from this study, it can be concluded that addition of FCCP to the diet has beneficial effects on fertility and milk yield by supporting blood IGF-1 concentration in transition period (pre- and postpartum period) in dairy cows and overcome problems resulted in fermentation process by its antibiotic resistance. However, to clarify its features on productivity and metabolism, more detailed studies should be done in dairy cows. It is thought that the results will contribute to herd management and give further insight into how molecules produced by bacteria affect the liver, brain, and, in particular, specific body functions, reproduction and milk production.

Welfare Statement

Trial was completely non-invasive. No animal was displaced from its home farm. The feed additive used was an already commercially available and legally approved additive. All experimental procedures involving the use of animals were in accordance with the animal welfare legislation and approved by Erciyes University Local Ethics Committee for Animal Experiments (HADYEK) (Kayseri, Turkey; date: 13.01.2016 protocol no: 16/007).

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