Indian Journal of Animal Sciences **95** (2): 87–95, February 2025/Article
https://doi.org/10.56093/ijans.v95i2.133411

Efficacy of Sothanasaka Sunthyadi Yoga a classical ayurvedic formulation on hemato-biochemical profiles in lactating Holstein Friesian crossbred cows

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Received: 16 February 2023; Accepted: 10 February 2025

ABSTRACT

The current investigation aimed to assess the safety profile of a polyherbal formulation Sothanasaka Sunthyadi Yoga on lactating Holstein Friesian crossbred cattle. A total of 30 animals were selected and divided into three groups. Group 1 received a regular diet (control). Group 2 was administered with Domperidone (10mg/100 kg body weight, orally, positive control) and group 3 was fed with the polyherbal formulation (20 gm/100kg body weight, orally, test group) for the period of 45 days. The effect was evaluated through hematological and biochemical alterations. No change in body weight were observed in all groups. However, there were significant alterations in lymphocyte and neutrophil values noted in groups 2 and 3 on day 60 compared to 0 day. The hemoglobin (Hb) concentration increased significantly from day 0 to day 60 in group 3. The glucose level in group 3 increased significantly on days 30 and 60 when compared with groups 1 and 3 as well as from day 0. Albumin levels increased substantially in all groups, with a significant decrease in total protein in group 2 on day 30 and globulin on day 60. Group 2 showed a significant increase in ALT, AST, ALP and LDH activity when compared with groups 1 and 3. In group 3, LDL and values decreased significantly on day 60, and HDL values decreased significantly on day 30 as compared to group 1. HDL levels in group 2 decreased significantly on day 30. Inflammatory markers, IFN-γ exhibited a significant change in group 3 compared to group 1 with no changes in TNF-α and IL-1β levels. All other parameters remain within a normal limit in the polyherbal-treated groups. In conclusion, the study found that polyherbal preparation Sothanasaka Sunthyadi Yoga treatment did not adversely affect the haemato-biochemical profile, indicating its safety for use in lactating cattle as a galactagogue.

Keywords: Biochemical, Galactagogue, Haematology, Polyherbal, TNF-α, IFN-γ

Galactagogues are medications, pharmaceuticals, foods or herbal supplements that help in milk production, continuation, and/or augmentation. They also boost secretory activity to restore and control milk production by stimulating alveolar tissue function (Zapantis *et al.* 2012). Galactogogues, whether synthetic or derived from plants, serve to stimulate, sustain, and enhance milk production (Mortel and Mehta 2013), orchestrating intricate processes that involve the interplay of various physical and physiological elements. Among these, hormones like prolactin (PRL) are pivotal. Nonetheless, factors such as somatotropin, cortisol, insulin, leptin, estrogen, progesterone, and medroxyprogesterone (Zuppa *et al.* 2010), along with oxytocin, recombinant bovine somatotropin (rBST), and thyrotropin-releasing hormone (TRH), also exert significant influence as galactogogues (Penagos Tabares *et al.* 2014). The majority of galactagogues mediate their effect by inhibiting dopamine receptor activity. These include metoclopramide, domperidone, chlorpromazine, and sulpiride. Domperidone and related category of galactagogue long term consumption notably, have significant side effects in mothers encompass xerostomia, gastrointestinal disturbances, cardiac arrhythmias, and extrapyramidal symptoms and hyperhidrosis (Zuppa *et al.* 2010 and McBride *et al.* 2023). Infants may exhibit symptoms such as intestinal discomfort, lethargy, and sedatio (Lawrence and Lawrence 2011, Suain Bon and Mahmud, 2022).

Historically, varieties of plants utilize to enhance milk production in both women and dairy animals (Abascal and Yarnell, 2008). Modern scientific research on the galactogogue properties of different plants has indicated their potential to increase milk synthesis, with evidence suggesting their safety for use in humans (Yoshida *et al.* 1998), cows (Sharif yanov *et al.* 1996, Latvietis *et al.* 2002), goats (Alamer 2009), and buffaloes (El-Alamy *et al.* 2001). Numerous herbal galactogogues have been identified as safe substances that, when administered in

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appropriate doses and even cost-effective. Incorporated food supplements of dairy herds are seeds, leaves, essential oils, roots, stems, and barks depending on their activity in those parts (Alamer 2009). The utilization of herbal derivative products in the dairy industry aligns with the emerging trend towards organic dairy farming (Oruganti 2011). This will add into successful dairy production by preserving good health and preventing stress in animals during production. Various herbal formulations offer a range of beneficial effects, including promoting growth, reducing inflammation, and combating oxidative stress (Ao *et al.* 2011, Huang *et al.* 2010). Shatavari has been identified as a galactagogue, antioxidant compound, immune-modulator, and immunostimulant in dairy animals (Kumar *et al.* 2008). Additionally, ginger, possesses anti-hyperglycemic, anti-lipidemic, antioxidant, and anti-inflammatoryroperties (Ali *et al.* 2008). Fenugreek globally have been accepted as antioxidant, anti- inflammatory and immunomodulatory agent (Dixit *et al.* 2005), besides numerous other pharmacological benefits such as antidiabetic, anticarcinogenic and, hypocholesterolemic (Sharma *et al.* 2014, Choubey *et al.* 2015, Sivajothi *et al.* 2018, Kuri *et al.* 2019). Despite the well-established scientific data available on individual phyto-ingredients for their pharmacological activity, new herbal formulations or substances must meet safety requirements to gain acceptance as medicine globally and establish a presence in the market (Joshua *et al.* 2008). Therefore, comprehensive short- and long-term toxicological information is necessary for herbal preparations intended for use as medicinal products, known as safety data. Now, world-wide safety pharmacological assessment is mandatory for any new compound formulation before its use as a medicine. Hence, in present study it was planned to examine the safety of a galactagogue drug formulation (Sothanasaka Sunthyadi Yoga) through the hematological and biochemical profile picture with sub-chronic exposure in dairy cattle.

MATERIALS AND METHODS

Plant materials, chemicals and reagents: A polyherbal galactagogue formulation "Ayush 13" (known as Sothanasaka Sunthyadi Yoga), containing 13 plants materials (*Asparagus racemosus, Cuminum cyminum, Carum carvi, Zingiber officinale, Embelia ribes, Allium sativum, Piper longum, Piper nigrum, Anethum sowa, Swertia chirata, Picrorhiza kurroa, Pistacia integerrima and Red Ochre* or *Gairika*) was compiled based on knowledge of individual plants materials in *Charak Shamhita* and Veterinary Ayurvedic documents in "The Veterinary Ayurvedic Formulary of India - Part- IV" by the Ministry of Ayush. This formulation has been recommended by the Central Council for Research in Ayurvedic Sciences (CCRAS), New Delhi for milk augmentation in dairy animals. Domperidone (synthetic dopamine antagonist) was used as a positive control

Experimental design: Lactating Holstein Friesian (HF) crossbred cows, available at the Dairy Farm of the Directorate of Livestock Farm Complexes of Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, were used in the present study as experimental animals. Prior to commencing the experiment, ethical permission for the inclusion of dairy cows for safety evaluation was obtained from the Institutional Animal Ethics Committee (IAEC) and the Committee for the Control and Supervision of Experiments on Animals (CCSEA), Ministry of Fisheries, Animal Husbandry, and Dairying, Government of India (Approval No. 25/23/2019- CPSEA; dated 9.12.2019).

Sub-chronic toxicity (repeated dose) study was conducted in thirty lactating HF crossbreed cows, evenly divided into three groups to avoid bias. The inclusion criteria for dairy cows in different groups were based on their history of daily milk production, similar parity, and lactation stage. Group 1 served as a control, with cows provided with normal routine dairy cattle feed according to their regular scheduled diet for lactating animals, without any additives. Group 2 cows served as a positive control and received Domperidone at a dosage of 100mg per 100 kg body weight, administered orally once a day. The dosage was selected based on a literature survey, considering safety and milk augmentation through repeated oral administration (Wan *et al.* 2008, Asztalos *et al.* 2017, Toledo *et al.* 2020). Group 3 served as the treatment group, with cows additionally fed a polyherbal formulation at a dosage of 20 grams per 100 kg of body weight for consecutive 45 days, administered twice a day. The dosage was selected based on the basic principle of Ayurveda, utilizing crude material (*Churana*) for therapeutics. All the animals were observed for 60 days, with samples collected on day 0, day 30, and day 60. These samples were collected according to the sub-chronic toxicity study protocol after repeated dosing of 30 days. Feeding continued for the next 15 days (total 45 days). The total observation period as per the ethical committee, IAEC (CCSEA) recommendation was 60 days and last sampling was on day 60 to discover any delayed residual toxic effects of the formulation.

Haemato-biochemical analysis: Blood samples were collected via jugular vein from all animals at 30 days intervals (day 0, 30, and 60). Blood was collected in EDTA vials for hematology and clot activator vials for biochemical parameters. All hematological parameters like total leucocyte count (TLC), differential leukocyte count (DLC), absolute lymphocyte count (ALC), absolute neutrophil count (ANC), total erythrocyte count (TEC), hemoglobin, packed cell volume (PCV), erythrocyte sedimentation rate (ESR), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) were estimated on fresh blood samples on the same day of sampling by standard laboratory method (Benjamin 1985, Kemal 2014).

Biochemical markers such as glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total

protein, albumin, creatinine, creatine kinase (CK), blood urea nitrogen (BUN), total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, calcium, and phosphorus were assessed after separating serum using commercial kits (ERBA Diagnostics Mannheim GmbH, Germany).

The inflammatory and immunological indicators, such as tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), and interferon-gamma (IFN-γ), were assessed using a commercial ELISA kit (Real-Gene Labs Germany) following the manufacturer's instructions.

Statistical analysis: All the parameters were analyzed using SPSS 26.0 version software. Data presented as Mean ± SE. The mean values between the groups and within groups at different time points were compared by 2-way ANOVA followed by the Duncan post hoc test at 5% level of significance ($p \leq 0.05$).

RESULTS AND DISCUSSION

Neutrophil and lymphocyte values changed significantly ($p<0.05$) but remained within the physiological limits within groups 2 and 3 on day 60 compared to day 0. No significant ($p>0.05$) difference in differential leukocyte count (DLC) and total leukocyte count (TLC) was noticed between the groups at different time intervals. Absolute lymphocyte count (ALC) in the herbal treatment group decreased significantly ($p<0.05$) on day 30 compared to day 0 and 60, and absolute neutrophil count (ANC) values on day 60 (Table 1).

The hemoglobin (Hb) concentration increased significantly ($p<0.05$) from day 0 to day 60 in group 3 but was non-significant in groups 1 and 2 (Table 2). No significant difference ($p>0.05$) was noticed with respect to total erythrocyte count (TEC), packed cell volume (PCV), erythrocyte sedimentation rate (ESR), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) among the different groups. These variations lie within the normal range and could be attributed to variations in individual animal responses only, indicating that the supplemented herbal formulation has no harmful effects on erythrocytic parameters.

The glucose level in group 3 increased significantly ($p<0.05$) on days 30 and 60 when compared with groups 1 and 3 as well as from day 0 (Table 3). The levels of total protein, albumin, globulin and A:G ratio in blood did not differ significantly in group 1 and 3, however, in group 2 a significant decrease ($p<0.05$) in total protein on day 30 and that of globulin on day 60 (Table 3).

In hepatic functional enzymes (ALT, AST, ALP and GGT) and renal functional enzymes (creatinine, BUN, LDH and CK) non-significantly ($p>0.05$) changed in control and herbal treated groups (Table 4). However, the synthetic treatment group showed a significant ($p<0.05$) increase in ALT, AST and ALP activity when compared with groups 1 and 3. The elevated activities of AST and ALT are indicative of cellular leakage and loss of the functional integrity of cell membranes in the liver. LDH significantly ($p<0.05$) increased on day 30 and 60 in the synthetic

Table 1. Effect of the different treatments on TLC and DLC in lactating cows.

Group	0 DAY	30 DAY	60 DAY
	TLC (x 10^3/ µl)		
1	11.58±0.72	12.19±0.34	12.33±0.41
2	12.64±0.74	12.89±0.29	13.25±0.49
3	12.72±0.99	11.72±0.78	11.38±0.53
	NEUTROPHILS (%)		
1	47.30±1.86^{a}	45.70±1.5^{a}	45.50±1.29^{a}
2	52.5±2.34^{b}	48.70±1.89^{ab}	45.80±2.15^{a}
3	49.9±1.16^{b}	48.50±2.02^{b}	43.20±1.87^{a}
	LYMPHOCYTES (%)		
1	50.10±2.38^{a}	52.40±1.73^{a}	52.80±1.84^{a}
2	43.70±3.49^{a}	48.60±1.75^{ab}	52.60±2.45^{b}
3	47.50±1.73^{a}	48.60±2.61^{ab}	54.5±1.75^{b}
	EOSINOPHILS (%)		
1	1.88±0.35	1.88±0.23	1.50±0.22
2	2.00±0.19	2.50±0.50	1.28±0.18
3	2.43±0.53	2.22±0.28	2.14±0.40
	ALC (x 10^3 /mm^3)		
1	568.12±22.74^{a}	554.15±23.61^{a}	574.26±23.49^{a}
2	537.35±36.59^{a}	541.82±40.18^{a}	584.97±38.65^{a}
3	597.91±57.16^{b}	493.06±21.65^{a}	559.74±20.03^{b}
	ANC (x 10^3 /mm^3)		
1	556.1±53.50^{a}	484.84±24.16^{a}	501.05±28.90^{a}
2	669.21±56.83^{a}	543.45±39.17^{a}	521.52±54.33^{a}
3	639.5±66.52^{b}	513.55±68.12^{ab}	453.56±50.57^{a}

Values presented are Mean ±S.E.M. (n=10) Values bearing dis-similar superscript in small letters differ significantly within a row. Two- way ANOVA; Significance difference: $p \leq 0.05$.

treatment group when compared with day 0 activity and when compared with control and herbal treatment groups on day 30 and 60.

Cholesterol increased significantly ($p<0.05$) in all the groups until day 30. However, non-significant ($p>0.05$) changes were observed in LDL, HDL, and triglyceride levels in all groups. In group 3, LDL values decreased significantly ($p<0.05$) compared to the control on day 60, and HDL values decreased significantly ($p<0.05$) compared to the control on day 30 (Table 5).

The inflammatory and immunological indicators did not differ significantly ($p>0.05$) in groups 1 and 3 within the time interval. The TNF-α value increased significantly ($p<0.05$) in group 2 on day 30 compared to group 1. The IL-1β levels did not differ significantly ($p>0.05$) across groups concerning time and between the groups at all time intervals. IFN-γ values in group 3 showed significantly ($p<0.05$) less activity on day 30 and 60 compared with group 1 (Table 6).

A decrease in TLC values in subclinical mastitic calves treated with polyherbal formulation at different doses (Kumar *et al.* 2018) indicated the ability to Ayush 13 provide immune protection against the pathogen. In addition to this, it also possesses antimicrobial, anti-inflammatory,

Table 2. Effect of various treatments on TEC, Hb, PCV and others in lactating cows.

Group	0 DAY	30 DAY	60 DAY
	TEC (x 10^6/µl)		
1	6.58±0.21	6.37±0.18	6.39±0.16
2	6.88±0.15	6.59±0.16	6.45±0.18
3	6.45±0.27	6.88±0.26	6.94±0.23
	Hb (g/dl)		
1	10.08±0.32^{a}	9.89±0.28^{a}	9.94±0.24^{a}
2	10.13±0.31^{a}	10.16±0.26^{a}	10.20±0.25^{a}
3	9.38±0.24^{a}	10.54±0.20^{b}	10.64±0.21^{b}
	PCV (%)		
1	28.14±0.70	27.41±0.66	27.62±0.71
2	28.50±0.91	29.42±0.83	28.25±0.89
3	27.17±0.58	28.15±0.46	28.14±0.66
	ESR (mm/24h)		
1	1.60±0.22	1.80±0.25	1.60±0.22
2	1.70±0.21	1.80±0.20	1.60±0.22
3	1.7±0.21	1.60±0.22	1.60±0.22
	MCV (Fl)		
1	42.77±1.45	43.09±1.21	43.32±0.69
2	41.42±1.11	44.69±0.84	43.81±0.91
3	42.09±1.58	40.91±1.05	40.57±0.72
	MCH (pg/dl)		
1	15.31±0.46	15.52±0.41	15.50±0.54
2	14.75±0.33	15.41±0.39	15.81±0.34
3	14.54±0.43	15.10±0.37	14.87±0.24
	MCHC (g/dl)		
1	35.84±1.01^{a}	36.08±1.26^{a}	35.87±1.43^{a}
2	35.54±0.43^{a}	35.53±0.24^{a}	36.12±0.20^{a}
3	35.99±0.53^{a}	36.37±0.19^{a}	36.63±0.26^{b}

Values presented are Mean ±S.E.M. (n=10)

Values bearing dis-similar superscript in small letters differ significantly within a row. (Two way ANOVA; Significance difference: $p \leq 0.05$).

Table 3. Effect of different treatments on calcium, phosphorous, glucose, total protein, albumin and globulin levels.

Group	0 DAY	30 DAY	60 DAY
	CALCIUM (mg/dl)		
1	10.72±0.29	9.52±0.39	9.40±0.47
2	11.10±0.33	10.44±0.35	10.01±0.33
3	11.14±0.42	10.29±0.48	10.44±0.24
	PHOSPHORUS (mg/dl)		
1	7.98±0.49	7.65±0.39	7.93±0.37
2	7.99±0.23	7.44±0.66	7.37±0.54
3	7.92±0.68	7.59±0.22	7.25±0.36
	GLUCOSE (mg/dl)		
1	74.61±4.53^{Aa}	77.75±2.71^{Aa}	78.34±4.13^{Aa}
2	77.86±6.07^{Aa}	80.28±3.14^{Aa}	78.15±3.24^{Aa}
3	70.88±5.33^{Aa}	97.88±2.53^{Bb}	99.96±3.11^{Bb}
	TOTAL PROTEIN (mg/dl)		
1	7.17±0.14^{a}	7.23±0.16^{a}	7.16±0.18^{a}
2	7.10±0.18^{a}	6.54±0.14^{b}	6.30±0.15^{b}
3	7.00±0.18^{a}	7.14±0.14^{a}	7.28±0.12^{a}
	ALBUMIN (mg/dl)		
1	2.51±0.09	2.78±0.09	2.81±0.10
2	2.32±0.06	2.70±0.09	2.82±0.12
3	2.41±0.08	2.67±0.13	2.80±0.06
	GLOBULIN (mg/dl)		
1	4.66 ±0.097^{a}	4.85±0.089^{a}	4.76±0.082^{a}
2	4.78±0.097^{ab}	5.04±0.089^{b}	4.48±0.082^{a}
3	4.59±0.097^{a}	5.07±0.089^{a}	4.68±0.082^{a}
	A: G RATIO		
1	0.55± 0.017^{a}	0.58±0.02^{a}	0.60±0.018^{a}
2	0.49± 0.017^{a}	0.54±0.02^{a}	0.63±0.018^{b}
3	0.54± 0.017^{a}	0.54±0.02^{a}	0.61±0.018^{a}

Values presented are Mean± S.E.M. (n=10)

Values bearing dis-similar superscript in capital letters differ significantly within a column. Values bearing dis-similar superscript in small letters differ significantly within a row (Two-way ANOVA; Significance difference: $p \leq 0.05$).

and galactogogic properties. While, when cattle exposed to high temperature and humidity that cause a decrease in the numbers of leukocytes this indicates that heat stress makes the favorable condition to increase in TLC and unfavorable environment for the improvement of immune status and productivity of the lactating cattle (Zecchini *et al.* 2003, Zhang *et al.* 2004). A significant increase in the leukocytes and lymphocyte countin18 herbal mixture-supplemented lactating HF cows has also been observed similar to the present investigation. This increase in leukocyte and lymphocyte values indicates a moderate increase in the cellular and humoral immune response (Shan *et al.* 2018). Further, supplementation of polyherbal anti-stressor medicine to buffaloes was found to be responsible for an increase in the levels of TLC, eosinophil, and monocyte count (Sivajothi *et al.* 2018). The increase in the TLC values with minor changes is suggestive of individual variations in the immune system.

N. sativa oil in sheep caused down regulation of lymphocytes and granulocytes during the experimental period indicating that *N. sativa* has nutritive and immunoprotective effects (Abd El-Halim *et al.* 2014). The effectiveness of liver tonics silymarin and choline chloride against Aflatoxin B1-infected calves has been evaluated and both were found effective in decreasing the TLC, lymphocytes, neutrophils and monocytes. However, silymarin showed more ameliorating effects than choline chloride (Naseer *et al.* 2016).

The outcomes of the present study are consistent with earlier finding, where a supplementation diet with a polyherbal additive to the lambs had no significant effect on hematological indicators. This shows that the bioactive components present in polyherbal like hydrolysable tannins, flavonoids and essential oils do not have an adverse effect on the lamb's hemopoietic system and at normal supplemented levels have significant health benefits (Dorantes-Iturbide *et al.* 2022). Similarly, *shatavari* was supplemented to dairy crossbred cows did not show significant alteration in Hb or PCV, except for a significant increase in the TEC

Table 4. Effect of synthetic and polyherbal formulation on biochemicals (liver and renal function) in lactating cows.

Groups	0 DAY	30 DAY	60 DAY
	AST (U/L)		
1	82.30±7.44^{Aa}	85.20±5.96^{Aa}	86.40±5.47^{ABa}
2	81.40±5.58^{Aa}	84.20±4.90^{Aa}	94.30±3.57^{Ab}
3	85.60±9.25^{Aa}	87.50±5.22^{Aa}	82.10±5.66^{Ba}
	ALT (U/L)		
1	37.10±2.18^{Aa}	38.70±2.24^{Aa}	39.70±1.20^{Ba}
2	36.70±2.37^{Aa}	39.70±2.08^{Aa}	45.40±1.00^{Ab}
3	39.10±3.49^{Aa}	41.20±2.68^{Aa}	40.60±1.96^{Ba}
	ALP (U/L)		
1	68.40±5.16^{A}	70.60±7.57^{A}	71.20±6.90^{AB}
2	67.60±5.24^{A}	75.90±9.97^{A}	84.20±11.81^{A}
3	63.10±5.07^{A}	64.90±5.67^{A}	65.70±4.58^{B}
	GGT (U/L)		
1	6.24±0.33^{Aa}	6.74±0.44^{Ba}	6.44±0.46^{ABa}
2	6.20±0.45^{Aa}	6.96±0.43^{Bab}	7.44±0.62^{Ab}
3	5.78±0.41^{Aa}	5.46±0.29^{Aa}	5.60±0.56^{Ba}
	LDH (U/L)		
1	162.02±12.97^{Aa}	155.42±9.41^{Aa}	161.95±5.75^{Aa}
2	172.25±14.75^{Aa}	211.33±9.89^{Bb}	222.57±10.15^{Bb}
3	165.16±12.75^{Aa}	151.24±8.04^{Aa}	147.24±6.22^{Aa}
	BUN (mg/dl)		
1	13.00±0.83	12.70±0.79	12.40±1.28
2	11.80±0.63	12.70±0.62	12.90±0.50
3	11.00±0.54	11.30±0.59	12.10±0.92
	CREATNINE (mg/dl)		
1	1.01±0.06	0.99±0.06	1.00±0.06
2	1.05±0.07	1.09±0.06	0.95±0.04
3	0.99±0.04	1.00±0.04	0.94±0.05
	CK (U/L)		
1	18.17±1.71	17.85±1.68	19.43±2.91
2	19.19±3.48	20.19±2.58	18.28±1.21
3	19.54±2.70	18.38±1.91	17.25±1.36

Values presented are Mean± S.E.M. (n=10)

Values bearing dis-similar superscript in capital letters differ significantly within a column

Values bearing dis-similar superscript in small letters differ significantly within a row (Two- way ANOVA; Significance difference: $p \leq 0.05$).

Table 5. Effect of different treatments on lipid profile in lactating cows.

Group	0 DAY	30 DAY	60 DAY
	CHOLESTEROL (mg/dl)		
1	99.35±8.78^{a}	148.85±9.63^{b}	144.33±10.03^{b}
2	96.02±5.75^{a}	150.24±10.93^{b}	167.61±12.92^{b}
3	102.91±12.86^{a}	148.27±12.79^{b}	141.67±15.40^{b}
	LDL (mg/dl)		
1	71.38±6.68^{Aa}	64.99±4.04^{Aa}	68.87±3.35^{Aa}
2	70.74±6.88^{Aa}	64.32±1.50^{Aa}	64.98±4.50^{ABa}
3	83.30±8.85^{Aa}	62.11±1.72^{Aa}	59.12±1.84 ^{Ba}
	HDL (mg/dl)		
1	57.04±4.82^{Aa}	77.80±6.52^{Aa}	76.48±6.51^{Aa}
2	47.09±3.95^{Aa}	63.30±4.39^{Ba}	76.04±5.51^{Aa}
3	57.58±6.19^{Aa}	70.85±4.09^{ABa}	74.31±5.92^{Aa}
	TRIGLYCERIDES (mg/dl)		
1	49.18±1.87	50.25±1.16	49.47±1.00
2	48.45±0.86	49.08±1.02	48.39±0.73
3	51.29±2.28	47.91±0.65	49.06±1.15

Values are expressed as Mean ± S.E.M. (n=10)

Values bearing dis-similar superscript in capital letters differ significantly within a column Values bearing dis-similar superscript in small letters differ significantly within a row. (Two-way ANOVA; Significance difference: $p \leq 0.05$).

Table 6. Effect of the synthetic drug and polyherbal formulation on TNF-α, IL-1β and IFN-γ.

Group	0 DAY	30 DAY	60 DAY
	TNF-α (pg/ml)		
1	21.01± 1.00^{Aa}	22.69±0.87^{Aa}	21.03±1.21^{Aa}
2	22.69± 2.54^{Aa}	27.36± 1.67^{Bb}	23.28± 2.57^{Aab}
3	21.76± 1.40^{Aa}	25.34± 1.70^{ABa}	22.54± 1.83^{Aa}
	IL-1β (pg/ml)		
1	1583.84± 77.59	1463.75± 83.89	1383.62± 91.00
2	1544.55± 117.26	1428.55± 101.17	1314.18± 62.99
3	1482.56± 93.43	1317.52± 122.42	1237.75±102.76
	IFN-γ (pg/ml)		
1	19.32± 1.23^{A}	21.01± 1.53^{A}	19.57± 0.81^{A}
2	18.95± 0.93^{A}	19.77± 0.90^{AB}	18.84± 1.02^{AB}
3	18.68± 1.13^{A}	17.75± 0.97^{B}	17.67± 1.04^{B}

Values are expressed as Mean ± S.E.M. (n=10)

Values bearing dis-similar superscript in capital letters differ significantly within a column Values bearing dis-similar superscript in small letters differ significantly within a row. (Two-way ANOVA; Significance difference: $p \leq 0.05$).

(Mishra 2008). Feeding *Lepidium sativum* and *Dioscorea bulbifera* in 1:1 ratio in early lactating cows for 14 days also showed improvement in Hb content. A significant increase in the Hb level and erythrocyte count in animals when fed with *Nigella sativa* seeds, oils and chamomile flowers has been reported. This favourable effect might be due to the main constituents present in these medicinal plants, particularly, the immunostimulant effect of essential oils. Moreover, chamomile has broad-spectrum antibacterial activity due to the presence of secondary metabolites terpenoids, flavonoids (Sanghai *et al.* 2017, El- Ghousein 2010, Abd El-Halim *et al.* 2014). Further, black seed or ginger fine powder feeding to the milking crossbred ewes for the long term after parturition maintained Hb, MCV, PCV, MCH or MCHC values, but increased the TEC values. This positive effect of medicinal plants is related to the presence of folic acid, iron and vitamin C; which are blood-forming factors that stimulate blood production in the bone marrow and improve the immune response in farm animals (Hendawy *et al.* 2019).

Serum biochemical parameters are key indicators of the physiological status in animals, including body or tissue health status and nutrient metabolism. In this study, a change in both calcium and phosphorus levels was

noticed within the group and between the groups at all time intervals although high calcium and low phosphorus was seen in the treatment groups (Table 3). Similarly, it has been reported that daily feeding of herbal supplements including *Lipidium sativum* and *Asparagus racemosus* to hypogalactic buffaloes for short term resulted in small increase in the level of mean serum calcium and phosphorus (Sharma *et al.* 2017). This could be due to the supplementation of mineral mixture in the diet along with the herbal preparations. Further, addition of herbal galactagogues (*Lipidium sativum, Trigonell afoenum* and *Asparagus racemosus)* routinely in animal diet led to a notable increase in calcium levels with non-significant increase in phosphorus levels reported (Roy *et al.* 2013). Feeding of herbal root powder to lactating crossbred cows in routine diet had a hypercalcaemic as well as hyper-phosphorusemic effects (Behera *et al.* 2013). Increase in plasma calcium level could be due to increase in the demand of body and release of calcium from reserve pool of the body such as bones and intracellular reserve into blood plasma to fulfil the body demand.

In the present study, the polyherbal formulation showed glucogenic characteristics. The findings are consistent with earlier works, which reported a significant elevation in the glucose level of milking buffaloes after supplemention with medicinal plant seeds (Fenugreek, Caraway, Black seed and *Lepidium sativum*) to their basic diet (El-nor *et al.* 2007). These plants have positive effect on digestibility and nutrient utilization. Fenugreek seeds contain saponins which stimulate anaerobic fermentation of organic matter that improve efficiency of utilization of nutrients. There are reports on increase in serum glucose levels with feeding of essential oils of medicinal plant (cinnamon, ginger and garlic oil) to the lactating goats (Kholif *et al.* 2012). The essential oils affect rumen fermentation which improve nutrient utilization by enhancing rumen propionate production which is the precursor for the biosynthesis of glucose in ruminants. These oils help in reducing methane gas emission thereby enhancing milk production and milk protein of lactating animals. Elevated glucose level helps in the synthesis of protein and lipids and their precursor for ascorbic acid production (Padayatty *et al.* 2003). When *Asparagus racemosus* supplemented to lactating Murrah buffaloes caused a change in plasma glucose levels during the treatment period to a better body condition score (>4.5). Balanced feeding might be responsible for a positive influence on propionate production in the rumen through an improvement of ruminal microflora (Singh *et al.* 2012). The results of the present study are supported by Kholif *et al.* (2012). Administration of essential oils of plants (garlic, cinnamon and ginger oils) to the lactating goats increases serum albumin, globulin values and A:G ratio, while decreasing the globulin levels. Feeding black seed oil to dairy buffaloes significantly increases the levels of albumin and total protein as compared to the control animals (Khattab *et al.* 2011). This could be attributed to the essential oils of different plants which improve ruminal microbial protein synthesis, and modulate ruminal fermentation to enhance nutrient utilization.

The absence of any substantial change in enzymes in herbal galactagogue treatment group implies that the polyherbal formulation did not cause hepatic damage or any other adverse effect. The level of enzymatic activity was prominent in synthetic galactagogue treatment group indicating long term supplementation has negative health impact. It has been previously shown that feeding *Asparagus racemosus* (Agrawal *et al.* 2008, Chawla *et al.* 2011, Selvaraj *et al.* 2019), *Allium sativum* (Pal *et al.* 2006, Rana *et al.* 2011), *Zingiber officinale* (Bhandari *et al.* 2003, Haniadka *et al.* 2013), *Cuminum cyminum* (Abbas *et al.* 2017) to the animals have hepatoprotective effect. Presence of these ingredients in poly- formulation will certainly assist in better digestion and hepatic function.

Biomarkers level such as BUN, Creatinine and CK lies within normal range indicated that the polyherbal formulation had no negative impact on the vital organs or tissues. Moreover, these plants materials help to maintaining and improvement of kidney function. Similar nephroprotective and hepatoprotective effects of polyherbal preparation (*Kamilari*) in animals have been reported (Rajesh and Latha 2004). Supplementation of polyherbal formulation has also reduced the AST, ALT and ALP enzymes activity altered by carbon tetrachloride (Rajesh and Latha 2004). They might responsible for the stabilizing the plasma membrane and hepatic repair. The anti-inflammatory potential of herbal formulation is reflected through low serum transaminases and hepatic parenchyma and regeneration of hepatocytes. Further, no change in the blood urea, ALP and AST activity with the treatment of plant seeds (fenugreek, caraway, black seed and *Lepidium sativum*) in dairy buffaloes has been reported (El-nor *et al.* 2007). This reflects an improvement occurred in the metabolic process with the addition of plants to animal ration. A decrease in serum ALT, AST and CK activity at calving after peri-parturient crossbred cows were given herbal combination (*Astragalus membranaceus)* in their routine diet had protected the liver from damage and fibrosis, reduced inflammation and improved immunity (Ran *et al.* 2022). This provides evidence of hepato-protective and immunity-improving potential of herbal plants.

It has been cleared from experimentation, that herbal medicines control the secretion of various cytokines. The presence of *Cinnamomum cassia*, *Echinacea purpurea* and *Zingiber officinale* might have increased the IL-1β level, while, *Curcuma longa* and *Allium sativum* decreased IL-1β. Similarly, *Allium sativum*, *Curcuma longa*, and *Tinospora cordifolia* plausibly decreased TNF-α level, while, *Asparagus racemosus*, *Picrorhiza kurroa* increased TNF-α level. *Allium sativum* alone have been earlier reposted to decrease the IFN-γ level while *Emblica officinalis* and *Withania somnifera* have increased IFN-γ (Spelman *et al.* 2006). Further, decreased IL-1β levels in lactating buffaloes has been noticed when fed Chinese herbal medicines (CHMs), which contained 18 different

herbs (Shan *et al.* 2018). This inhibitory response of CHMs on IL-1β levels might have a significant role in mediating immune-related diseases. When animals suffered from acute or chronic inflammation or pathogen challenges, relatively higher concentrations of IFN-γ a secreted into the blood. Supplementing Holstein dairy heifers with herbal formulations caused a decline in serum IFN-γ levels, indicating that herbal diets have the capability to improve and modify the immunity and physiological status of dairy heifers has been reported (Qiao *et al.* 2013). Indian medicinal plants like *Actinidia macrosperma, Allium sativum,* Aloe vera gel*, Asparagus racemosus, Azadirachta indica, Emblica officinalis* and *Curcuma longa* having immunostimulatory activity which can be used to cure various ailments and could also enhance body resistance against infections (Kumar *et al.* 2011). Adding herbs to the diet reduced the circulating IFN-γ in different species such as chicks, hens, piglets or dairy cows indicating good immunity status and relatively higher productive performance (Chen *et al.* 2003, Ma *et al.* 2004, Zhang *et al.* 2004). In the present investigation feeding of polyherbal to the HF dairy cows maintained the animal was in healthy condition and plant material itself did not have a negative impact on animal health.

Cholesterol concentrations are generally lower in the early stages of lactation and subsequently increase throughout lactation, along with intensive steroid synthesis (Ling *et al.* 2003). This indicates that there is a positive correlation between fertility parameters and cholesterol levels during different stages of gestation and lactation. Supplementing black seed oil to the lactating buffaloes had earlier resulted in decrease in plasma cholesterol when compared to normal animals (Khattab *et al.* 2011). The high levels of unsaturated fatty acids naturally present in black seeds, which promote the excretion of cholesterol into the intestine, allowing it to be oxidized to bile acids. A significantly lower triglyceride, total cholesterol and LDL levels have been reported in the animals supplemented with herbs *Plantago lanceolata* and/or garlic leaf. Iridoid glycosides prevent and improve abnormal glycolipid metabolism by reducing oxidative stress and the formation of advanced glycation end products, which are possibly related to the lower triglyceride and total cholesterol levels in the herbal diet groups (Redoy *et al.* 2020). Similarly, allicin in garlic leaves reduce the availability of 3-hydroxy-methylglutaryl concentration and this might be a contributory factor for the decreasing serum cholesterol concentration in the garlic leaf diet group.

Findings of the present investigation indicate that the polyherbal formulation which contained 13 medicinal plant materials and is being recommended as galactagogue or milk augmentation in livestock by CCRAS has many favorable effects on the dairy cows. It does not have any adverse or toxic effect as it did not cause appreciable changes in hematological and biochemicals indicators. Moreover, the formulation has overall positive impact on the immune status and animal performance to tolerate against stress during course of feeding period. To conculde, the present study suggests that Ayush-13 polyherbal formulation is safe and can be used as a galactagogue for augmentation of milk production in animals.

ACKNOWLEDGMENT

The financial assistance provided by Central Council for Research in Ayurvedic Sciences, Ministry of Ayush, Government of India, New Delhi (India) in the form of research grant (F.No.3-53/2019-CCRAS/Admin./IMR/6096) is gratefully acknowledged. The authors are thankful to the Director of Research, Dean PGs and Director of Livestock Farm, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana for all the help to carry out this work. Further, I would like to thank the Head of the Department of Veterinary Pharmacology and Toxicology for providing time-to-time help during the course of study.

CONFLICT OF INTEREST

The authors declare that there are no potential conflicts of interest with respect to the research, authorship and /or publication of this article.

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