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Effect of Forskolin from Coleus Forskohlii (Colegex®) on Diet-Induced Obesity in Mice and Weight Management by Reducing Adipogenesis: An In Vivo Study

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ABSTRACT:

Obesity and overweight have posed a serious threat to humanity, requiring urgent efforts to establish secure and efficient therapeutic methods. Additionally, it is a metabolic condition that represents a risk to life and calls for the rapid development of effective and secure treatment. There are now only a limited number of such therapy options accessible for obesity. The present study evaluated the anti-obesity effects of Coleus forskohlii also known as Colegex® in high-fat diet -induced obese mice. Five groups of six mice each were divided from the 30 C57 black male mice. Group I was provided with a normal control and received 0.5% CMC, while Group II was given a high-fat diet condition and received 0.5% CMC as well. Rosuvastatin, 10 mg/kg b.w. was received by Group III as a reference standard. Colegex® was given to Group IV at a low dose, 205.41 mg/kg b.w. and to Group V at a high dose, 308.25 mg/kg b.w. daily with HFD for 28 days. Body weight and food intake were measured during the study period. On the 29th day of the study period, biochemical analyses, including lipid profile tests, renal function tests, and liver function tests, were evaluated. The results of this study clearly proved that Colegex® treatments effectively reduced the accumulation of adipose tissue and lowered blood cholesterol, triglycerides, and LDL levels while elevating HDL levels in HFD-induced obese mice. Therefore, this study suggests that it may be useful in reducing obesity.

KEYWORDS: : Coleus forskohlii, Colegex®, HFD-induced, Rosuvastatin, Body weight, food intake, biochemical analyses, Weight Management.

INTRODUCTION

Currently, obesity is the biggest public health issue, with 600 million of the world's 1.9 billion adults (18 years and older) being clinically obese [1]. Adipose cell size increases associated with obesity are correlated with the quantity of fat that has accumulated in the cytoplasm of adipocytes [2]. Fatty acid synthase, lipoprotein lipase, and adipocyte fatty acid-binding protein are a few of the enzymes that control this alteration in the adipocytes' metabolism [3]. In the developed world, obesity is a persistent problem since it raises the risk of chronic illnesses including diabetes mellitus and cardiovascular disease. Weight-loss dietary supplements are frequently used to treat obesity without sufficient clinical support [4]. Herbal supplements are becoming more popular among dietary supplements [5] and are occasionally seen as safe because they are "natural" form. However, new research suggests that herbal products, particularly those used for weight loss, can result in adverse reactions such significant hepatic failure [6]. The primary risk factor for type 2 diabetes is obesity or being overweight. A common strategy for preventing excessive weight gain is the use of allopathic and pharmaceutical medications [7]. While these medications are often effective, substantial unpleasant side effects may limit their overall utility [8, 9]. The growing popularity of medicinal herbal supplements is a result of their success in treating a variety of chronic diseases. In comparison to many chemically manufactured

medications, they are less expensive and have fewer or no hazardous side effects [10]. Accordingly, recent preliminary findings suggested that natural compounds with a lower risk of producing severe toxicity and herbs with a long history of use may be beneficial in lowering hunger and stimulating significant weight reduction [11]. Therefore, there is a critical unmet need for alternate methods to prevent obesity and limit weight gain.

Coleus forskohlii (CF), often known as Coleus in English, is a medicinal herb with a wide range of ethnopharmacological uses. Additionally, C. forskohlii is utilized in Ayurvedic medicine to treat a number of diseases and conditions, such as inflammatory conditions, hypertension, respiratory issues, aging, and weight control [12, 13]. Terpenoids, flavonoids, and alkaloids are among the abundant secondary metabolites found in C. forskohlii [14]. Forskolin, a labdane diterpene with therapeutic significance due to its capacity to promote weight loss, is the main bioactive component of C. forskohlii root. The only species that has been found to have large amounts of forskolin is C. forskohlii [15]. Despite hormone-wise stimulating adenylate cyclase (AC), forskolin works by increasing the build-up of cyclic adenosine monophosphate (cAMP). Lipolysis occurs when protein kinase A (PKA) is bound by cAMP and made active. PKA then phosphorylates the lipases it has activated, causing them to become effective. Given this forskolin's method of action, the extract of C. forskohlii is believed to have an anti-obesity effect, which has been shown in certain preclinical trials [16–19]. C. forskohlii standardized to contain 10–20% forskolin is widely accessible as a dietary supplement, despite the absence of convincing evidence from human research regarding its weight-reduction effect.

Therefore, it was shown that forskolin from the plant C. forskohlii improved body weight, lipid metabolism, and hormone levels linked to obesity in mice fed a high-fat diet (HFD). These unique characteristics of forskolin indicate that they could work as a strong anti-obesity agent to reduce excessive body fat formation and enhance blood lipid profiles by improving lipolysis activity in conjunction with the increased breakdown of fatty acid accumulation. Based on this observation, the current investigation was conducted to see if C. forskohlii (Colegex®) would have more inhibitory effect on body weight gain and serum lipoprotein levels in an obese mouse model caused by HFD compared to the standard. To the best of our knowledge, this is the first study to use an obese mouse model caused by an HFD to examine the synergistic anti-obesity benefits of C. forskohlii (Colegex®).

MATERIALS AND METHODS

Preparation of *C. forskohlii* extract:

C. forskohlii (Colegex®) is a standardized extract manufactured and registered by Ingex Botanicals Pvt. Ltd., Nelamangala, Bangalore, Karnataka, India.

Experimental animals:

30 C57 Black male mice (18–23 g) were divided into five groups, and each group consisted of six animals. They were taken from the animal house of Radiant Research Services Pvt. Ltd. in Karnataka, India. Animal experiments were carried out in accordance with CPCSEA Registration Number 1803/PO/RcBi/S/2015/CPCSEA's rules and regulations for controlling and supervising research studies on animals. Picric acid was used to mark each animal, and a unique number was given to each one. The animal was housed in a standard stainless steel cage with access to regular food and water in bottles. Water was provided *ad libitum* by Aqua Guard on service. Animals have constant access to clean, drinkable water that isn't contaminated. They were maintained in these cages under standard laboratory conditions, including a temperature of 22±3°C, a relative humidity range of 30–70%, and a cycle of 12 hours of light and 12 hours of darkness. Under the guidance of qualified professionals, every procedure involving animals was carried out in an ethical way. Before the study was permitted to begin, the Institutional Animal Ethical Committee (IAEC) of Radiant Research Services Pvt. Ltd. reviewed and authorized the research protocol.

Experimental methods:

Total 30 C57 Black male mice were divided into five groups, and each group consists of six animals. The administration of a high-fat diet was carried out for 30 days to all groups except the normal control group. Animals received respective assigned treatment along with a high-fat diet (HFD) daily for 28 days after induction. Group I was served as a normal control treated with 0.5% CMC, and Group II was served as a high-fat diet control and received 0.5% CMC along with the high-fat diet. Group III received Rosuvastatin (10 mg/kg body weight) as the reference standard along with high fat diet. Group IV received a low dose of *C. forskohlii* (Colegex®) (205.41 mg/kg b.w.), and Group V received a high dose of *C. forskohlii* (Colegex®) (308.25 mg/kg b.w.) daily along with HFD for 28 days. Thus all groups, with the exception of the normal control group, also received a high-fat diet for 28

days. Body weight was measured at the beginning of the trial, once a week after that, and on the day of sacrifice. The amount of food consumed was measured by difference before being given to the cage, and the remaining portions which were measured on the next day. On the 29th day, which marked the end of the experiment, animals that had been fasting the night before but had been given access to water were given a mild isoflurane anesthetic before having their blood drawn into 0.5-ml tubes using a retro-orbital puncture. The serum was separated using cold centrifugation (4°C) of the vials for 10 min at 4000 rpm for biochemical analysis such as lipid profile tests, renal function tests, and liver function tests. Animals were then decapitated and slaughtered, and the liver, heart, and adipose tissues were removed and collected for weight measurement.

Statistical analysis:

Mean±sem was used to express the values. One-way anova and the Dunnet test were used to determine the significance of the *in vivo* data. The criteria for significant data was $P < 0.05$.

RESULTS

Effect of *C. forskohlii* (Colegex®) on Mice Body Weight

The effect of *C. forskohlii* (Colegex®) on the body weight of mice under diet-induced obesity is shown in Table 1 and Figure 1. The results of this study revealed that significant difference in body weight was found during the experimental period among the groups observed with the administration of *C. forskohlii* (Colegex®) at four weeks.

Effect of *C. forskohlii* on Mice Feed Consumption

The feed intake of *C. forskohlii C. forskohlii* (Colegex®) from normal and treated mice is presented in Table 2 and Figure 2.

Effect of *C. forskohlii* on Lipid Profile

C. forskohlii (Colegex®) administration caused a significant effect on serum lipid parameters in the high-fat diet mice model (Table 3 and Figure 3).

Effect of *C. forskohlii* (Colegex®) on Liver Function Test in Mice

The liver function test of *C. forskohlii* (Colegex®) in mice showed remarkable changes among the liver marker enzymes such as bilirubin, albumin, protein, ALP, SGOT, and SGPT in all the treatment groups (Table 4 and Figure 4).

Effect of *C. forskohlii* on Renal Function Test

The renal functions of *C. forskohlii* (Colegex®) in normal and treated mice are shown in Table 5 and Figure 5. There are no remarkable changes in blood urea and serum creatinine values in all the groups.

Effect of *C. forskohlii* (Colegex®) on Organ Weight

There was significant difference between the organ weights of the liver, heart, epididymal adipose, and subcutaneous adipose of the high-fat diet and other experimental groups. Organ weights were significantly reduced in all the treatment groups when compared with high fat control group.

Table 1: Effect of *C. forskohlii* (Colegex®) on Mice Body Weight

Body Weight (g)						
Group	**Treatment**	**Basal**	**Week 01**	**Week 02**	**Week 03**	**Week 04**
Group I	Normal Control	25.75±0.44***	26.92±0.46***	27.72±0.43***	28.43±0.31***	28.90±0.18***
Group II	High Fat Diet Control	33.63±0.81	36.80±0.77	39.75±0.80	42.92±0.66	46.18±0.79
Group III	Reference Standard (Rosuvastatin 10 mg/kg b.w)	33.70±0.41	35.67±0.43	37.53±0.46*	38.90±0.41***	40.35±0.33***
Group IV	*C. forskohlii* (Colegex®) Low dose (205.41 mg/kg b.w)	33.73±0.34	36.45±0.28	38.97±0.17	41.18±0.42*	43.88±0.33**
Group V	*C. forskohlii* (Colegex®) High dose (308.25 mg/kg b.w)	33.70±0.30	36.28±0.23	38.27±0.35	40.22±0.36**	42.02±0.36***

Values were expressed as mean ± SEM (n = 6), Statistical significances are compared between HFD control (Group II) versus other treatment groups (GI, GIII, GIV and GV) (* P Value < 0.05; ** P Value < 0.001 and *** P Value < 0.0001).

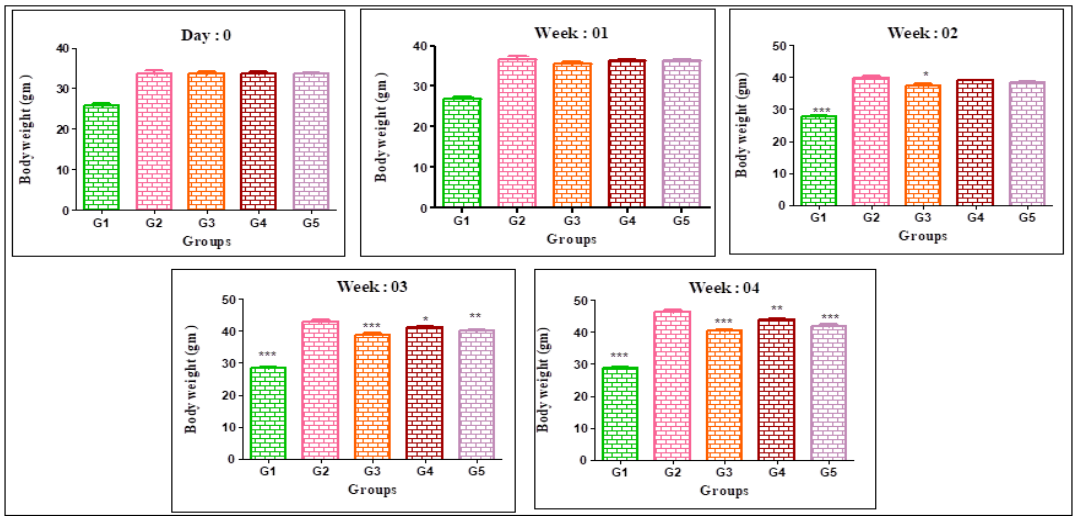

Figure 1: Effect of *C. forskohlii C. forskohlii* (Colegex®) on Mice Body Weight

Table 2: Effect of *C. forskohlii* (Colegex®) on Mice Feed Consumption

Feed Consumption (gm)

Groups	Treatment	Week 01	Week 02	Week 03	Week 04
Group I	Normal Control	15.33±0.27***	15.64±0.17***	16.01±0.16***	16.64±0.19***
Group II	High Fat Diet Control	12.61±0.15	12.99±0.11	13.17±0.07	13.74±0.17
Group III	Reference Standard (Rosuvastatin 10 mg/kg b.w)	12.70±0.13	13.29±0.12	13.44±0.16	14.14±0.15
Group IV	*C. forskohlii* (Colegex®) Low dose (205.41 mg/kg b.w)	12.63±0.09	13.11±0.12	13.29±0.11	14.01±0.14
Group V	*C. forskohlii* (Colegex®) High dose (308.25 mg/kg b.w)	12.66±0.10	13.20±0.10	13.39±0.11	14.07±0.08

Values were expressed as mean ± SEM (n = 6), Statistical significances are compared between HFD control (Group II) versus other treatment groups (GI, GIII, GIV and GV) (* P Value < 0.05; ** P Value < 0.001; *** P Value < 0.0001)

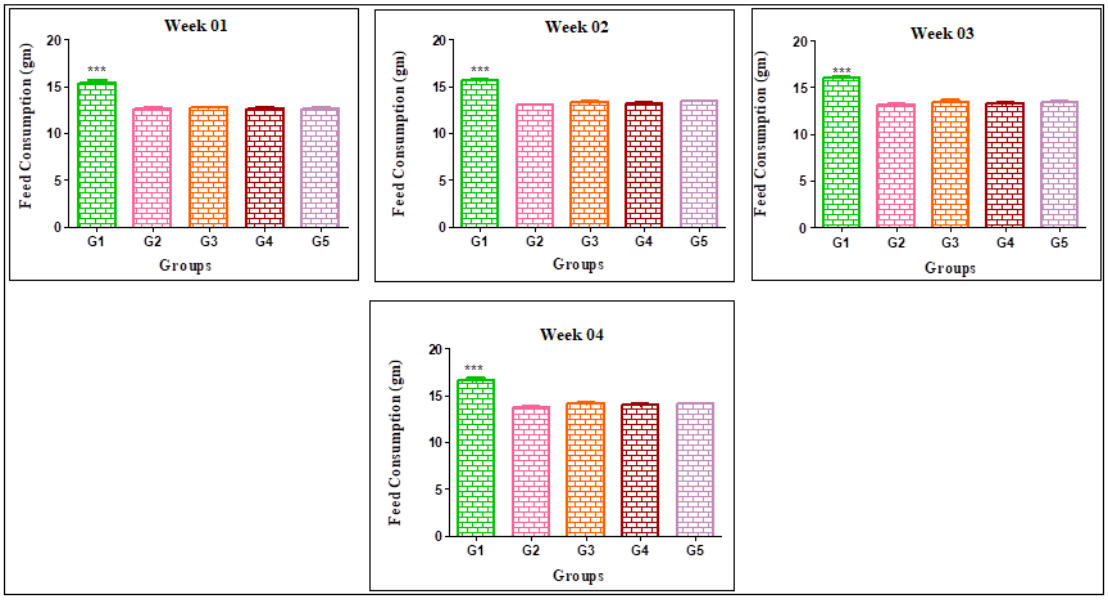

Figure 2: Effect of *C. forskohlii* (Colegex®) on Feed Consumption in Mice

Table 3: Effect of *C. forskohlii* (Colegex®) on Lipid Profile

		Lipid Profile Test (mg/dl)				
Group	**Treatment**	**Cholesterol**	**Triglycerides**	**HDL**	**LDL**	**VLDL**
Group I	Normal Control	79.17±1.01 ***	93.33±1.58 ***	33.50±0.67 ***	42.00±1.06 ***	18.67±0.32 ***
Group II	High Fat Diet Control	165.67±3.13	188.33±2.97	16.33±0.49	86.33±1.91	37.67±0.59
Group III	Reference Standard (Rosuvastatin 10 mg/kg b.w)	114.67±2.58 ***	125.17±3.18 ***	29.50±0.56 ***	63.17±2.24 ***	25.03±0.64 ***
Group IV	*C. forskohlii* (Colegex®) Low dose (205.41 mg/kg b.w)	147.50±2.03 ***	160.67±3.63 ***	23.33±0.95 ***	78.17±1.38 ***	32.13±0.73 ***
Group V	*C. forskohlii* (Colegex®) High dose (308.25 mg/kg b.w)	139.33±1.52 ***	149.67±3.27 ***	24.04±0.39 ***	70.33±0.99 ***	29.93±0.65 ***

Values were expressed as mean ± SEM (n = 6), Statistical significances are compared between HFD control (Group II) versus other treatment groups (GI, GIII, GIV and GV) (* P Value < 0.05; ** P Value < 0.001; *** P Value < 0.0001).

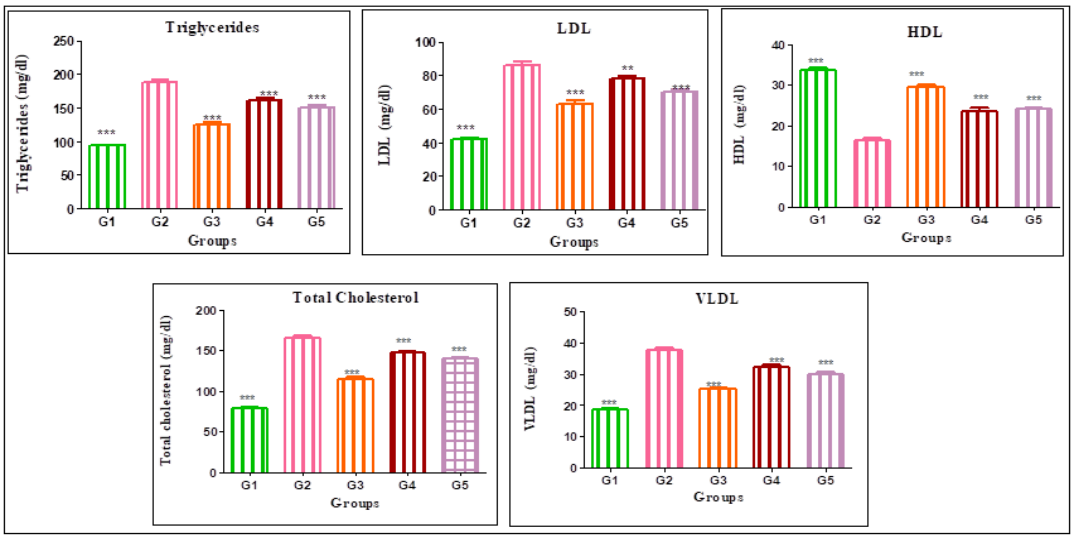

Figure 3: Effect of *C. forskohlii* (Colegex®) on Lipid Profile Test in Mice

Table 4: Effect of *C. forskohlii* (Colegex®) on Liver Function Test

		Liver Function Test					
Group	**Treatment**	**Bilirubin (mg/dl)**	**Albumin (gm/dl)**	**Protein (gm/dl)**	**ALP (IU/L)**	**SGOT (IU/L)**	**SGPT (IU/L)**
Group I	Normal Control	0.49 ±0.03	4.52 ±0.19	6.40 ±0.19	88.67 ±2.53***	30.83 ±1.40	20.17 ±0.60
Group II	High Fat Diet Control	0.55±0.02	4.48±0.22	6.53±0.10	182.17±2.52	60.50±2.20	30.33±0.84
Group III	Reference Standard (Rosuvastatin 10 mg/kg b.w)	0.50 ±0.03	4.50 ±0.16	6.45 ±0.11	126.50 ±2.23***	43.92 ±1.59***	23.50 ±0.72***
Group IV	*C. forskohlii* (Colegex®) Low dose (205.41 mg/kg b.w)	0.52 ±0.02	4.60 ±0.15	6.43 ±0.10	149.50 ±2.85***	51.50 ±1.06**	26.67 ±0.88***
Group V	*C. forskohlii* (Colegex®) High dose (308.25 mg/kg b.w)	0.51±0.03	4.53 ±0.16	6.35 ±0.28	139.67 ±2.69***	49.50 ±1.61***	24.17 ±0.60***

Values were expressed as mean ± SEM (n = 6), Statistical significances are compared between HFD control (Group II) versus other treatment groups (GI, GIII, GIV and GV) (* P Value < 0.05; ** P Value < 0.001; *** P Value < 0.0001).

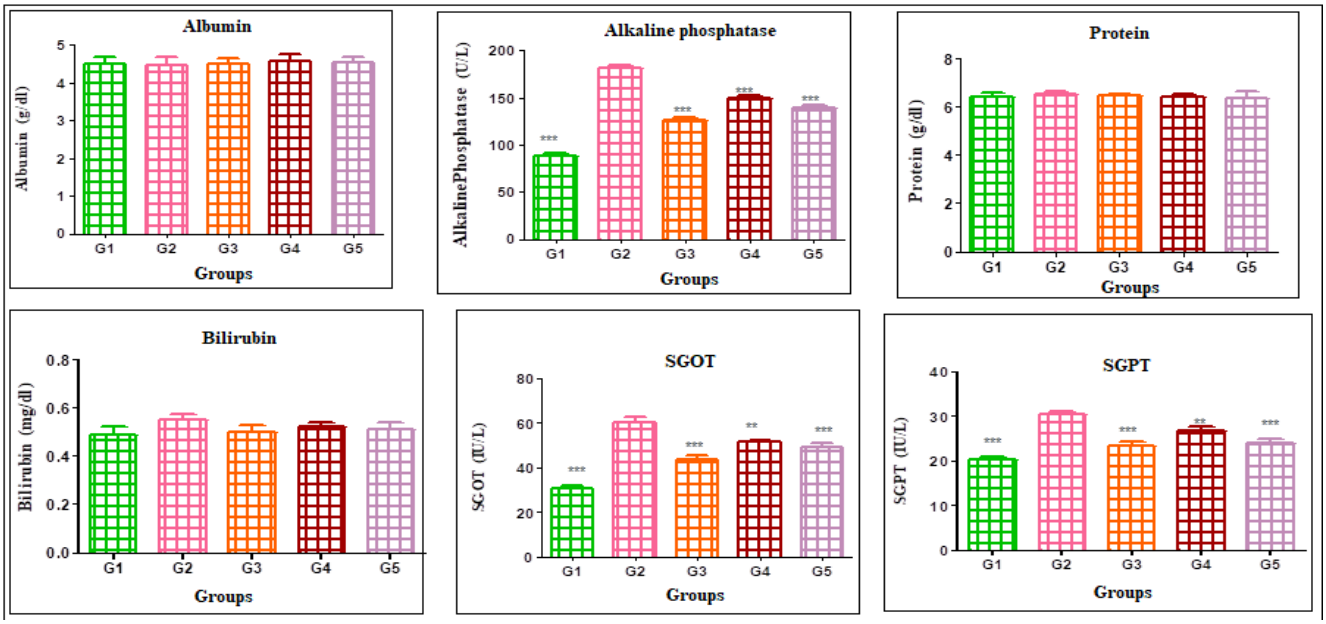

Figure 4: Effect of *C. forskohlii* on Liver Function Test in Mice

Table 5: Effect of *C. forskohlii* (Colegex®) on Renal Function Test

Renal Function Test (mg/dl)			
Group	**Treatment**	**B.Urea**	**S. Creatinine**
Group I	Normal Control	30.00±1.18	0.80±0.04
Group II	High Fat Diet Control	32.67±0.56	0.87±0.03
Group III	Reference Standard (Rosuvastatin 10 mg/kg b.w)	31.67±0.71	0.85±0.04
Group IV	*C. forskohlii* Low dose (205.41 mg/kg b.w)	32.50±0.67	0.83±0.04
Group V	*C. forskohlii* High dose (308.25 mg/kg b.w)	32.00±0.37	0.85±0.02

Values were expressed as mean ± SEM (n = 6), Statistical significances are compared between HFD control (Group II) versus other treatment groups (GI, GIII, GIV and GV) (* P Value < 0.05; ** P Value < 0.001; *** P Value < 0.0001).

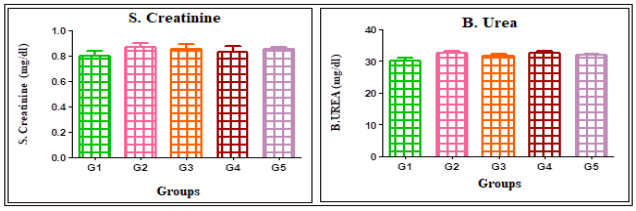

Figure 5: Effect of *C. forskohlii* (Colegex®) on Renal Function Test in Mice

Table 6: Effect of *C. forskohlii* (Colegex®) on Organ Weight

Organ Weight (mg)					
Group	**Treatment**	**Liver**	**Heart**	**Epididymal Adipose**	**Subcutaneous adipose**
Group I	Normal Control	1613.17±25.83***	160.17±4.66***	384.33±1.58***	431.67±3.12***
Group II	High Fat Diet Control	2374.83±35.99	186.67±1.26	832.33±14.17	922.00±11.28***
Group III	Reference Standard (Rosuvastatin 10 mg/kg b.w)	1892.67±55.70***	171.83±1.47**	633.50±7.59***	696.17±11.73***
Group IV	*C. forskohlii* (Colegex®) Low dose (205.41 mg/kg b.w)	2032.00±33.57***	176.17±2.36*	726.83±8.18***	807.50±11.47***
Group V	*C. forskohlii* (Colegex®) High dose (308.25 mg/kg b.w)	1937.00±23.33***	174.33±1.41**	694.83±6.10***	765.50±13.78***

Values were expressed as mean ± SEM (n = 6), Statistical significances are compared between HFD control (Group II) versus other treatment groups (GI, GIII, GIV and GV) (* P Value < 0.05; ** P Value < 0.001; *** P Value < 0.0001).

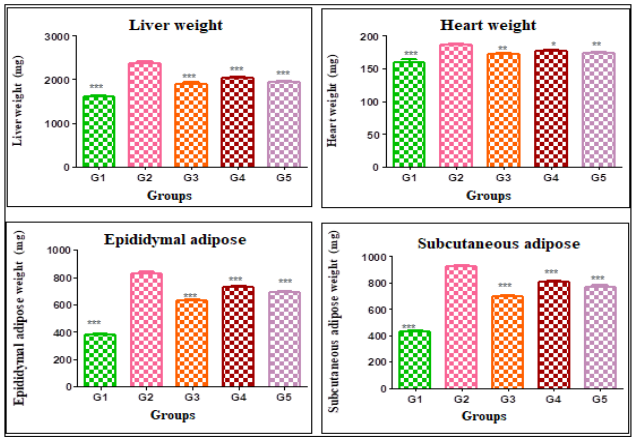

Figure 6: Effect of *C. forskohlii* (Colegex®) on Organ Weight in Mice

DISCUSSION

Coleus forskohlii extract, a common herbal extract in weight-loss products, is believed to help in weight management due to the activity of forskolin, which increases lipolysis and fat loss by activating adenylate cyclase [20]. Among the well-known methods to combat obesity are lifestyle and behavioral modification, drugs, and surgical intervention. Only marginal weight loss can be achieved by a high obese individual with lifestyle and behavioral therapy, greater physical activity, and a high-quality diet with fewer calories. Additionally, numerous studies [21-24] raised the question of the effectiveness of diet and exercise treatments in lowering the burden of obesity and associated diseases. By lowering glucose, triglycerides, and cholesterol while regulating the total lipid profile, *C. forskohlii* (Colegex®) was discovered to offer considerable weight-reduction benefits. Due to its similarity to obese human beings, the high-fat diet-induced obesity model in mice is regarded as an effective tool for studying human obesity. This study assessed the anti-obesity effect of *C. forskohlii* (Colegex®) in a mouse model by tracking body weight, food intake, lipid excretion, a number of biochemical indicators associated with obesity, a renal function test, a liver function test, and relative organ weight.

The purpose of the current study was to examine the impact of weight loss on mice that became obese due to a high-fat diet. Significant differences in body weight and changes in body weight due to dietary intake were noticed in treated animals, and a slight reduction in nutritional intake was observed in the experimental group. When compared to the high-fat diet control group, there was a discernible decrease in body weight in each group. Compared to the high-fat diet control group, the mice's feed consumption was not significantly different between the *C. forskohlii* (Colegex®) treated groups. However, compared to the high-fat diet control group, the normal control group showed a considerable increase in feed consumption.

As compared with the High Fat Diet Control group, all of the groups' levels of biochemical markers such as cholesterol, triglycerides, LDL, and VLDL were substantially lower, according to the Lipid Profile Test. So compared with those in the high-fat diet control group, the HDL level in the overall group was considerably higher. In addition to the high-fat diet control group, all the groups' levels of the biochemical markers SGOT, SGPT, and alkaline phosphatase were significantly lower. When compared to the high-fat diet control group, the levels of protein, albumin, and bilirubin did not significantly change in any of the groups. Especially compared to the High Fat Diet Control group, the renal function parameters of B. urea and S. creatinine levels in *C. forskohlii* (Colegex®) were not significantly different. Our investigation's findings support this, as shown by the fact that *C. forskohlii* (Colegex®) medication suppresses the growth of visceral adipose tissue (epididymal and subcutaneous). In addition, the weight of the mice's organs, including their liver, heart, epididymal adipose tissue, and subcutaneous adipose tissue, significantly decreased across the entire spectrum as compared to the high-fat diet control group.

CONCLUSION

In Ayurveda, a number of herbs are mentioned as aids in controlling obesity. However, there hasn't been any attempt at a comprehensive, well-planned screening to find a successful herbal weight loss supplement. Therefore, the current study directly shows that Colegex® administration effectively lowers the build-up of adipose tissue, lowers blood cholesterol, triglycerides, and LDL, and raises HDL levels in HFD-induced obese mice. The liver profile and organ weight are also seen normalizing. Therefore, Colegex® has the ability to cause weight loss in HFD-induced obese mice. The results of this study provide a solid foundation for further research into Colegex®, a natural product source with the potential to be transformed into pharmaceutical ingredients for the prevention and treatment of obesity and other metabolic conditions in humans. However, these formulations can be recognized as a potentially safe and successful intervention for the management of obesity.

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