INTERNATIONAL JOURNAL OF PHARMACOLOGY AND THERAPEUTICS
ISSN 2249 – 6467

RESEARCH ARTICLE

ANTI-OBESITY POTENTIAL OF PGE_2 ANALOGUE MISOPROSTOL AND PG SYNTHESIS INHIBITOR INDOMETHACIN ON HIGH FAT DIET INDUCED OBESITY IN WISTAR RATS.

Anurag Pandey*, Amit Goyal, Upendra K. Jain, Kuldeep K. Sharma

Department of Pharmacology & Drug Research, Chandigarh college of Pharmacy, Landran, Mohali (Punjab) 140307, India.

Correspondence author: Anurag Pandey

ABSTRACT

The present study was undertaken to investigate the anti-obesity potential of PGE_2 analogue Misoprostol and PG synthesis inhibitor Indomethacin in HFD induced obesity in Wistar rats. Experimental obesity was induced by feeding rats with HFD for 10 weeks. HFD treatment caused significant increase in body weight, body mass index, Lee index; weight of different fat depots, serum glucose, cholesterol, TG, LDL, VLDL, feed intake (Kcal) and decrease in serum HDL and feed intake (gm) in HFD control group which were assessed as an index of obesity. Enzymatic kits and physical parameters had been used for the measurement of investigation. Misoprostol (100 and 200 mcg/kg; *p.o.*) and Indomethacin (20 mg/kg; *p.o.*) were used as the test drugs. The end of the study had shown the pharmacological beneficial effects of Misoprostol and Indomethacin on obesity induced in wistar rats.

Keywords: PGE_2, mPGES-1, HFD, Misoprostol, Obesity, Indomethacin.

INTRODUCTION:

Obesity is a complex metabolic disorder characterized by an excessive accumulation of fat in the body to an extent which adversely affects the health of an individual. It is a direct consequence of perpetual imbalance between energy intake and expenditure with storage of extra calories in the form of fat in the adipose tissue (Ainsle *et al*., 2000).

Various Peptides and biological substances are involved in the pathogenesis of obesity these substances may be the major targets for drug actions on experimental obesity. Little is known about the contribution of PGE_2 in obesity. *Ex-vivo* studies have shown a decrease in PGE_2 during diet-induced obesity (Barness *et al*., 2007; Freemask *et al*., 2001). Level of PGE_2 decreased due to the deficiency in one of the multiple enzymes in adipocytes required for its synthesis. Decrease in PGE_2 during diet-induced obesity caused by a down-regulation of microsomal prostaglandin E_2 synthase-1 (mPGES-1). Prostaglandin E_2 (PGE_2) is an anti-lipolytic agent and has been shown to negatively affect adipocyte differentiation *in-vitro* (Gaskins *et al*., 1988; Pierre *et al*., 2007). PGE_2 deficiency may be responsible for increase adipocyte differentiation in obesity. The role of PGE_2 in adipogenesis regulation *in-vivo* remains to be established. Indomethacin, an inhibitor of prostaglandin biosynthesis, decrease endogeneously synthesized prostaglandins & markedly enhances adipose conversion (Funk *et al*., 2001; Smith *et al*., 1996). PGE_2 has been recognized to have an effect on adipocytes by inhibiting lipolysis and

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stimulating the secretion of leptin ensuring its role in body weight homeostasis (Fain *et al*., 2000). PGE_2 inhibits adipocytes differentiation (Xu *et al*., 2007; Fujimori *et al*., 2010). It is believed that PGE_2 is responsible for the stimulation of leptin release hence can be used in the treatment of obesity (Fain *et al*., 2000).

MATERIALS AND METHODS:

Chemicals and Reagents

Casein (Modern Diary, New Karnal, India) and Cholesterol (Thomas Baker, Mumbai, India) were used to prepare high fat diet. Misoprostol (SUN PHARMA Ranipool East Sikkim 737135, Batch no. BSL1261A, Mfg Date 06/2012, Exp Date 05/2014). Indomethacin (JAGSONPAL PHARMACEUTICALS LTD Rudrapur-263153, Uttarakhand, Batch no. JR09A043, Mfd Date 06/2011, Exp Date 05/2014) were used as the test drugs. The estimation kits for serum glucose, cholesterol, HDL and triglycerides were obtained from Coral Diagnostics Ltd., Mumbai, India. All other chemicals used in the present study were of analytical quality. All drug solutions were freshly prepared before use.

High fat diet induced obesity

Experimental obesity was produced by feeding high fat diet (containing; Powdered Normal chow, 365g; Lard, 310g; Casein, 250g; Cholesterol, 10g; Vitamin mix and mineral mix, 60g; dl-Methionine, 03g; Yeast powder, 01g; Nacl, 01g were added to make 1.0 kg of diet) (Srinivasan *et al.,* 2005) to rats for a period of 10 weeks. Mineral mix was composed of 5.57g; KCl, 32mg; $MgSO_4$, 2.29g; $FeSO_4.7H_2O$, 108g; $CaHPO_4$, 70mg; $CuSO_4.5H_2O$, 0.1mg; $MnSO_4.H_2O$, 0.01mg; $ZnSO_4.H_2O$, 28.7mg; KI, 0.025mg; $COCl_2.6H_2O$, 9mg and MgO, 0.15mg. The vitamin mix contained Retinol acetate, 5000 IU; cholecalciferol, 400 IU; 7-hydrochloride, dehydrocholesterol, 2-nicotinamide, 45mg; D-panthenol, 5mg; pyridoxine 2mg; ascorbic acid, 75mg; folic acid, 1000µg and cyanocobalamin, 5µg. The High Fat Diet contained 5.33 Kcal/gm while the normal chow contains 3.80 Kcal/gm.

Animals

Male Wistar Albino Rats (170-230 gm) were employed. They were procured from Indian Institute of Integrative Medicine, Jammu, India and were housed in the departmental animal house, Chandigarh college of Pharmacy, Landran, Mohali, Punjab and maintained on normal chow diet (Ashirwad Industries Pvt. Ltd, Ropar, Punjab, India) and water *ad libitum*; at 12-12 hr light/dark cycles; temperature 25±2ºC and relative humidity 55±5 %. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and care of the animals were carried out as per the guidelines of Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA), Ministry of Environment and Forests, Government of India (Reg. No. 1201/9/08/CPCSEA).

Assessment of anthropometric parameters

The increase in the body weight as compared to age matched control group was regarded as obesity. Body Mass Index (BMI) i.e. weight (g)/ height (cm) ^{2} (Novelli *et al.,* 2007), Lee index i.e. (Body Wt) $^{1/3}$/ano-nasal length (cm) x 1000 (Bernardis *et al.,* 1982) were calculated before and after the treatment as an index of obesity. Body weight was assessed biweekly. Food intake measurements for individual rats were recorded every two weeks. To evaluate the effect of high fat diet and drug treatment, adipose tissue (Epididymal, retroperitoneal and mesenteric fat depots) were isolated,

freed from surrounding tissues, weighed individually and after that total weight was calculated (Ainslie *et al.,* 2000).

Assessment of biochemical parameters

The hyperlipidaemia was assessed by estimating the levels of total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL) and triglycerides in blood serum using commercially available kits. Values were expressed in mg/dl. Additionally glucose level in serum was also estimated by using commercially available kits. Values were expressed in mg/dl.

Estimation of serum total cholesterol

The total cholesterol was estimated by cholesterol oxidase peroxidase CHOD-POD method (Allain *et al.,* 1974) using commercially available kit (Coral Diagnostic kit, Mumbai) at 505 nm spectophotometrically.

Estimation of serum triglyceride

The serum triglyceride was estimated by glycerophosphate oxidase peroxidase GPO-PAP method (Werner *et al.,* 1981) using commercially available kit (Coral Diagnostic kit, Mumbai) at 505 nm spectophotometrically.

Estimation of high density lipoprotein (HDL)

The HDL was estimated by cholesterol oxidase peroxidase CHOD-POD method (Allain *et al.,* 1974) using commercially available kit (Coral Diagnostic kit, Mumbai).

Estimation of very low density lipoprotein (VLDL) and low density lipoprotein (LDL) level

VLDL and LDL concentrations were calculated from the Friedewald equation (Friedewald *et al.,* 1972).

VLDL Level

Serum VLDL levels (mg/dl) = Triglyceride level/5 and

LDL Level

Serum LDL levels (mg/dl) = Total cholesterol - (HDL level + VLDL level)

Estimation of serum glucose

The glucose concentration was estimated by glucose oxidase peroxidase GOD-POD method (Trinder *et al*., 1969) using commercially available kit (Vital diagnostics, Mumbai, India) at 505 nm spectophotometrically.

EXPERIMENTAL PROTOCOL:

Animals were divided into different groups each comprising six animals (n=6). The drugs were administered by oral route.

Group I: {Normal Control; n=6}

Normal rats were maintained on standard chow diet and water *ad libitum for* 10 weeks. No treatment was given to these rats.

Group II: {High Fat Diet Control; n=6}

Normal rats were maintained on high fat diet for ten weeks to produce obesity.

Group III: {Misoprostol per se; n=6}

Normal rats were maintained on chow diet for 6 weeks and then misoprostol 100 mcg/kg/day; *i.p* with normal chow diet for 4 weeks.

Group IV: {Indomethacin per se; n=6}

Normal chow diet for 6 weeks and then indomethacin 20 mg/kg/day; *p.o* with normal diet for 4 weeks.

Group V: {Misoprostol 100 mcg/kg/day p.o; n =6}

Normal rats were maintained on high fat diet for 6 weeks and then misoprostol 100 mcg/kg/day *i.p.* with high fat diet for 4 weeks.

Group VI: {Misoprostol 200 mcg/kg/day p.o; n =6}

Normal rats were maintained on high fat diet for 6 weeks and then misoprostol 200 mcg/kg/day *i.p* with high fat diet for 4 weeks.

Group VII: {Misoprostol 100 mcg/kg/day from day one p.o; n=6}

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Normal rats were maintained on high fat diet and then misoprostol 100 mcg/kg/day *i.p.* for 10 weeks

Group VIII: {Indomethacin 20 mg/kg/day p.o; n=6}

Normal rats were maintained on high fat diet for 6 weeks and indomethacin 20 mg/kg/day *p.o.* with high fat diet for 4 weeks.

Group IX: {Indomethacin 20 mg/kg/day from day one p.o; n=6}

Normal rats were maintained on high fat diet and indomethacin 20 mg/kg/day *p.o.* for 10 weeks.

STATISTICAL ANALYSIS

Results were expressed as the mean ± Standard Deviation (S.D.). Data obtained from various groups were statistically analyzed using one way ANOVA followed by Tukey's multiple range test; $p < 0.05$ was considered to be statistically significant.

RESULTS

The administration of misoprostol *per se* (100 and 200 mcg/kg/day *p.o;* 6 weeks) and indomethacin *per se* (25 mg/kg/day *p.o*; 4 weeks) to rats fed on standard diet did not produce significant effects on various parameters of obesity assessed in normal rats fed on standard diet. Obesity was produced by high fat diet (58% calories as fat, 25% protein and 17% carbohydrate, as percentage of total kcal) administered for 10 weeks to rats treated as HFD control.

Effect of high fat diet and of various pharmacological interventions on various parameters studied.

Anthropometric Parameters.

In high fat diet model, a significant increase ($p < 0.05$) in body weight, body mass index, Lee index, feed consumption (in kilocalories) (Kcal) and decrease in feed consumption (gm) were observed in rats fed over high fat diet as compared to age matched normal rats fed on standard diet (Fig. 1, Fig. 2, Fig. 3, Fig. 4, Fig. 5 and Table 1). Administrations of misoprostol in both high and low doses produced significant decrease ($p < 0.05$) in body weight, body mass index (BMI) and Lee index as compared to HFD control group while indomethacin showed no effect on theses parameters (Fig. 6, Fig. 7, Fig. 8, Fig. Fig. 10 and Table 4).

Fat depots.

Administration of high fat diet (HFD) for 10 weeks caused a significant ($p < 0.05$) increase in body fat depots: epididymal, retroperitoneal, mesenteric fat depots and total fat depot (Fig. 11 and Table 3). Treatment with misoprostol produced significant decrease ($p < 0.05$) in body fat depots while indomethacin showed no effect: epididymal, retroperitoneal, mesenteric fat depots and total fat in comparison to HFD control. (Fig. 13 and Table 6).

Serum glucose and lipid profile.

There was significant increase ($p < 0.05$) in serum concentration of glucose observed after 10 week in HFD control group as compared to age matched normal fed animals on standard diet. Moreover, there was a significant ($p < 0.05$) increase in serum concentration of cholesterol, triglycerides, LDL, VLDL and decrease in HDL observed in HFD control group as compared to age matched normal animals on standard diet. (Fig. 7 and Table 2). Treatment of HFD rats with misoprostol and misoprostol in low and high doses produced a significant decrease ($p < 0.05$) in serum level of glucose, total cholesterol, triglyceride, VLDL, LDL and significant increase in the level of HDL while shows no effect. As compared to HFD control. (Fig. 14 and Table 5).

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Table 1. Effect of normal diet and HFD on the body weight, body mass index, lee index, feed intake in gram and feed intake in Kcal.

Parameters	Normal diet control	High fat diet
Initial Body weight (gm)	195±23.90	180±12.34
Final Body weight (gm)	250±27.60	350.65±15.10[a]
Body mass index (g/cm^2)	0.525±0.027	0.76±0.55[a]
Lee index (gm/cm)	267.60±4.80	320.65±12.66[a]
Feed intake (gm)	23.13±1.25	18.55±0.89[a]
Feed intake (Kcal)	93.10±3.70	110.37±5.70[a]

All values were expressed as Mean ± S.D; [a] = $P < 0.05$ vs standard diet Control.

Table 2. Effect of normal diet and HFD on the serum glucose and serum lipid profile.

All values were represented as Mean ± S.D; [a] = $P < 0.05$ vs normal diet Control.

Parameters	Normal diet control	High fat diet
Serum glucose (mg/dl)	98.60±10.47	159.15±11.32[a]
Serum cholesterol (mg/dl)	55.68±5.21	129.71±7.10[a]
Serum triglyceride (mg/dl)	77.70±12.17	140.32±8.91[a]
Serum HDL (mg/dl)	30.30±7.63	25.10±5.71[a]
Serum VLDL (mg/dl)	15.54±2.43	28.06±1.78[a]
Serum LDL (mg/dl)	9.84±4.85	76.01±0.39[a]

Table 3. Effect of normal diet and HFD on the various fat pads.

All values were expressed as Mean ± S.D; [a] = $P < 0.05$ vs. Normal Control.

Parameters	Normal diet control	High fat diet
Epididymal fat (gm)	1.7±0.07	5.32±0.24[a]
Mesenteric fat (gm)	1.9±0.38	5.60±0.45[a]
Retroperitoneal fat (gm)	1.6±0.13	5.20±0.47[a]
Total fat	5.20±0.58	16.12±1.06[a]

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Table 4. Effect of various pharmacological interventions on the body weight, body mass index, lee index, feed intake in gram and feed intake in Kcal.

Parameters	Initial Body weight (gm)	Final Body Weight (gm)	Body mass index (gm/cm^2)	Lee index (gm/cm)	Feed intake (gm)	Feed intake (Kcal)
Indomethacin						
Normal diet control	195±23.9	250±27.6	0.52±0.27	267.60± 4.80	23.13±1.25	93.10±3.70
Indomethacin *per se*	196±24.8	246±23.20	0.50±0.42	263.2± 7.15	20.97±2.56	90.07±9.87
High fat diet (HFD)	180±12.3	350.65± 15.10	0.76±0.55[a]	320.65± 12.66	18.55±0.89	110.37±5.7
HFD + Indomethacin	190.54± 20.70	347.12± 23.11	0.73±0.29[b]	317±0.67[b]	16.12±7.63	104.92±9.6 3
HFD+Indomethacin (20mg) from day one	190.27± 16.14	346.27± 10.92	0.71±0.28[b]	317±9.82[b]	16.64±4.76	102.94±9.6 3
Misoprostol						
Normal diet control	195±23.9	250±27.6	0.525± 0.027	267.60± 4.80	23.13±1.25	93.10± 3.70
Misoprostol *per se* (100)	195±22.9	235±22.7	0.54±0.47	247.7± 5.37	20.77±2.48	82.18± 6.70
HFD + Misoprostol (100mcg)	185±25.13	290.42± 25.62[b]	0.64±0.30[b]	300.10± 12.95[b]	15.10±2.24[b]	96.94±3.75[b]
HFD+ Misoprostol (200mcg)	187.42± 38.46	285.32± 10.12[b]	0.60±0.30[b]	290.12± 10.87[b]	13.12±4.65[b]	90.92± 9.60[b]
HFD+ Misoprostol (100mcg) from day one	180.34± 35.16	280.52± 9.82[b]	0.56±0.20[b]	285.13± 9.87[b]	14.16±5.23[b]	87.42± 11.13[b]

All values were expressed as Mean ± S.D; [a] = $P < 0.05$ vs. Normal Control., [b] = $P < 0.05$ vs. High fat diet.

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Table 5. Effect of various pharmacological interventions on the serum glucose and serum lipid profile.

Parameters	Serum glucose (mg/dl)	Serum total cholesterol (mg/dl)	Serum triglyceride (mg/dl)	Serum HDL (mg/dl)	Serum VLDL (mg/dl)	Serum LDL (mg/dl)
Indomethacin						
Normal standard diet control	92.5± 12.7	53.5±5.7	75.7±10.6	32.1±5.7	14.9±2.7	5.32± 9.9
Indomethacin *per se*	95.3± 11.07	50.4±2.07	74.6±8.70	32.7±3.27	14.92±2.86	2.78± 1.87
High fat diet (HFD)	150.21 ±4.87[a]	132.20± 7.16[a]	140.30± 6.18[a]	22.67± 2.98[a]	27.10±2.16[a]	75.49± 8.90[a]
HFD + Indomethacin	148.40 ±6.72[b]	130.10± 8.19[b]	138.25± 7.13[b]	23.83± 3.84[b]	26.71±3.25[b]	73.46± 7.67[b]
HFD+Indomethacin from day one	148.12 ±3.32[b]	130.17± 5.13[b]	137.32± 7.75[b]	21.79± 2.31[b]	26.61±2.24[b]	73.32± 6.87[b]
Misoprostol						
Normal standard diet control	92.5± 12.7	53.5±5.7	75.7±10.6	32.1±5.7	14.9±2.7	5.32± 9.9
Misoprostol *per se*	93.7± 5.09	53.9±4.17	72.8±8.60	32.6±3.18	13.96±2.76	5.10± 8.60
High fat diet (HFD)	150.21 ±4.87[a]	132.20± 7.16[a]	140.30± 6.18[a]	22.67± 2.98[a]	27.10±2.16[a]	75.49± 8.90[a]
HFD + Misoprostol high	140.26 ±4.46[b]	125±5.66[b]	132±5.68[b]	28.91± 2.98[b]	23.10±4.81[b]	69.12± 8.80[b]
HFD + Misoprostol Low	145.27 ±3.29[b]	129.16± 4.22[b]	137.83± 7.32[b]	25.83± 3.67[b]	23.32±3.67[b]	70.21± 9.81[b]
HFD + Miso from day one	135.45 ±5.87[b]	122±8.71[b]	129±7.82[b]	30.32± 3.45[b]	22.08±4.71[b]	67.11± 9.71[b]

All values were expressed as Mean ± S.D; [a] = $P < 0.05$ vs. Normal Control., [b] = $P < 0.05$ vs. High fat diet.

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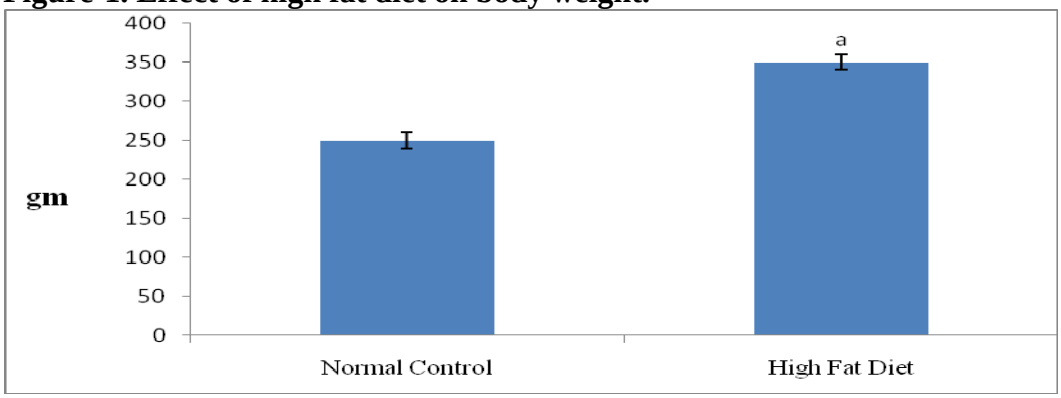
Table 6. Effect of various pharmacological interventions on the various fat pads.

Parameters	Epididymal fat	Mesentric fat	Retroperitoneal fat	Total fat
Indomethacin				
Normal diet control	1.8±0.09	2.12±0.36	1.6±0.15	5.52±0.60
Indomethacin *per se*	1.7±0.42	1.99±0.51	1.49±0.46	5.18±1.39
High fat diet (HFD)	5.66±0.43[a]	5.75±0.49[a]	5.82±0.45[a]	17.23±1.41[a]
HFD + Indomethacin	5.60±0.61[b]	5.73±0.34[b]	5.62±0.41[b]	16.95±1.36[b]
HFD+Indomethacin from day one	5.57±0.77[b]	5.71±0.65[b]	5.76±0.57[b]	17.04±1.99[b]
Misoprostol				
Normal diet control	1.8±0.09	2.12±0.36	1.6±0.15	5.52±0.60
Misoprostol *per se*	1.7±0.33	1.59±0.57	1.3±0.79	4.49±1.69
High fat diet (HFD)	5.66±0.43[a]	5.75±0.49[a]	5.82±0.45[a]	17.23±1.41[a]
HFD + Misoprostol (200)	4.21±0.27[b]	4.71±0.20[b]	4.18±0.37[b]	13.1±0.84[b]
HFD + Misoprostol (100)	4.90±0.46[b]	5.32±0.53[b]	5.21±0.51[b]	15.43±1.67[b]
HFD+Misoprostol from day one	4.23±0.24[b]	4.82±0.16[b]	4.73±0.20[b]	13.78±0.60[b]

All values were expressed as Mean ± S.D; [a] = $P < 0.05$ vs. standard diet Control. [b] = $P < 0.05$ vs. High fat diet.

Figure-1. Effect of high fat diet on body weight.



All values were expressed as Mean ± S.D; [a] = $p < 0.05$ vs normal control.

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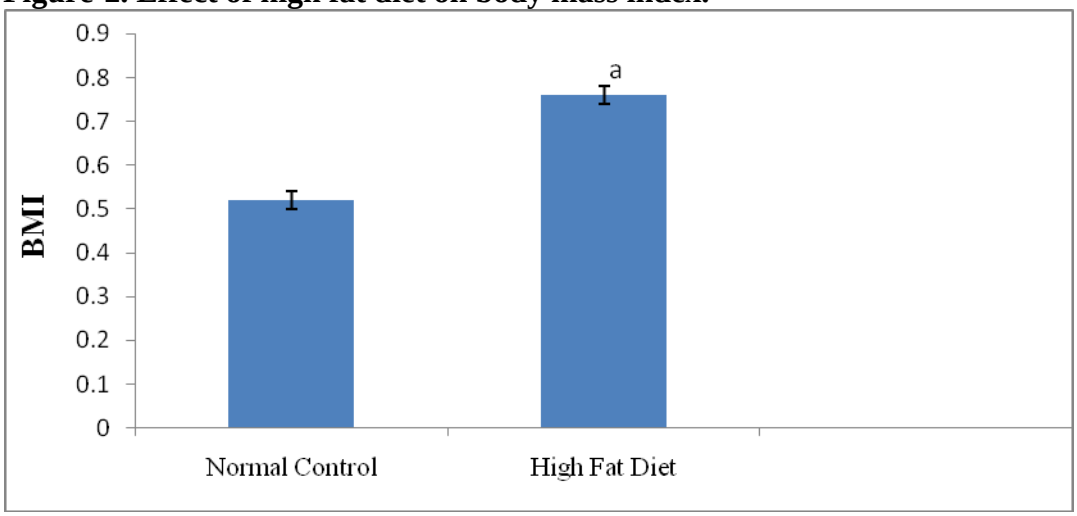
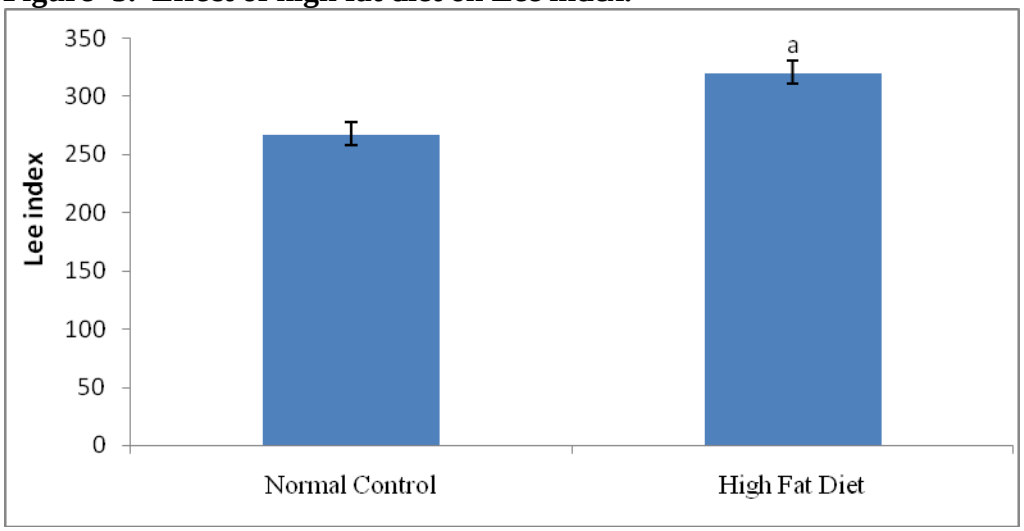
Figure-2. Effect of high fat diet on body mass index.



All values were expressed as Mean ± S.D; [a] = p <.05 vs normal control.

Figure- 3. Effect of high fat diet on Lee index.



All values were expressed as Mean ± S.D; [a] = p < 05 vs normal control.

Figure- 4. Effect of high fat diet on feed intake in gram.

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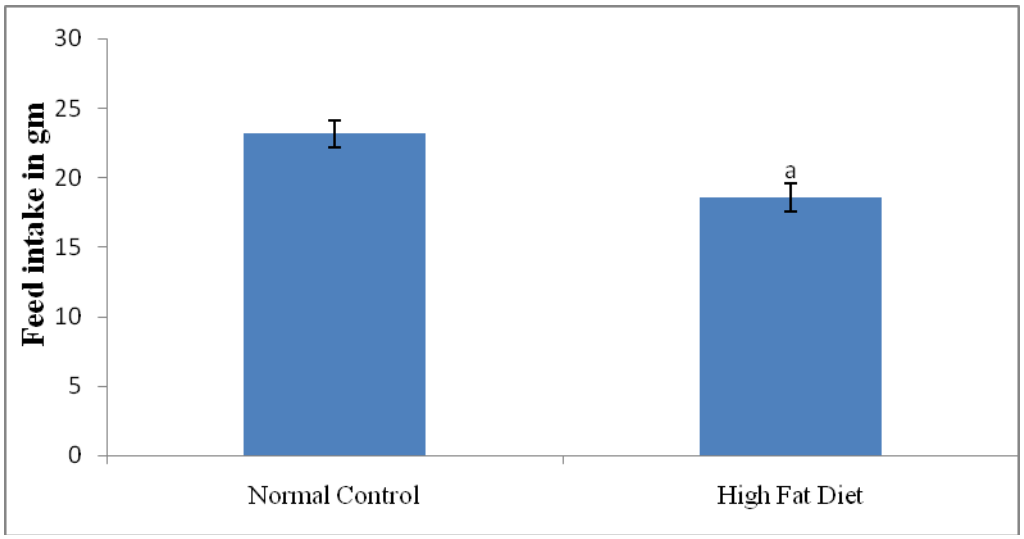
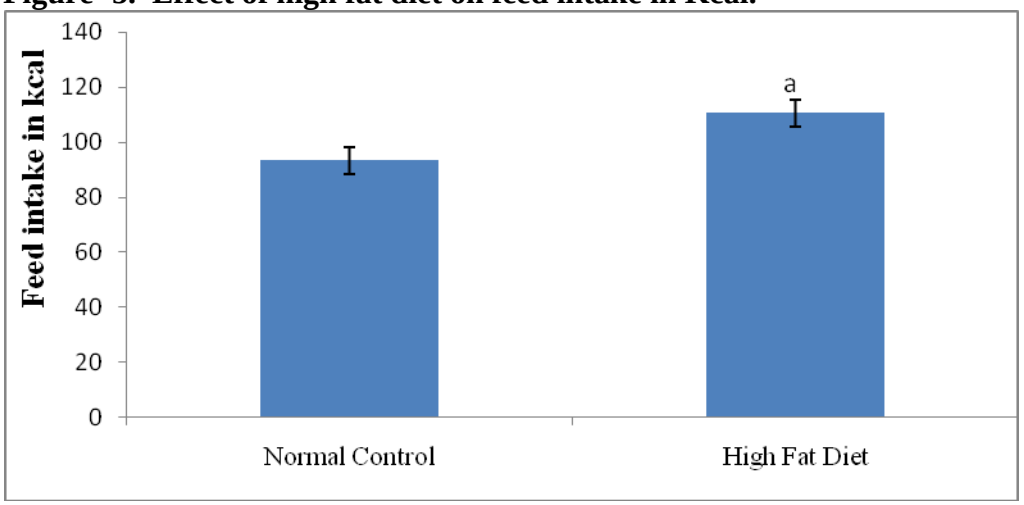


All values were expressed as Mean ± S.D; [a] = p <.05 vs normal control.

Figure- 5. Effect of high fat diet on feed intake in Kcal.



All values were expressed as Mean ± S.D; [a] = p <.05 vs normal control.

Figure- 6. Effect of high fat diet on various fat pads weight.

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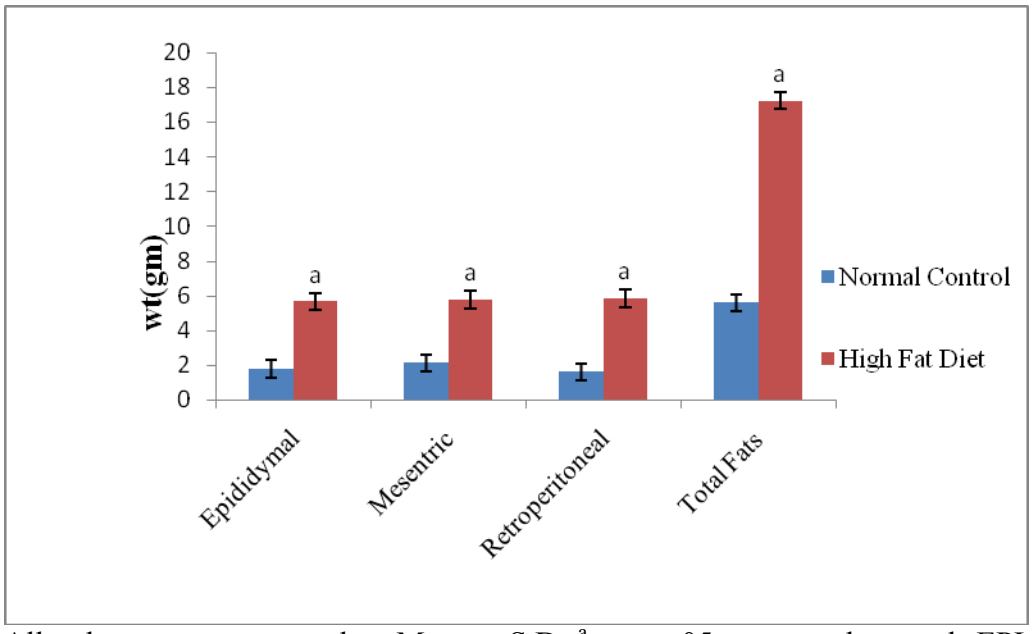
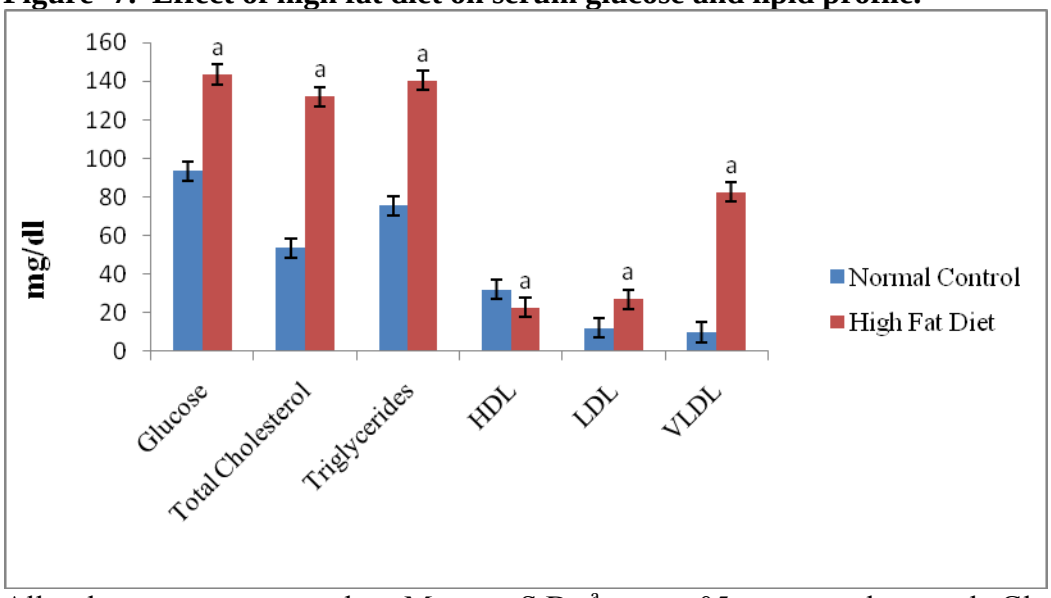


All values were expressed as Mean ± S.D; [a] = p <.05 vs normal control; EPI- epididymal fat., MES- mesenteric fat., RET- retroperitoneal fat., TF- Total fat.

Figure- 7. Effect of high fat diet on serum glucose and lipid profile.



All values were expressed as Mean ± S.D; [a] = p <.05 vs normal control; Glu- glucose., TG- triglyceride., TC- total cholesterol HDL- high density lipoprotein., LDL- low density lipoprotein., VLDL- very low density lipoprotein.

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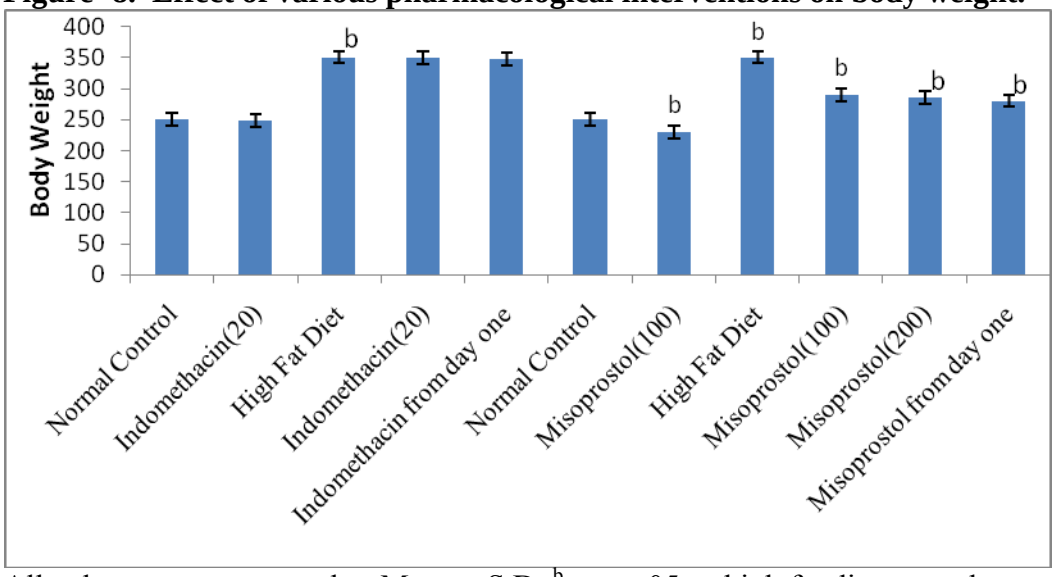
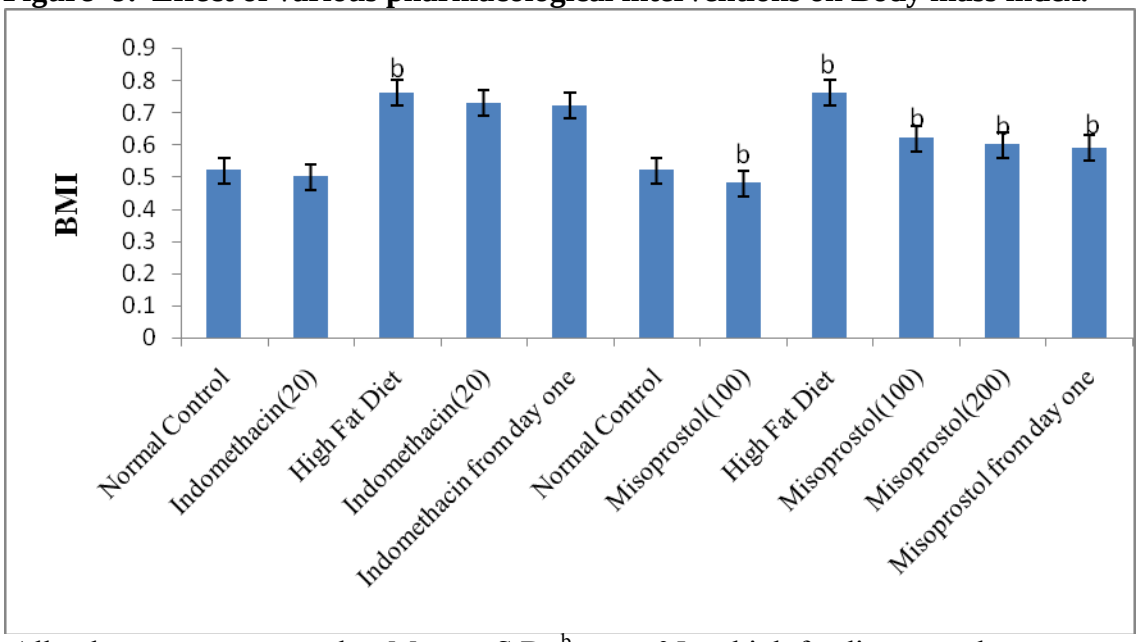
Figure- 8. Effect of various pharmacological interventions on body weight.



All values were expressed as Mean ± S.D; [b] = p <.05 vs high fat diet control.

Figure- 9. Effect of various pharmacological interventions on Body mass index.



All values were expressed as Mean ± S.D; [b] = p <.05 vs high fat diet control.

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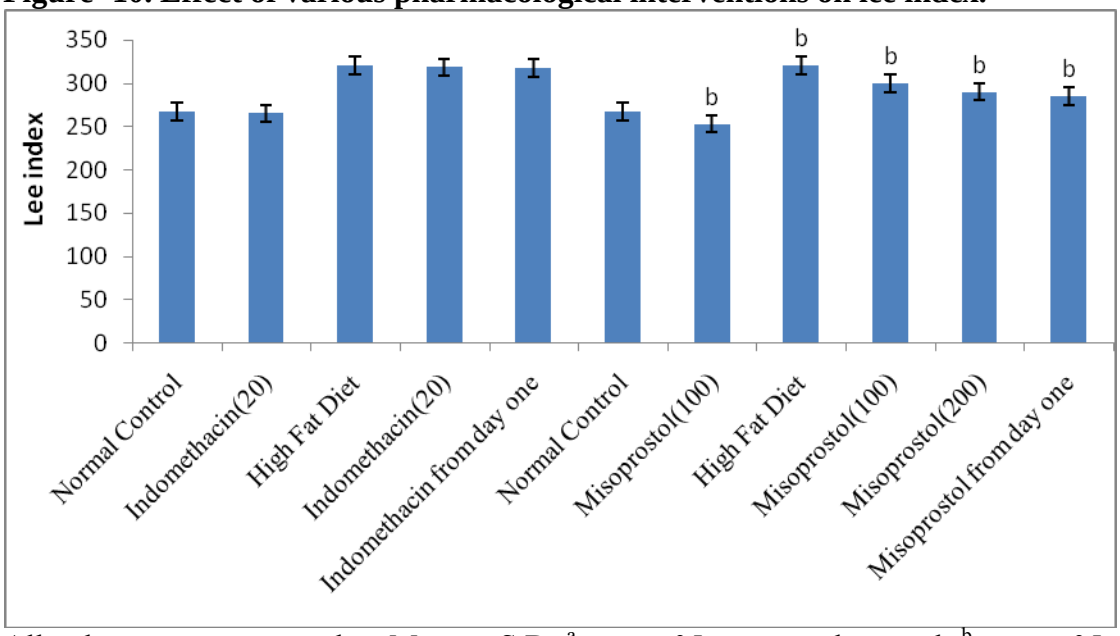
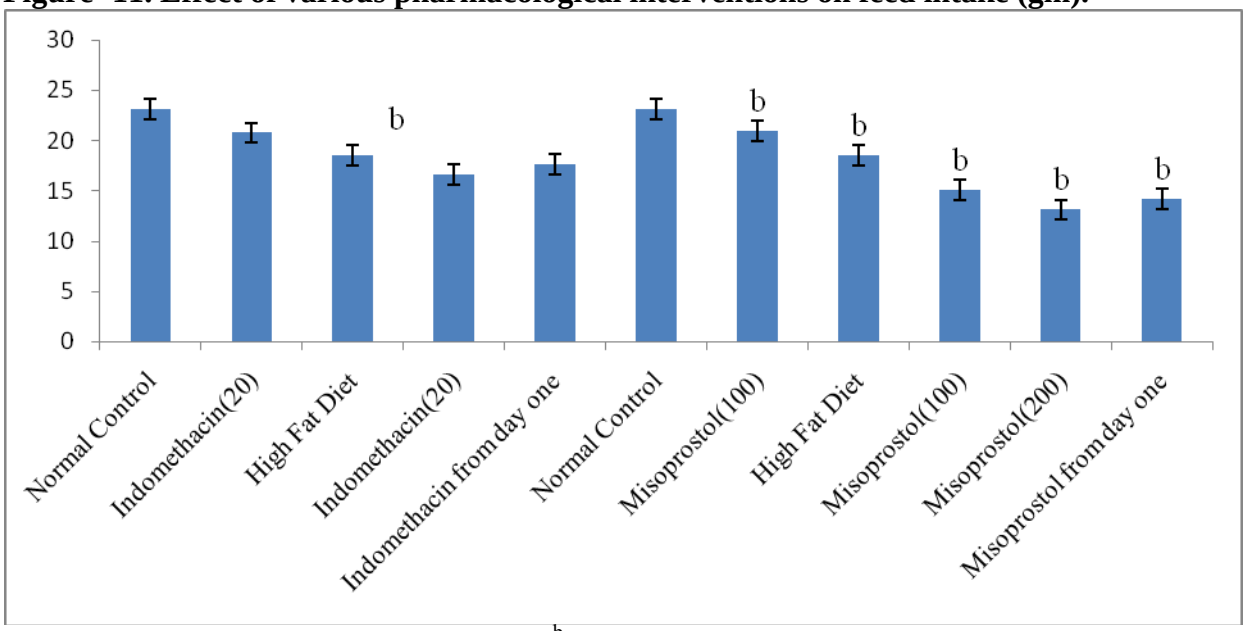
Figure- 10. Effect of various pharmacological interventions on lee index.



All values were expressed as Mean ± S.D; [a] = $p < .05$ vs normal control; [b] = $p < .05$ vs high fat diet control.

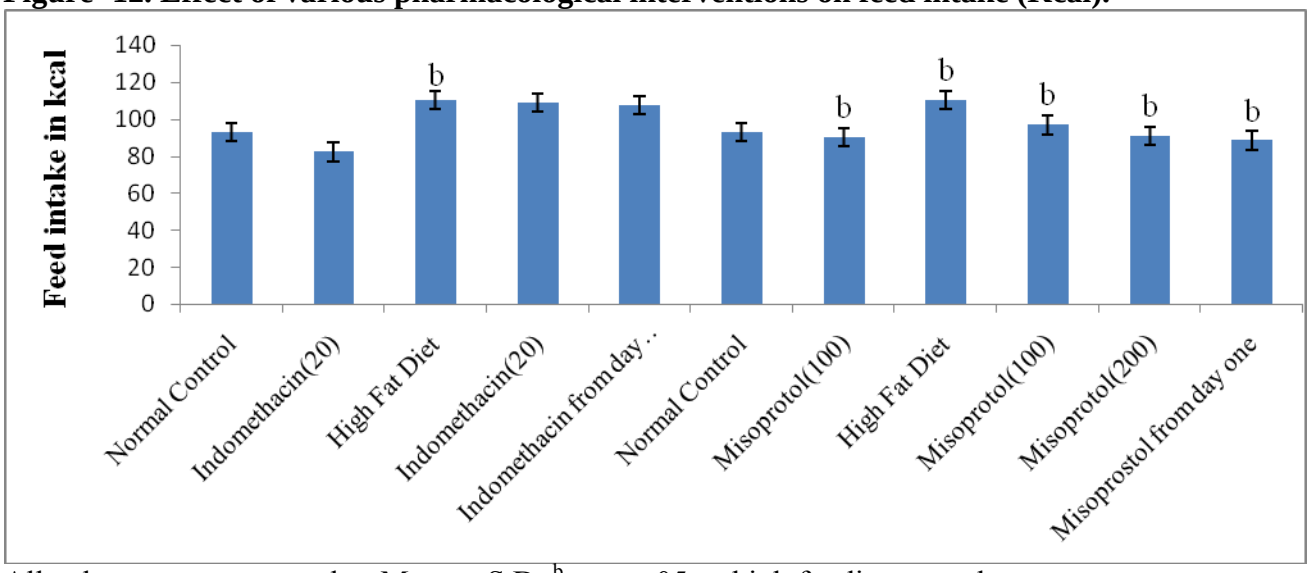
Figure- 11. Effect of various pharmacological interventions on feed intake (gm).



All values were expressed as Mean ± S.D; [b] = $p < .05$ vs high fat diet control

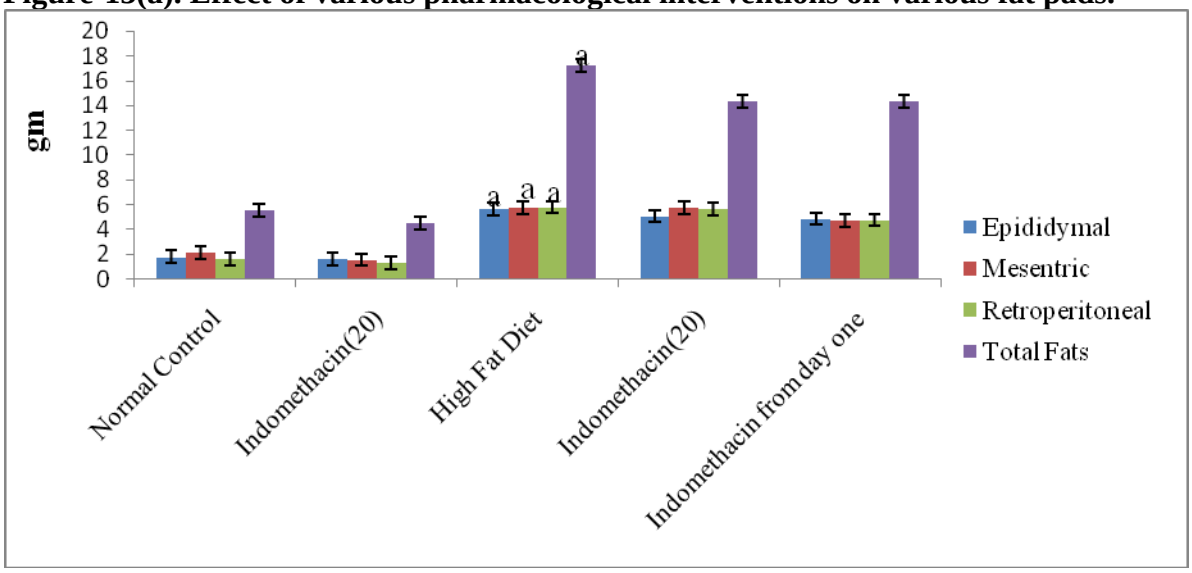
ISSN 2249 – 6467

Figure- 12. Effect of various pharmacological interventions on feed intake (Kcal).



All values were expressed as Mean ± S.D; [b] = $p < .05$ vs high fat diet control

Figure-13(a). Effect of various pharmacological interventions on various fat pads.

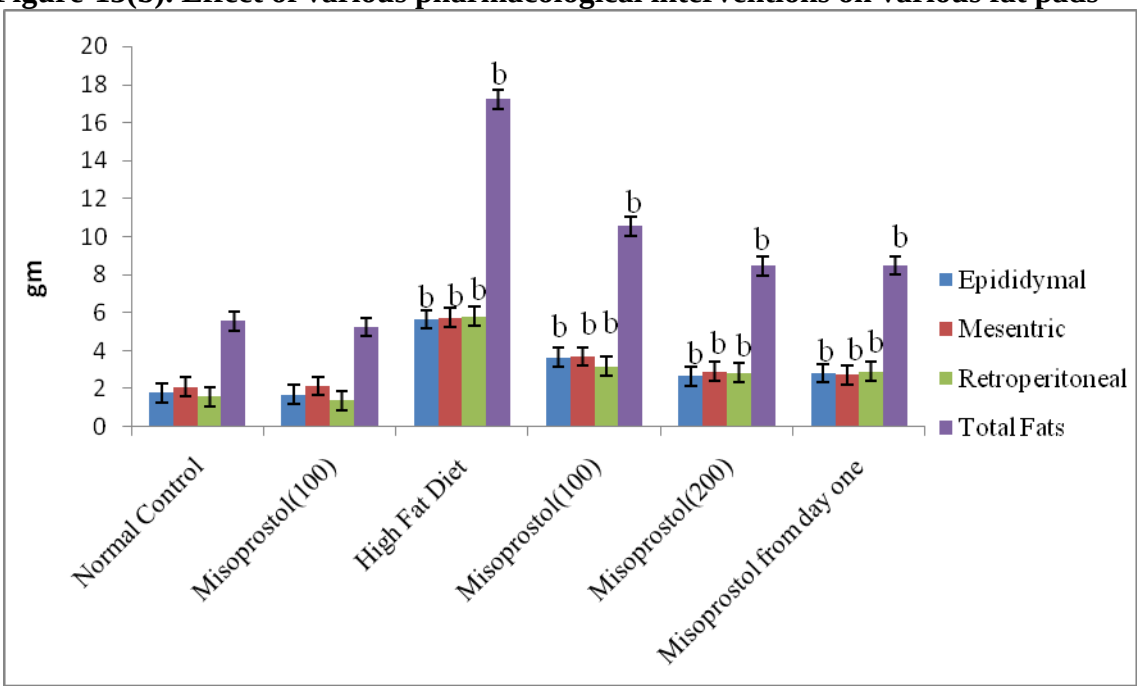


(a)

All values were expressed as Mean ± S.D; [a] = $p < .05$ vs normal control.

ISSN 2249 – 6467

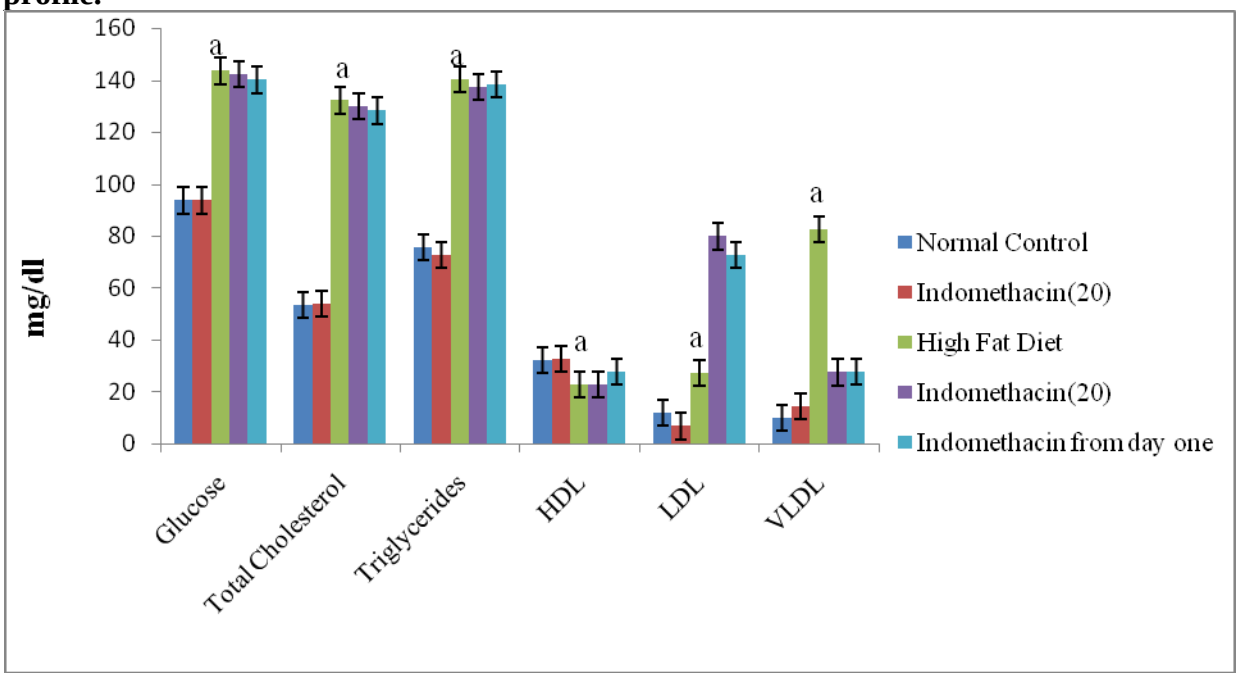
Figure-13(b). Effect of various pharmacological interventions on various fat pads



(b)

All values were expressed as Mean ± S.D; [b] = $p < .05$ vs high fat diet control.

Figure- 14(a). Effect of various pharmacological interventions on serum glucose and lipid profile.

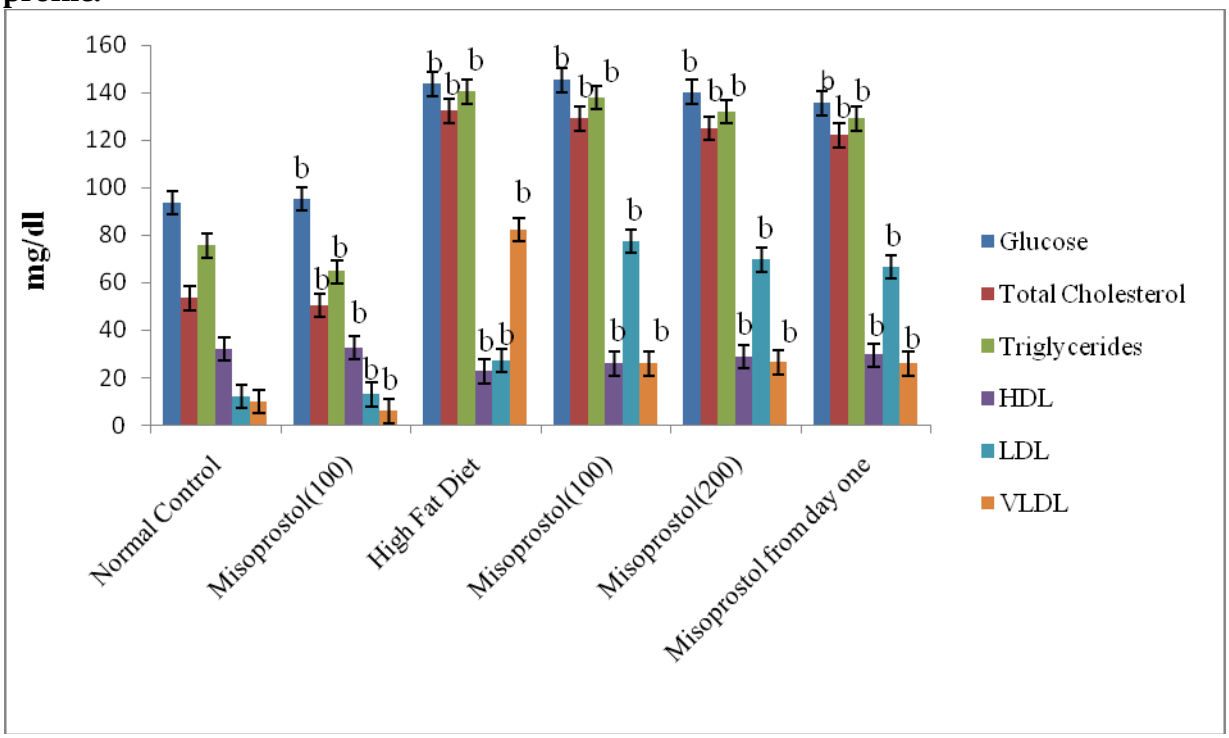


(a)

All values were expressed as Mean ± S.D; [a] = $p < .05$ vs normal control.

ISSN 2249 – 6467

Figure- 14(b). Effect of various pharmacological interventions on serum glucose and lipid profile.



(b)

All values were expressed as Mean ± S.D; ^{b} = p <.05 vs high fat diet control.

DISCUSSION

The present study was undertaken to determine the role of misoprostol and prostaglandin synthesis inhibitor indomethacin on high fat diet induced obesity in wistar rats. We observed that misoprostol has positive effect in the alteration of various parameters of obesity and indomethacin does not alter the parameters of Obesity.

Obesity is a metabolic disorder characterized by an excessive accumulation of fat in the body to an extent which adversely affects the health of an individual. It is a direct consequence of perpetual imbalance between energy intake and expenditure with storage of extra calories in the form of fat in the adipose tissue (Ainsle *et al*., 2000). In obesity, there is an increase in intake of high fat and high energy food and a decrease in daily energy expenditure (Labib, 2003). HFD has been used to develop experimental obesity characterized with dyslipidemia and insulin resistance in rodents (Woods *et al.*, 2003). HFD- fed rats exihibited significant increase in body weight, plasma glucose, insulin, triglycerides and total cholesterol level as compared to normal powdered diet (NPD)-fed control rats (Srinivasan *et al.*, 2005). High fat diet (HFD) for 10 weeks causes obesity by increasing deposition of fats in the body. The lipogenesis was upregulated by HFD in rats lead to elevation of plasma lipids (Storlien *et al.*, 1986) which is characterized by elevated TG levels (Van Itallie, 1985), LDL-C levels (Rosenson *et al* .,2002) and decreased serum HDL-C (Glueck *et al.*, 1980) in obese rats (Wood *et al.*, 2003). Further, feeding with high fat diet caused hyperglycemia in rats (Ikemoto *et al.*, 1995). Therefore the serum lipid levels

(total cholesterol, LDL, VLDL, HDL, and triglycerides) and glucose levels were estimated in present study as the marker of hyperlipidemia and hyperglycemia. In present study high fat diet (HFD) induction for 10 weeks leads to obesity and dyslipidemia as evidence by gain in body weight, increased feed intake (KCal), body mass index, lee index and decreased feed intake (in grams) (Storlien *et al*., 1986), increase in triglyceride levels. Diet and physical exercise remain as main stay in obesity management; nonetheless antiobesity drugs may be required either to reduce appetite or to inhibit fat absorption (Freemask *et al*., 2001). Various factors are found to be involved in obesity including genetic, environmental, behavioral, and socio-economic factors (Chen *et al*., 2006). Increase PGE_2 levels might expect in obese fat tissue. Recent ex-vivo studies show a decrease in PGE_2 during diet-induced obesity (Barness *et al*., 2009; Freemask *et al*., 2001). Level of PGE_2 decreased due to the deficiency in one of the multiple enzymes in adipocytes required for its synthesis. Decrease in PGE_2 during diet-induced obesity caused by a down-regulation of microsomal prostaglandin E_2 synthase-1 (mPGES-1). Misoprostol which serves as Prostaglandin E_2 (PGE_2) is an antilipolytic agent has been shown to negatively affect adipocyte differentiation in vitro (Gaskins *et al*., 1989; Tsuboi *et al*., 2004). PGE_2 deficiency may be responsible for increase adipocyte differentiation in obesity. The role of PGE_2 in adipogenesis regulation in vivo remains to be established. Misoprostol which is a PGE_2 analogue was given to rats at the dose of 100 mcg/kg and 200 mcg/kg; *p.o.* for 10 weeks in one protocol and for 4 weeks in other protocol. Various physical parameters such as body weight, Body mass index, Lee Index, are used as the parameters of development of obesity. Several biochemical parameters are also used such as cholesterol, very low density lipoproteins, low density lipoproteins, triglycerides and glucose levels were also determined.

Administration of misoprostol in low and high dose for 10 weeks to the high fat diet fed animals decreased the parameters of obesity as compared to HFD control group, administration of misoprostol in low and high dose for 4 weeks start from the end of 6^{th} week to the high fat diet fed animals also decreased the parameters of obesity as compared to HFD control group. Indomethacin was given at the dose of 20 mg/kg *p.o* for 10 weeks in one protocol and for 4 weeks in other protocol. Indomethacin, an inhibitor of prostaglandin biosynthesis, decrease endogeneously synthesized prostaglandins & markedly enhances adipose conversion (Funk *et al*., 2001; Smith *et al*., 1996). PGE_2 has been recognized to have an effect on adipocytes by inhibiting lipolysis and stimulating the secretion of leptin ensuring its role in body weight homeostasis (Fain *et al*., 2000). Administration of Indomethacin 20 mg/kg for 10 weeks to the high fat diet fed animals does not decreased the parameters of obesity as compared to HFD control group instead the parameters were found to be increased as compared to the HFD control group, administration of Indomethacin 20 mg/kg for 4 weeks start from the end of the 6^{th} week to the high fat diet fed animals does not decreased the parameters of obesity as compared to HFD control group. For these reasons, the present study was undertaken to explore the role of PGE_2 in High Fat Diet-induced obesity.

7. Conclusion.

It has been observed that PGE_2 plays beneficial role in obesity; also this study has provided a rational pharmacological basis for Anti-obesity potential of PGE_2.

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