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Evaluation of *Mangifera indica* leaves for its Anti Obesity Activity in Rats.

Danilae George, and Jyothi Y*.

Dept. of Pharmacology, Krupanidhi College Of Pharmacy, No 12/1, Carmelaram Road, Chikka Bellandur, Carmelaram Post, Varthur Hobli, Bengaluru, Karnataka 560035, India.

ABSTRACT

The present study was undertaken to evaluate anti-obesity effect of Ethanolic extract of *Mangifera indica* leaves on rats fed on HFD (High Fat Diet) along with exercise. The study was conducted for 40 days. High Fat Diet was used to induce obesity. Along with the induction of obesity, exercise, orlistat, low, intermediate and high dose of *Mangifera indica* were tested for 40 days. The various manipulative options studied to include swimming test (physical exercise), orlistat (200mg/kg), ethanolic extract of *Mangifera indica* low dose (100mg/kg), ethanolic extract of *Mangifera indica* intermediate dose (300mg/kg), and ethanolic extract of *Mangifera indica* high dose (900 mg/kg). The parameters were evaluated including body weight on alternate days for 40 days. Biochemical parameters such as HDL, LDL, Triglycerides and total cholesterol were measured using diagnostic kits. Blood glucose level was measured. On 41st days animals were sacrificed and their organ weights (heart, liver, spleen and kidney), and fat pad weights (epididymal and mesenteric fat pads) were measured. There was a significant reduction in body weight, Triglycerides, total cholesterol, LDL, Blood glucose levels, organ and fat pad weights and increase in HDL level of the animals treated with Ethanolic extracts of *Mangifera indica* and exercise. The present study revealed that [HFD + Intermediate dose of ethanolic extract of *Mangifera indica* (300 mg/kg) + exercise] group showed more potential effects than rest of all treatment groups.

Keywords: Anti-obesity, High Fat Diet, Orlistat, *Mangifera indica*.

*Corresponding author

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INTRODUCTION

Obesity is a medical condition in which excess body fat gets accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. Among the multiple factors contributing to its etiology, the sedentary life styles, white collar jobs, lack of exercise, psychological factors, and the consumption of energy rich diets are the major ones [1, 2]. Due to obscure etiology, the treatment of obesity is difficult and challenging. Further, the cause of concern is the non-availability of drugs for its treatment and the short-term efficacy and limiting side effects of the available drug [3].

A compound that selectively limits the intestinal absorption of dietary fat, in excess of that manageable by dietary manipulation alone could become a useful therapeutic agent for the management of obesity.

Orlistat is a pharmacological agent that promotes weight loss in obese subjects via inhibiting of gastric and pancreatic lipase, an enzyme that is crucial for the digestion of the long chain triglycerides and has been proven to be useful in facilitating both weight loss and weight maintenance [4].

However, because orlistat can result in undesirable side effects, such as faecal incontinence, flatulence, and steatorrhea, its use may be limited. Therefore, it may be worthwhile to search the natural substances that show potent inhibitory activity against pancreatic lipase and have fewer side effects [5].

Natural dietary supplements have been considered promising candidates for weight loss and anti-obesity. Mango (*Mangifera indica*L.), belonging to the family Anacardiaceae, is widely distributed in many tropical and sub-tropical regions; it is one of the most popular edible fruits in the world [6].

The leaves of mango (ML) are also used as an antidiabetic agent in Nigerian folk medicine. Mangiferin present in *Mangifera* extracts has shown enhanced lipolysis and inhibited PL and LPL activities in female Zucker rats [7].

Reducing the absorption of fat can be an effective adjunct to dieting in obese patients. Since ML has shown to inhibit both PL and LPL, it is possible that the extract affects both intestinal fat absorption and the uptake of fatty acids in adipose tissue, if enough of the active components enter the blood stream [8].

Comprehensive herbal drug therapeutic regimen offers time tested safe and effective support to conventional therapy in the management of obesity. Combination of adequate dietary management and physical activity would provide an integrated approach to the management of obesity and hence the plant extract of *Mangifera indica* leaf has been chosen for this study.

Physical exercise can be used effectively by itself or in combination with dietary restriction to trigger weight loss. So present study is intended to study the evaluation of *Mangifera indica* leaves for antiobesity activity along with exercise.

MATERIALS AND METHODS

Chemicals and reagents

Triglycerides and Cholesterol Kit (Span Diagnostics, Bangalore, India), Orlistat Capsules 120 mg (Torrent Pharmaceuticals LTD. India). The ingredients for High Fat Diet were procured from college laboratory (Table no. 1). All other reagents used in the experiments were of analytical grade and of the high quality.

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Table No. 1: Composition of High Fat Diet

Composition of diet	High fat diet (HFD)gm
1. **FAT:**	
a. Lard	230
b. Vegetable oil	50
2. **Carbohydrate:**	
a. Dextrin	97
b. Cornstarch	98
c. Sucrose	130
3. **Protein:**	
a. Casein	325
4. **Vitamin mix**	30
5. **Mineral mix**	40
6. total weight(g)	1000
7. Energy density(kcals)	5.15
8. % Macronutrient(kcals)	
a. Fat	50
b. Carbohydrate	25
c. protein	25

Ingredients expressed by weight (gm), HFD (High Fat Diet).

Description of diet [9]

Animals

Data were obtained from laboratory based studies by using female Sprague-Dawley rats weighing between 150-200 gms, maintained at room temperature, 40-60% humidity and 12±1 h light-dark cycle. During obesity induction rats weighing 150-200gm were taken for the study, and they were broadly divided into eleven groups. Group one was normal control (Normal pellet diet was fed) and ten groups were fed with HFD (High Fat Diet) to induce obesity and water *ad libitum*. Experimental protocols were followed as per Institutional Animal Ethical Committee guidelines. Animal Ethical committee clearance (CPCSEA No.2015/PCOL/01) was obtained for the procurement of animals.

Experimental design

The female Sprague-Dawley rats were divided into eleven groups. Each of the groups consist of six animals as follows:

1. Normal Control (rats will be fed on normal chow diet)
2. HFD Control (rats will be fed on HFD alone)
3. HFD + Exercise [10]
4. HFD + Orlistat (200mg/kg Diet) [11]
5. HFD + Orlistat (200mg/kg Diet) [11] + Exercise
6. HFD + Ethanolic extract of *Mangifera indica*(Low dose)
7. HFD + Ethanolic extract of *Mangifera indica*(Medium dose)
8. HFD+ Ethanolic extract of *Mangifera indica*(High dose)
9. HFD + Ethanolic extract of *Mangifera indica*(Low dose) + Exercise
10. HFD + Ethanolic extract of *Mangifera indica* (Medium dose) + Exercise
11. HFD + Ethanolic extract of *Mangifera indica* (High dose) + Exercise

Exercise protocols [10]

Swimming

The rats were adapted to the water before the training began. The adaptation consisted of swimming for 30 minutes, once per day for five days, in water at a temperature of 31°C. After adaptation, the rats were trained by swimming for 60 minutes/day, five days a week for eight weeks, with a constant overload

equivalent to 5% of their body weight. The water tanks were 50 cm in height and 30 cm in diameter, and the overload was attached to the animal's chest using an appropriate vest.

Measurement of Body weight:

The body weight (gm) was recorded on day 1 and then on alternate days for 40 days in each group.

Estimation of Biochemical parameters:

At the end of the experiment, on 41st day, blood samples were collected from overnight fasted animals under inhalation of anaesthesia by retro-orbital puncture method. Serum was separated by centrifugation at 2500 rpm for 15 min and was used for further experiments, i.e. total cholesterol, HDL and triglyceride levels were estimated by CHOD-PAP method and GPO-PAP method. LDL levels were calculated by the method of Johnson *et al*. Blood glucose was estimated by using Glucometer.

Estimation of Organ and fat pad weights:

On the 41st day, the animals were sacrificed by cervical dislocation. Different organs (kidney, liver, heart, spleen) and fat pads (mesenteric, epididymal fat pads) were collected and weighed.

Statistical analysis:

The results are expressed as mean ± SEM. Comparisons between the treatment groups and control were performed by one way analysis of variance (ANOVA) followed by Dunnett's multiple range tests. In all tests the criterion for statistical significance are $p < 0.05$.

RESULTS

Body weight

High Fat Diet substantially increased body weights of rats in 40 days, when compared to the normal control group. When compared with the HFD control group, all the treatment groups showed a significant decrease in body weight. HFD + intermediate dose of ethanolic extract of *Mangifera indica* (300 mg/kg) + exercise showed more potential effect than all the other treatment groups (Table 2).

Table: 2 Effect of treatment and exercise on body weight

Sl.NO	EXPERIMENT GROUPS	1 WEEK	4 WEEK	6 WEEK
1.	Normal control	164.16 ± 1.54	177.5 ± 2.14	199.16 ± 2.71
2.	HFD (high fat diet) control	164.16 ± 1.54	230 ± 1.83**	269.16 ± 1.54**
3.	HFD + Exercise	165 ± 2.24	220.83 ± 2.39**	248.33 ± 2.11^{**b}
4.	HFD + LD (low dose)	168.33 ± 2.47	228.33 ± 2.79**	250.83 ± 2.71^{**b}
5.	HFD + LD + Exercise	166.66 ± 2.47	207.5 ± 4.43^{**b}	230.83 ± 2.71^{**b}
6.	HFD + MD (medium dose)	163.33 ± 3.80	200.83 ± 4.73^{**b}	213.33 ± 4.22^{*b}
7.	HFD + MD + Exercise	158.33 ± 2.47	182.5 ± 2.50^{b}	209.16 ± 2.39^{b}
8.	HFD + HD (high dose)	165 ± 3.87	202.5 ± 4.43^{**b}	215.83 ± 4.73^{**b}
9.	HFD + HD + Exercise	160 ± 2.24	184.16 ± 2.39^{b}	209.16 ± 2.71^{b}
10.	HFD + Orlistat	165.83 ± 3.27	216.66 ± 4.01^{**c}	233.33 ± 2.11^{**b}
11.	HFD + Orlistat + Exercise	163.33 ± 2.47	210.83 ± 2.01^{**b}	225 ± 3.65^{**b}

All values are represented as mean ± SEM, n = 6. *****p<0.001,** ****p<0.01,** ***p<0.05**, when compared to **normal control group**, ^{a}**p<0.001,** ^{b}**p<0.01,** ^{c}**p<0.05**, when compared to **HFD control.**

Serum biochemical parameters

Rats fed with HFD showed increased levels of Triglycerides, LDL, and total cholesterol and decreased levels of HDL levels, when compared to normal control. All treatment groups significantly suppressed the rise

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of lipid profile and caused in the rise of HDL levels. . HFD + intermediate dose of ethanolic extract of *Mangifera indica* (300 mg/kg) + exercise showed more potential effect than all the other treatment groups (Table 3).

Table: 3 Effect of treatment and exercise on serum biochemical parameters

Sl.NO	Experiment Groups	Triglycerides	Cholesterol	HDL	LDL	BLOOD GLUCOSE
1.	Normal control	98.48 ± 0.17	75.96 ± 0.11	51.5 ± 0.12	38.53 ± 0.04	100.15 ± 0.11
2.	HFD (high fat diet) control	150.17 ± 0.009 ^{**b}	145.34 ± 0.008 ^{**b}	27.34 ± 0.03 ^{**b}	65.55 ± 0.01 ^{**b}	150.15 ± 0.007 ^{**b}
3.	HFD + Exercise	130.53 ± 0.005 ^{**b}	120.38 ± 0.009 ^{**b}	30.47 ± 0.006 ^{**b}	47.83 ± 0.003 ^{**b}	133.28 ± 0.006 ^{**b}
4.	HFD + LD (low dose)	145.83 ± 0.007 ^{**b}	140.17 ± 4.21 ^{**b}	30.3 ± 0.007 ^{**b}	55.16 ± 0.003 ^{**b}	145.49 ± 0.005 ^{**b}
5.	HFD + LD + Exercise	125.63 ± 0.007 ^{**b}	120.16 ± 0.004 ^{**b}	38.61 ± 0.004 ^{**b}	47.17 ± 0.006 ^{**b}	135.48 ± 0.02 ^{**b}
6.	HFD + MD (medium dose)	115.57 ± 0.004 ^{**b}	110.43 ± 0.004 ^{**b}	41.31 ± 0.003 ^{**b}	40.67 ± 0.002 ^{**b}	126.80 ± 0.003 ^{**b}
7.	HFD + MD + Exercise	105.37 ± 0.002 ^{**b}	100.50 ± 0.003 ^{**b}	45.83 ± 0.003 ^{**b}	40.16 ± 0.003 ^{**b}	120.44 ± 0.004 ^{**b}
8.	HFD + HD (high dose)	121.83 ± 0.002 ^{**b}	115.66 ± 0.004 ^{**b}	39.50 ± 0.02 ^{**b}	42.50 ± 0.004 ^{**b}	128.17 ± 0.003 ^{**b}
9.	HFD + HD + Exercise	111.67 ± 0.002 ^{**b}	110.82 ± 0.007 ^{**b}	41.28 ± 0.003 ^{**b}	41.17 ± 0.004 ^{**b}	123.82 ± 0.002 ^{**b}
10.	HFD + Orlistat	125.66 ± 0.005 ^{**b}	120.63 ± 0.006 ^{**b}	38.82 ± 0.004 ^{**b}	45.82 ± 0.004 ^{**b}	130.01 ± 0.004 ^{**b}
11.	HFD + Orlistat + Exercise	118.82 ± 0.004 ^{**b}	113.76 ± 0.006 ^{**b}	40.55 ± 0.003 ^{**b}	42.55 ± 0.003 ^{**b}	126.81 ± 0.002 ^{**b}

All values are represented as mean ± SEM, n = 6. *****p<0.001,** ****p<0.01,** ***p<0.05**, when compared to **normal control group**, ^{a}**p<0.001,** ^{b}**p<0.01,** ^{c}**p<0.05**, when compared to **HFD control.**

Table: 4 Effect of treatment and exercise on organ weights

Sl. NO	EXPERIMENT GROUPS	HEART WT (gm)	LIVER WT (gm)	SPLEEN WT (gm)	KIDNEY WT (gm)
1.	Normal control	1.21 ± 0.003	7.07 ± 0.003	0.24 ± 0.003	1.54 ± 0.003
2.	HFD (high fat diet) control	1.25 ± 0.003 **	7.15 ± 0.004 **	0.28 ± 0.003 **	1.57 ± 0.003 **
3.	HFD + Exercise	1.24 ± 0.002 **	7.15 ± 0.004 **	0.27 ± 0.003 **	1.57 ± 0.003 **
4.	HFD + LD (low dose)	1.24 ± 0.002 **	7.15 ± 0.004 **	0.28 ± 0.003 **	1.57 ± 0.003 **
5.	HFD + LD + Exercise	1.24 ± 0.002 **	7.14 ± 0.003 **	0.27 ± 0.003 **	1.56 ± 0.003 **
6.	HFD + MD (medium dose)	1.24 ± 0.002 **	7.13 ± 0.006 ^{**b}	0.27 ± 0.003 **	1.55 ± 0.003 ^{**b}
7.	HFD + MD + Exercise	1.22 ± 0.004 ^{b}	7.11 ± 0.006 ^{**b}	0.25 ± 0.003 ^{b}	1.55 ± 0.003 ^{**b}
8.	HFD + HD (high dose) +	1.24 ± 0.002 **	7.13 ± 0.004 ^{**b}	0.27 ± 0.003 **	1.56 ± 0.003 **
9.	HFD + HD + Exercise	1.22 ± 0.004 ^{b}	7.12 ± 0.006 ^{**b}	0.25 ± 0.003 ^{b}	1.55 ± 0.003 ^{**b}
10	HFD + Orlistat	1.24 ± 0.004 **	7.14 ± 0.003 **	0.27 ± 0.003 **	1.56 ± 0.003 **
11.	HFD + Orlistat + Exercise	1.22 ± 0.004 ^{b}	7.13 ± 0.004 ^{**b}	0.26 ± 0.003 ^{*b}	1.56 ± 0.003 **

All values are represented as mean ± SEM, n = 6. *****p<0.001,** ****p<0.01,** ***p<0.05**, when compared to **normal control group**, ^{a}**p<0.001,** ^{b}**p<0.01,** ^{c}**p<0.05**, when compared to **HFD control.**

Blood glucose

Treatment showed a significant decrease in blood glucose levels when compared with the HFD control group. HFD + intermediate dose of ethanolic extract of *Mangifera indica* (300 mg/kg) + exercise showed more potential effect than all the other treatment groups (Table 3).

Organ and Fat Pad weights

Treatment groups showed a significant activity in decreasing the organ and fat pad weights. HFD + intermediate dose of ethanolic extract of *Mangifera indica* (300 mg/kg) + exercise showed more potential effect than all the other treatment groups (Table 4 and 5).

Table: 5 Effect of treatment and exercise on fat pad weights

Sl.NO	EXPERIMENT GROUPS	EPIDIDYMAL FAT(gm)	MESENTRIC FAT (gm)
1.	Normal control	5.50 ± 0.04	4.57 ± 0.06
2.	HFD (high fat diet) control	7.96 ± 0.04**	7.04 ± 0.06**
3.	HFD + Exercise	7.67 ± 0.06**	6.64 ± 0.10**
4.	HFD + LD (low dose)	7.26 ± 0.25^{**b}	6.91 ± 0.18**
5.	HFD + LD + Exercise	6.83 ± 0.11^{**b}	6.35 ± 0.13^{**b}
6.	HFD + MD (medium dose)	6.43 ± 0.07^{**b}	5.57 ± 0.13^{**b}
7.	HFD + MD + Exercise	5.64 ± 0.10^{b}	4.87 ± 0.05^{b}
8.	HFD + HD (high dose)	6.57 ± 0.09^{**b}	5.87 ± 0.08^{**b}
9.	HFD + HD + Exercise	5.90 ± 0.03^{b}	5.08 ± 0.04^{**b}
10	HFD + Orlistat	6.89 ± 0.03^{**b}	6.30 ± 0.02^{**b}
11.	HFD + Orlistat + Exercise	6.31 ± 0.08^{**b}	5.61 ± 0.09^{**b}

All values are represented as mean ± SEM, n = 6. *****p<0.001,** ****p<0.01,** ***p<0.05**, when compared to **normal control group**, ^{a}**p<0.001,** ^{b}**p<0.01,** ^{c}**p<0.05**, when compared to **HFD control.**

DISCUSSION

In the present work an attempt was made to evaluate the effect of ethanolic extract of *Mangifera indica* leaves for its anti-obesity activity on rats together with the role of exercise on weight reduction. The ethanolic extract was chosen for the reason that most important potent chemical constituents are present in the ethanolic extract which may also be relevant to the treatment regimen intended in this study.

During the induction of obesity by high fat diet, it was well observed that the rats had increased in weight, the biochemical parameters like LDL, blood glucose, cholesterol and triglycerides, the organ and fat pad weights were also higher and a decrease in HDL level than that of normal was observed. This indicates that the diet given was appropriate to induce obesity.

The values obtained from body weights, organ and fat pad weights and the serum biochemical parameters shows that the ethanolic extract of *Mangifera indica* at intermediate dose of 300mg/kg, together with exercise gives most promising results for management of obesity. High dose together with exercise was found to be equally effective. Reducing the absorption of fat can be an effective adjunct to dieting in obese patients. Since *Mangifera indica* leaves has shown to inhibit both PL and LPL, it is possible that the extract affects both intestinal fat absorption and the uptake of fatty acids in adipose tissue, if enough of the active components enter the blood stream. By inhibiting both PL and LPL the drug inhibits the digestion of triglycerides to free fatty acids and monoglycerides. Thus it is excreted unchanged in faeces.

Diet and physical exercise remain as main stay in obesity management; nonetheless anti-obesity drugs are required to either reduce appetite or to inhibit fat absorption. Various factors are found to be involved in obesity including genetic, environmental, behavioral and socio-economic factor.

The present study indicates that administration of HFD to the animals for 40 days significantly ($p<0.01$) increased body weight, LDL, triglycerides, cholesterol, blood glucose, organ weights (heart, liver, spleen and kidney) and fat pad weights (epididymal fat and mesenteric fat) and caused a decrease in HDL level when compared with the normal control. HFD (high fat diet) is a standard diet widely used to induce obesity in

experimental animals. The composition of HFD is pork fat, vegetable oil, sucrose, casein, Nacl, dextrin, corn starch, vitamin mix and mineral mix. Earlier research indicates that exposure of these ingredients to the experimental animals alters the metabolic mechanisms resulting in obesity. The data indicated that HFD induced obesity is due to hyperlipidemia and hyperglycemia were evidence by gain in body weight, increase in triglyceride level and as well as increasing in the glucose levels. Our observation also indicates that HFD administration for 40 days increased parameters suggested for obesity. Similar mechanisms could have contributed in increased body weight, altered lipid profile, and enhanced fat deposition in the present study.

When obese animals were subjected to physical exercise for 40 days, we found that there was significant difference ($p<0.01$) in body weight, lipid profile, fat deposition and blood glucose level compared to HFD control. Physical exercise increases the metabolic rate in the body. It enhances the digested fat to provide energy. The regular exercise was also reported to enhance the breakdown of deposited fat contributed in reduced body weight, normalize altered lipid profile, and regulate blood glucose. The earlier research indicated that exercised animals had increased in energy expenditure through exercise training and contributed in the lower body weight gain and higher free fatty acid (FFA) mobilization from other adipose tissue. Our study suggests that similar mechanism might have followed in this study too when obese animals were subjected to exercise.

Administration of orlistat for 40 days reversed the obesity parameters significantly ($p<0.01$) compared to the HFD control. Orlistat is a standard drug widely used experimentally to reduce obesity in animals. The earlier research indicated that orlistat is a pancreatic lipase inhibitor and decrease body weight. Pancreatic lipase is the key enzyme for dietary fat digestion and inhibition of the enzyme could be an effective way to alter fat absorption. Orlistat binds covalently to the active site on pancreatic lipase and forms a stable complex. The complex undergoes a conformational change in the enzyme that leads to a lid-like structure on the lipase, hence exposing the catalytic active site. This operation leads to acylation of a hydroxyl group on serine residue burden on the active site of the enzyme making it inactive as lipase. The inactivated lipase is unable to hydrolyze fats into fatty acids and monoglycerides, which lead to their passage with faeces.

When obese animals were subjected to combination of physical exercise and orlistat for 40 days, we observed that the reversal in parameters was more prominent ($p<0.01$) compared to individual exercise and orlistat treatment. The results suggest that the mechanism mentioned above have potentiated the anti-obesity action when used in combination.

When we consider the treatment groups, it was evident that the obesity parameters were significantly ($p<0.01$) reduced. The active ingredient in *Mangifera indica* which is responsible for anti-obesity, Mangiferin, inhibit both PL and LPL, it is possible that the extract affects both intestinal fat absorption and the uptake of fatty acids in adipose tissue, if enough of the active components enter the blood stream. So we can say that enough of the active component required to show the action entered the blood stream.

When the obese animals were subjected to physical exercise in combination with the drug treatment the reduction of the anti-obesity parameters were more significant ($p<0.01$) than the individual exercise and treatment groups. The result suggests that the above mentioned mechanism for physical exercise and Mangiferin might have potentiated the anti-obesity action when used in combination.

So from all the above findings we conclude that, the combination of intermediate dose (300 mg/kg) of the drug and exercise had shown the most promising effect as compared to all other groups. These observations indicates that intermediate dose of ethanolic extract of leaves of *Mangifera indica* (300 mg/kg) in combination with exercise have reduced the parameters for anti-obesity activity. This suggests that the group could have produced synergic effects when used in combination. So, proper treatment with physical exercise, play a vital role in controlling obesity.

CONCLUSION

It can be concluded that HFD + *Mangifera indica* intermediate dose (300 mg/kg) + Exercise group is effective in reducing Body weight, Lipid parameters, organ weight, mesenteric and epididymal fat when compared to HFD control.

Exercise shows higher free fatty acid (FFA) mobilization from adipose tissue, Mangiferin affects both intestinal fat absorption and the uptake of fatty acids in adipose tissue and orlistat shows pancreatic lipase inhibitory activity, because of that reason obese rats are reducing body weight.

If opportunity permits, deeper and thorough research work shall be carried out in this field. Based on results obtained we conclude that HFD + ethanolic extract of leaves of *Mangifera indica* intermediate dose (300 mg/kg) + Exercise group was more effective than rest of all HFD combination groups.

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