Potential Benefits of Ethanol extract of Anredera cordifolia for Antiobesity of High Fat diet-Induced Obesity in White Male Rat Wistar

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Abstract

Obesity-related deaths continue to rise, and thus losing weight in overweight and obese patients is critical to prevent complications. *Anredera cordifolia (Ten,) Steenis*, species of succulent plant of the genus Basellaceae, is widely used in herbal medicine to decrease body weight. This study evaluated the potential benefits of Anredera cordifolia ethanol extract to reduce body weight in high-fat diet-induced obesity rat model. This was an experimental with post-test only control group design study involving 36 obese rats. They were divided into two groups: three control groups (K1, K2, K3) and three treatment groups (P1, P2, P3). All the groups were induced with high-fat diet, except K1 control group that received a standard diet. K2 group received no treatment, and K3 group was given orlistat. Whereas, treatment group received Anredera cordifolia ethanol extract at different dose, such as 50 mg/kg BW (P1), 100 mg/kg BW (P2), and 150 mg/kg BW (P3). After 4 weeks of treatment, all groups of rats were sacrificed. ERK levels and PPARγ in abdominal visceral adipose tissue were measured using ELISA and immunohistochemistry. Body weight and abdominal circumference were measured through anthropometric examination. Weight loss was observed in the groups that received 100 and 150 mg/kg BW Anredera cordifolia ethanol extract, followed by the decrease in ERK levels and PPAR expression. Ethanol extract of *Anredera cordifolia* used as an antiobesity in this study decreased PPARγ transcription factor and reduced ERK levels to inhibit adipogenesis.

Keywords: Anredera cordifolia, Rat obesity model, High fat diet, ERK levels, PPARγ

Introduction

Obesity is defined as an accumulation of mature adipocytes in adipose tissue. It is characterized by the increase in adipose tissue mass[1-5] due to the increase in adipocyte number

(hyperplasia) or adipocyte volume (hypertrophy)[5]. Both processes may also occur due to the maturation of adipocyte progenitor cells (preadipocytes) into adipocytes[6]. Therefore, in addition to controlling food intake and increasing energy expenditure[7], the principle of weight loss is also effective through a mechanism that inhibits adipogenesis by slowing the process of adipocyte proliferation and differentiation, which is expected to reduce overweight and obesity[8].

Peroxisome Proliferator Activated Receptor (PPARγ) is a transcription factor important to the differentiation and proliferation of adipocyte cells, making PPAR a key factor in the adipogenesis process[9]. The extracellular signal-regulated kinase (ERK) plays a role in adipogenesis[10]. Previous research suggested that the inhibition of ERK pathway during early stages of differentiation slowed down adipogenesis, which implied that ERK pathway played a positive role in adipogenesis[11].

This study evaluated the potential benefits of using Anredera cordifolia ethanol extract as antiobesity to reduce body weight by measuring ERK levels and PPAR expression as molecular protein parameters.

Materials and Methods

Material

Anredera cordifolia were collected from Tiganderket highland, Kabanjahe, North Sumatra, Indonesia. Phytochemical screening test was carried out for ethanol extract of *Anredera cordifolia* (EEAC), which identified flavonoids, saponins, tannins, and steroids/triterpenoids.

Male Wistar rats, 8 weeks old, weighing between 100 and 150 grams, healthy and active in appearance (eating and drinking, no injuries, body defects or hair loss) during the study were the inclusion criteria for the research subjects. The exclusion criteria were rats that suffered other diseases or injuries during the study and those that did not survive until the end of the study. Rats were individually housed in a cage at a temperature range of 22-25°C. They were subjected to a 12-hour light/dark cycle based on when the experiments were carried out.

Grouping of Rats

All of the rats were acclimatized for one week. A total of 36 rats were randomly divided into 3 control groups (K1, K2, K3) and 3 treatment groups (P1, P2, P3). All the groups were induced with high-fat diet, except for K1 control group that received a standard diet. K2 control group received no treatment after high-fat diet and K3 control group received orlistat. Treatment groups received different dose of *Anredera cordifolia* ethanol extract, such as P1 received 50 mg/kgBW dose, P2 received 100 mg/kgBW dose, and P3 received 150 mg /kgBW dose. Animal model was considered obese when their body weight increased by more than 20% from their initial weight[9]. After high-fat diet induction for 8 weeks, the rat sbujects received the treatment accordingly to their group for 4 weeks. Next, all the rat subjects were sacrificed using intraperitoneal injection of ketamine at a dose of 75 mg/kg BW. Through open abdomen procedure, all fat contained in the abdomen was isolated and placed on Petri dishes. ERK levels were examined by ELISA and PPAR γ expression was examined by immunohistochemical methods.

ELISA Examination Procedure

The measurement of ERK levels was carried out by first isolating adipose tissue from the abdominal cavity. After that, adipose tissue was washed in normal saline, fixed in 10% neutral-buffered formalin solution, and frozen using liquid nitrogen in a round microbottle vessel.[12]

Examination Procedure of Expression PPARγ

Assessment of adipose tissue PPARγ expression was done semi-quantitatively across a broader spectrum, using Immunoreactive Score (IRS) category by Remmele and Stegner[10]. IRS evaluated the percentage score of cell distribution and staining intensity score. IRS was determined by multiplying the percentage score of cell distribution with staining intensity score. The IRS category was further subdivided as follows: 0 = No protein expression, 0-3 = Low protein expression, 4-8 = Moderate protein expression, 9-12 = High protein expression.

Statistical Analysis:

The data were analyzed using SPSS software version 20.0 using *One way annova test*, post hoc LSD analysis, *Kruskal Wallis*, and *Mann Whitney* analyses. P-values less than 0.05 ($P < 0.05$) were considered statistically significant.

Results and Discussion

Results:

The investigation of the potential benefits of using *Anredera cordifolia* as antiobesity in male Wistar rat obesity model induced by high-fat diet involved the measurement of body weight, abdominal circumference, protein molecular ERK levels by ELISA method, and PPARγ expression at adipose tissues of fat abdominal visceral. The characteristics of the experimental animal sample, such as the male Wistar rats, were in the form of body weight and abdominal circumference before and after high-fat diet and after treatment. The body weight of rats before and after high-fat diet induction for 8 weeks as obese animal model is shown in Table 1 below. The body weight of rats was relatively the same before high-fat diet, with p>0.05 from one way annova test. Dependent t-test revealed a significant increase in body weight of rat subjects from each group after being fed a high-fat diet for 8 weeks (p<0.05).

Table 1. Body weight (BW) of experimental animals before and after high-fat diet induction

Groups	BW before (gram) Mean ± SD	P value	BW before (gram) Mean (SD)	BW after (gram) Mean (SD)	p value
K1 (n=6)	106.67 ± 8.04		106.67 ± 8.04	178.33± 3.72	0.027**
K2 (n=6)	110.83 ± 12.69	0.787*	110.83 ± 12.69	219.67±21.18	0.043**
K3 (n=6)	118.67 ± 16.90		118.67 ± 16.90	223.67±17.95	0.043**
P1 (n=6)	112 ± 11.98		112 ± 11.98	215.83±18.87	0.043**
P2 (n=6)	114.67 ± 18.48		114.67 ± 18.48	218.33±22.39	0.028**
P3 (n=6)	110.67 ± 15.54		110.67 ± 15.54	208.17±17.29	0.028**

Note: The average value is presented in the form of the mean (SD)
p>0.05 *with one way annova test***
**=significant (p<0.05) with dependent t test

The abdominal circumferences before and after high-fat diet induction are shown in Table 2 below. Dependent t-test revealed that there were differences in abdominal circumference of rat subjects from each group before and after high-fat diet induction with p<0.005. Abdominal circumference of rats was relatively the same before high-fat diet induction for 8 weeks, with p>0.05 from Kruskal-Wallis test.

Table 2. Abdominal circumference (AC) before and after high-fat diet induction

Groups	AC before (cm) Median (min-max)	p value	AC before (cm) Median (min-max)	AC after (cm) Median (min-max)	p value
K1 (n=6)	9.9 (9.5-10.1)		9.9 (9.5-10.1)	12.8(12-12.8)	0.027**
K2 (n=6)	10.05 (9.5-10.3)		10.05 (9.5-10.3)	14 (13-14.5)	0.043**
K3 (n=6)	10.05 (9.7-10.2)	0.748*	10.05 (9.7-10.2)	14 (13.5-14.6)	0.043**
P1 (n=6)	10 (9.9-10.2)		10 (9.9-10.2)	14 (13.5-14.5)	0.042**
P2 (n=6)	10 (9.8-10.2)		10 (9.8-10.2)	13.7 (13.5-15)	0.027**
P3 (n=6)	9.95 (9.8-10.3)		9.95 (9.8-10.3)	13.85(12.5-14.3)	0.028**

Note: Data is in the form of median (min-max)
*p < 0.05 statistically significant
**=significant (p<0.05) with dependent t tes *p>0.05 with One way Annova test

The body weight of the obese model rat group decreased after 4 weeks of treatment using *Anredera cordifolia* ethanol extract. The decrease was observed in P2 and P3 treatment groups receiving 100 mg/kg BW and 150 mg/kg BW (P3) *Anredera cordifolia* ethanol extract, respectively. But, P1 treatment group receiving 50 mg/kg BW *Anredera cordifolia* ethanol extract did not show weight reduction.

Body weight after high-fat diet and treatment is shown in Table 3. The average weight loss in K3 control group receiving orlistat was 22 grams, compared to 11 grams weight loss in P2 treatment group and 4 grams weight loss in P3 treatment group.

Table 3. Body weight after high-fat diet induction and treatment

Groups	BW (obesity)	BW after treatment	p value
	Median (min-max)	Median (min-max)	
K1 (n=6)	180 (171-181)	212.5 (208-215)	0.027*
K2 (n=6)	231 (195-242)	261 (209-290)	0.043*
K3 (n=6)	220 (198-248)	198 (189-235)	0.068
P1 (n=6)	215 (191-241)	217 (190-223)	0.686
P2 (n=6)	210 (200-260)	199.50 (198-248)	0.075
P3 (n=6)	211.5(180-231)	207.50 (190-228)	0.528

Note: Data is in the form of median (min-max)
*=significant (p<0.05) with dependent t test.

Table 4 shows the abdominal circumference of all rat subjects after high-fat diet induction and treatment. P1 and P2 treatment groups receiving 50 and 100 mg/kg BW *Anredera cordifolia* ethanol extract, respectively showed a significant decrease in abdominal circumference (p<0.05). On the other hand, P3 treatment group receiving 150 mg/kgBB *Anredera cordifolia* ethanol extract did not show a significant decrease in abdominal circumference (p>0.05). There was also no significant decrease in abdominal circumference (p>0.05) in K3 control group receiving orlistat.

Table 4. The abdominal circumference after high-fat diet induction and treatment.

	AC obesity	AC after treatment	p value
	Median (min-max)	Median (min-max)	
K1 (n=6)	12.8(12-12.8)	13.6 (13.4-13.8)	0.026*
K2 (n=6)	14 (13-14.5)	16.5 (15-17)	0.041*
K3 (n=6)	14 (13.5-14.6)	14 (13.2-14)	0.063
P1 (n=6)	14 (13.5-14.5)	13.7 (13.3-14.4)	0.041*
P2 (n=6)	13.7 (13.5-15)	13.35 (13.2-13.5)	0.043*
P3 (n=6)	13.85(12.5-14.3)	13.4 (13-14)	0.345

Note: Data is in the form of median (min-max)
*p < 0.05 statistically significant
*=significant (p<0.05) with dependent t test

Table 5 shows the ERK level in adipocytes of the rat subjects. The mean ERK level in K1 control group was 9.012± 2.38 ng/ml. The mean ERK level in K2 control group was 10.17± 2.98 ng/ml. The mean ERK level in K3 control group was 11.11 ±1.40 ng/ml. While, the mean ERK levels of the treatment group were 8.62± 1.28 ng/ml, 8.97±1.29 ng/ml, and 10.22 ±2.30 ng/ml, respectively for P1,

P2, P3 treatment groups. The mean ERK levels decreased in P1 and P2 treatment groups compared to the mean ERK levels in K1, K2, and K3 control groups.

Table 5. ERK levels in adipocytes

ERK Levels(ng/ml) adipose cells		
Group	Mean±SD	p value
K1	9.012±2.38	
K2	10.17±2.98	
K3	11.11±1.40	0.349
P1	8.62± 1.28	
P2	8.97±1.29	
P3	10.22±2.30	

*p < 0.05 statistically significant
One way annova test

We found that there was a significant difference in PPAR *Immunoreactive Score* (IRS) immunohistochemical staining results among the subject groups (p<0.05). There was a significant difference in IRS PPARγ between K1 control group and K3 control group, which also significantly different from P1, P2, and P3 treatment groups with p<0.05. There was a significant difference in IRS PPAR between K2 control group and P1, P2, and P3 treatment groups with p<0.05. There was a significant difference in IRS PPAR between K3 control group and P1, P2, and P3 treatment groups. P3 (p<0.05) showed a significant difference between P1 and P2 treatment groups. There was a significant difference between P1 treatment group and P2 and P3 treatment groups (p<0.05).

The IRS value for all samples in the standard diet control group (K1) was 9, indicating that all samples in the group had high PPAR protein expression. In contrast, the IRS value for all samples in K2 group was 6 (6–9), indicating that PPAR protein expression in this group was moderate to high. The samples in the high-fat diet control group with orlistat (K3) displayed low to moderate levels of PPARγ protein, according to a protein expression level score of 3 (3-6) in this group. The expression of PPAR protein was low in P1, P2, and P3 treatment group receiving different doses of *Anredera cordifolia* ethanol extract. Table 6 and Fig 1 display the analysis results of PPAR protein expression from immunohistochemical expression.

Table 6. IRS Expression Score PPPAR γ results of immunohistochemical

Groups	Total scoreIRS PPARγ	P value	Groups	Post hoc				
				K2	K3	P1	P2	P3
K1	9		K1	0.126	0.004*	0.004**	0.002**	0.002**
K2	6 (6-9)		K2		0.056	0.008**	0.004**	0.004**
K3	3 (3-6)	0.000*	K3			0.310	0.009**	0.017**
P1	3		P1				0.017**	0.004**
P2	2 (2-3)		P2					0.699
P3	2		P3					

*p < 0.05 statistically significant
*= significant (p<0.05) with Kruskal Wallis test
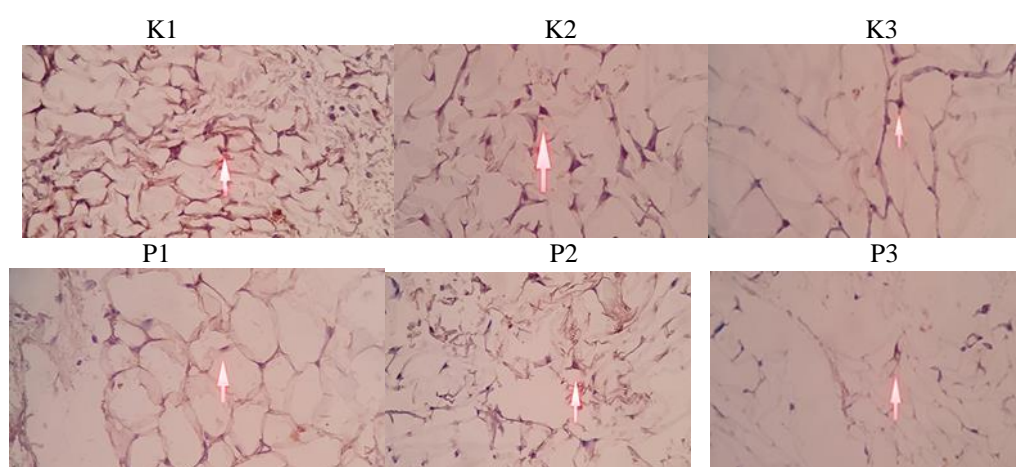**=significant (p<0.05) *with Mann Whitney test*

Figure 1. The immunohistochemistry labeling with anti-PPARγ antibodies revealed the morphology of adipocyte visceral adipose tissue in control and treatment groups. The treatment groups (P1, P2, P3) showed significant changes in the PPAR-gamma immunohistochemistry stained cells compared to the control group (arrows; 400x magnification).

Discussion:

There was a significant difference in the mean body weight between K1 control group receiving standard diet control group and K2 and K3 control groups induced by high-fat diet, as well as all subjects in treatment groups (p<0.05). The result of this study was consistent with other research, where the increase in body weight due to high-fat diet led to higher body weight than a standard diet[11]. A high-fat diet lasting for 8 weeks is commonly used to induce obesity in experimental animal models [12] and produces negative effects[13], indicating that diet is the primary cause of the obesity epidemic[14].

The use of *Anredera cordifolia* ethanol extract as an antiobesity agent has been shown to reduce weight in P2 and P3 treatment groups receiving 100 and 150 mg/kgBW *Anredera cordifolia* ethanol extract. But, P1 treatment group receiving 50 mg/kgBW *Anredera cordifolia* ethanol extract did not show weight reduction. In this study,

body weight decreased by 10.5 grams in P2 group and 4 grams in P3 groups. Whereas, K3 control group showed 22 grams weight loss. In this study, a dose of 100 mg reduced body weight for 4 weeks longer than a dose of 150 mg/kg BW.

This study also found that *Anredera cordifolia* ethanol extract at doses of 50 and 100 mg/kg BW resulted in significant decreases in abdominal circumference (p<0.05), but not at a dose of 150 mg/kg BW (p> 0.05). A dose of 100 mg/kg BW resulted in a greater reduction in abdominal circumference than a dose of 50 mg/kg BW. The use *Anredera cordifolia* ethanol extract could significantly reduce abdominal circumference at a dose of 50 mg/kg BW (P1) and 100 mg/kg BW (P2). There was no significant decrease in abdominal circumference at a dose of 150 mg/kg BW (P3). The administration of orlistat in K3 control group did not show a significant decrease in abdominal

circumference (p>0.05). In conclusion, the use of *Anredera cordifolia* ethanol extract could also reduce abdominal circumference. Previous study reported that the use of orlistat inhibited fatty acid synthase[12].

We found that the ERK levels of K2 control group were the highest. It was stated in earlier studies that rats induced by high-fat diet experienced adipose tissue hypertrophy as a result of increased ERK activity[13]. In this study, high-fat diet induced rats had higher body weights than rats given standard diet. ERK levels were decreased in P1 and P2 treatment groups. But, there was no decrease in ERK levels in P3 treatment group. The decrease in ERK levels was compared to K2 control group. The treatment group receiving 150 mg/kg BW *Anredera cordifolia* ethanol extract showed a slight increase in ERK levels as compared to the mean ERK level in K2 control group. As we know, ERK signal is triggered during the beginning process of adipogenesis, resulting in the increase in ERK levels. It is believed that ERK activation plays a role in the development of fat (adipogenesis)[14]

Another research, however, based on in vitro studies reported conflicting observations. The research reported that continued activation of ERK would reduce adipogenesis. It was due to the fact that this sustained activation could inhibit the expression of PPARγ through MAPK-mediated phosphorylation[15]. The reduction in ERK levels in

the treated rat group with 50 and 100 mg/kg BW *Anredera cordifolia* ethanol extract suggested that *Anredera cordifolia* extract could aid weight loss by inhibiting the process of adipogenesis. ERK levels were greater in K3 control group receiving orlistat compared to K2 control group receiving no treatment. Orlistat treatment did not lower ERK levels. Enhanced ERK activation would boost the hypertrophy of adipocyte cells[16].

PPARγ is found in many tissues but is especially abundant in adipose tissue. It has a significant impact on a variety of metabolic disorder. Moreover, it stimulates preadipocyte differentiation into adipocytes in adipose tissue, as well as mobilization of bone marrow-derived circulating progenitor cells into white adipose tissue and differentiation into adipocytes[17]. The study showed that there were significant differences in PPARγ expression in the treatment group compared to the control group (p<0.05) Previous research has shown that lower PPARγ expression indicated a decrease in adipogenesis[18]. In this study, decreased ERK levels were observed in the treatment groups, which suggested the inhibition of adipogenesis process, in addition to a decrease in PPARγ expression, which is a transcription factor of the adipogenesis process. This is in accordance with previous studies which stated that a decrease in the adipogenesis process involved a decrease in the expression of PPARγ and a decrease in ERK levels[19-21]

Conclusion

The use of ethanol extract of *Anredera cordifolia* as an anti-obesity agent by reducing the PPARγ expression and ERK levels so that the process of adipogenesis decreases. The effective dose for weight loss and abdominal circumference

reduction was 100 mg/kgBW. Toxicity or cytoxicity of *Anredera cordifolia* ethanol extract should be studied to learn the range of dosage acceptable for applications.

Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- The author has signed an animal welfare statement.
- Ethical Clearance: The project was approved by the local ethical committee in Universitas Sumatera Utara, Medan, Indonesia.

- Ethic Statement: All animal experiments complied with ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines. The research protocol applied in this research has been approved by The Research Ethics Committee at Medical Faculty, Universitas Sumatera Utara (approval No. 705./KEP/USU/2022).

Authors' Contribution Statement

R.R conceived this idea, based on the expressions of I. L. F, R.Z.H, S. S. W. supervised the project. S. I. and D. P.P carried out the experiment, wrote the manuscript, and performed the analysis. All authors discussed the results and contributed to the final manuscript

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الفوائد المحتملة لمستخلص الإيثانول من نريديرا كورديفوليا لمقاومة السمنة بسبب السمنة التي يسببها النظام الغذائي عالي الدهون في ذكور الفئران البيضاء

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[3] قسم علم الأدوية ، كلية الطب ، جامعة سومطرة أوتارا ، ميدان ، إندونيسيا
[4] قسم طب المجتمع ، الصحة العامة ، كلية الطب ، جامعة سومطرة أوتارا ، ميدان إندونيسيا
[5] قسم الأحياء ، كلية الرياضيات والعلوم الطبيعية ، جامعة سومطرة أوتارا ، ميدان ، إندونيسيا
[6] قسم طب الأنف والأذن والحنجرة ـ جراحة الرأس والرقبة ، كلية الطب ، جامعة سومطرة أوتارا ، ميدان ، إندونيسيا
[7] كلية الصيدلة ، جامعة الأندلس ، بادانغ ، إندونيسيا
[8] قسم أمراض النساء والولادة ، كلية الطب ، جامعة سومطرة أوتارا ، ميدان ، إندونيسيا
[9] قسم الطب النفسي ، كلية الطب ، جامعة سومطرة أوتارا ، ميدان ، إندونيسيا

الخلاصة

تستمر الوفيات المرتبطة بالسمنة في الارتفاع ، لذلك من الضروري إنقاص الوزن لتجنب المضاعفات ، نريديرا كورديفوليا هو نوع من النباتات النضرة من الجنس، باسيللسيا يستخدم على نطاق واسع في طب الأعشاب لتقليل وزن الجسم. تهدف الدراسة الحالية إلى تقييم الفوائد المحتملة لمستخلص الإيثانول من نريديرا كورديفوليا لنماذج الفئران السمنة لتقليل الوزن الناجم عن نظام غذائي عالي الدهون. من خلال تجريب مع اختبارات ما بعد فقد تم تصميم مجموعة ضابطة مع نموذج سمنة 36 جرذًا ، مقسمة إلى مجموعتين: ثلاث مجموعات تحكم (K1، K2، K3)وثلاث مجموعات معالجة (K1، K3، P1) (K4) P2، P3) ، أعطيت جميع مجموعات تحتوي على نسبة عالية من الدهون باستثناء K1 نظام غذائي قياسي ، K2 بدون علاج ، و K3 مع أورليستات. تلقت مجموعة العلاج من مستخلص الإيثانول نريديرا كورديفوليا بجرعات مختلفة ، P1 50 مجم / كجم من وزن الجسم ، P2 100 مجم / كجم من وزن الجسم، و P3 150 مجم / كجم من وزن الجسم. بعد 4 أسابيع من العلاج، قُتلت جميع مجموعات الفئران ، وتم قياس مستويات ERK و PPARγ في الأنسجة الدهنية الحشوية في البطن باستخدام ELISA والكيمياء المناعية. يتم قياس وزن الجسم ومحيط البطن أثناء فحص القياسات، وقد لوحظ فقدان الوزن عند تناول مستخلص الإيثانول نريديرا كورديفوليا بجرعات 100 و 150 مجم / كجم من وزن الجسم، مع انخفاض مستويات ERK وPPARγ . يستخدم مستخلص الإيثانول من نريديرا كورديفوليا كمضاد للسمنة. تقلل آلية فقدان الوزن هذه من عامل نسخ PPARγ وتقلل من مستويات ERK بحيث تقل عملية تكوين الدهون.

الكلمات المفتاحية: نريديرا كورديفوليا ، نموذج بدانة الفئران ، نظام غذائي عالي الدهون ، مستويات ERK ،PPARγ.