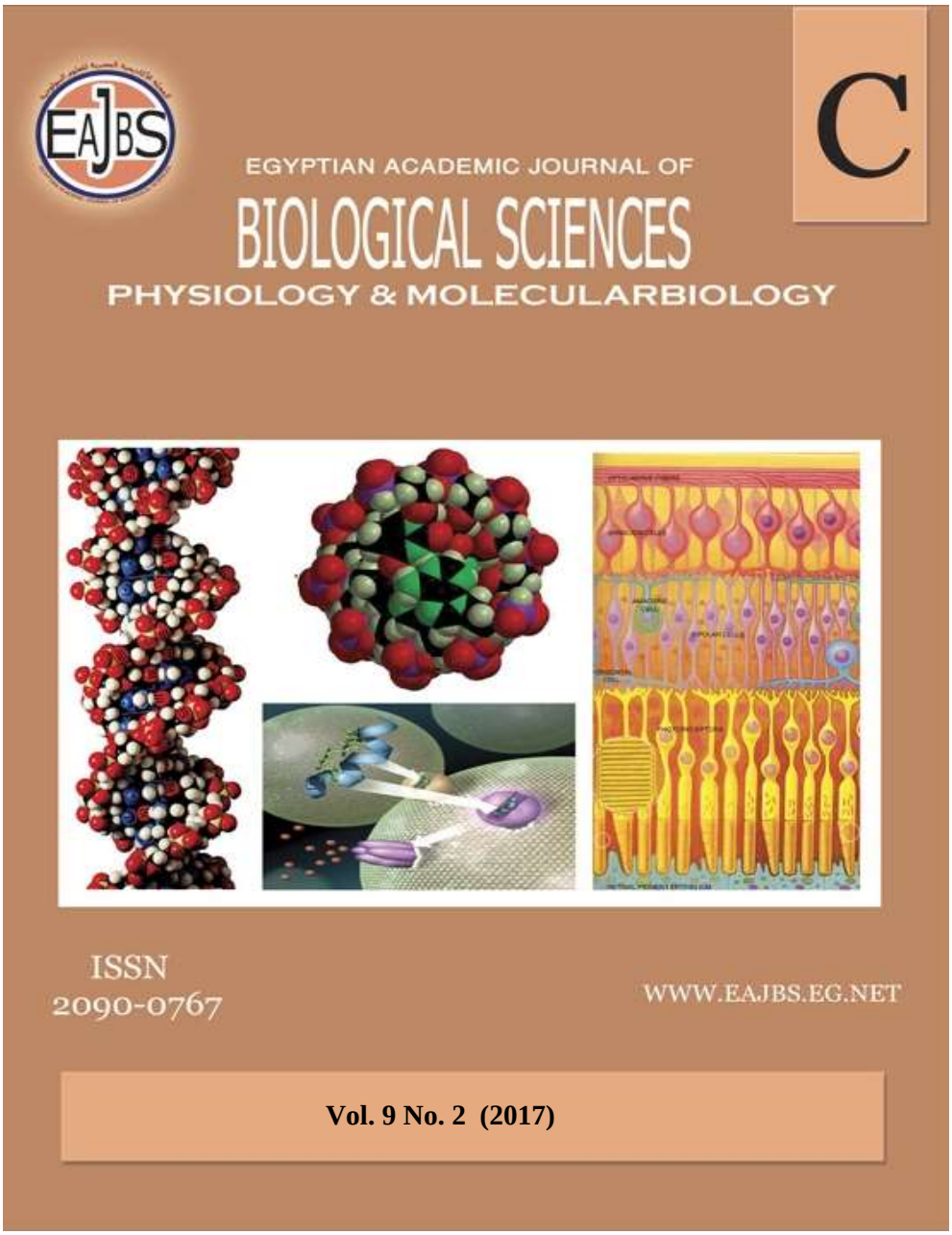

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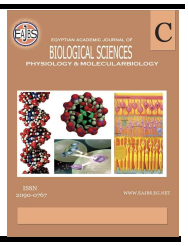

Uncaria tomentosa (cat claw) Counteracts Chronic Fipronil-induced Endocrine Disruption Induced Insulin Resistance and Hepatic Damage in Male Albino Rats

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ABSTRACT

The current study investigated the ability of *Uncaria tomentosa* (cat claw) to counteract fipronil (FIP) induced metabolic abnormalities. A total of 20 male adult albino rats were randomly divided into 4 groups (5 rats each). Control rats received only dis. water, Uncaria group was treated by dietary Uncaria 5g/kg, fipronil group rats treated with 3.23 mg/kg of FIP, and fipronil and Uncaria co-treated group was given 3.23 mg/kg FIP with 5g/kg dietary Uncaria. The doses were given every day for consecutive 12 weeks. Body weight, food intake and food conversion ratio (FCR) were determined. Blood samples were collected for estradiol and lipid profile estimation. Plasma liver enzymes were assayed. .Glucose and insulin were determined for Homa IR calculation. Liver tissues and abdominal fat were fixed for histopathological examinations. FIP-treated rats had no influence on body weight gain however, it increased ($P<0.05$) the food conversion ratio than other groups. Estradiol level was significantly ($P<0.05$) reduced by FIP however Uncaria ameliorated this decrease. Rats administrated FIP exhibited significantly higher cholesterol, triglycerides (TG), low-density lipoproteins (LDL) and liver enzymes (AST, and ALT) more than those in the other groups while it decreased ($P<0.05$) high-density lipoproteins (HDL). FIP produced a significant increase in insulin resistance (HOMA-IR) that was ameliorated by Uncaria. The liver of FIP-treated rats revealed vacuolar degeneration, lymphocytic infiltration and focal necrosis. Moreover, FIP increased diameter of fat cells. Uncaria combated FIP induced insulin resistance, liver damage and adiposity. Cat claw could effectively protect against metabolic disruption induced by FIP.

INTRODUCTION

Nowadays, Synthetic chemicals that are used in various agricultural and industrial aspects can lead to widespread contamination of the environment. The use of pesticides, antimicrobials, plasticizers, and flame retardants have been demonstrated to possess a serious concern on human health

(Casals-Casas and Desvergne, 2011). These compounds or materials are called endocrine-disrupting chemicals (EDCs). They can perturb hormonal balance and cause reproductive abnormalities (Kwintkiewicz and Giudice, 2009), developmental anomalies (Foster, 2006) and metabolic abnormalities (Newbold et al., 2008).

EDCs act chiefly by deregulating natural hormones due to their powerful effect for binding androgen or estrogen receptors (Tabb and Blumberg, 2006). They can bind these hormone receptors and act as antagonists thus blocking their action (Mnif *et al.*, 2011). Moreover, EDCs could perturb the synthesis, transport, metabolism and elimination of hormones, thus declining the blood level of the natural hormones (Cocco, 2002).

The Metabolic Syndrome (MS), also it is known as insulin resistance syndrome, is a prevalent multifactorial disease, that has been widely spread in the world. It is characterized by mainly 3 metabolic disorders; increase visceral adipose tissue, dyslipidemia, glucose intolerance with or without declined insulin sensitivity (Kaur, 2014).

Fipronil (FIP) is a member of the phenylpyrazole and is being widely used to combat ticks and fleas on the domestic animals. Insects that resist various types of insecticides are sensitive to FIP and therefore it is commonly used as an insecticide in many houses (Bobé *et al.*, 1997). FIP acts as the non-competitive blocker of GABA gated chloride channels in insects' central nervous system causing their death by paralysis (Hainzl *et al.*, 1998). FIP is metabolized primarily by mammalian hepatic tissue (de Medeiros et al., 2015) which behold as central organ for metabolism connecting the general circulation with the alimentary tract (Iwakiri and Groszmann, 2006). The hepatotoxic effect of FIP was previously described by previous study of Silva, (2008) as well as its adipogenic effect (Sun *et al.*, 2016).

Emerging herbal medication has been widely used to counteract the side effects of chemical medications along with these herbs, is cat claw *(Uncaria tomentosa).* This plant could cure several diseases like cardiac disease (Wang et al., 2007), arthritis (Piscoya *et al.*, 2001), inflammatory conditions (Sandoval et al., 2002) and cancer (Kośmider *et al.*, 2017). This plant is also thought to have a hepatoprotective effect (Navarro *et al.*, 2017)

The current research was performed to study the chronic effect of the oral FIP gavage on estradiol (E2) hormone level, liver function, lipid mass and profile, insulin resistance in adult male albino rats beside investigating possible protecting effect of cat claw.

MATERIALS AND METHODS

Animals:

A total of 16 adult male albino rats 150-160 g weight were bought from the Laboratory Animal House of Faculty of Veterinary Medicine, Suez Canal University, Egypt. They were kept to be acclimatized for 14 days before the beginning of the experiment. Rats were maintained in saw dust covered cages in a controlled room temperature around (24±2 °C). The experimental animals were allowed to free access for water and standard rodent diet. The protocols of this study were approved and conducted according to the ethical guidelines for the use of animals in laboratory experiments of the Faculty of Veterinary Medicine, Suez Canal University, Egypt.

Experimental Design:

Rats were grouped randomly into 4 groups (5 rats each). The control rats fed on a standard diet and received only dis. Water via gavage daily. Uncaria treated rats were given the standard diet with 5 g /kg Uncaria tomentosa (Food Now Co., USA) and received only dis. Water via gavage daily. Fipronil group treated with

3.23 mg/kg (1/30 of LD_{50}) of FIP (Zhejiang Yongnong Chem. Co., China) via gavage daily and got standard diet only. The last group treated with 3.23 mg/kg (1/30 of LD_{50}) of FIP via gavage daily and got a standard diet with 5 g /kg *Uncaria tomentosa*. The treatment continued for consecutive 12 weeks.

Body weight gain and food conversion ratio (FCR)

The body weight was obtained at the beginning and the end of the experimental period. Cumulative weight gain was obtained by subtracting the latter two values. Food intake was recorded during the experimental period. Food conversion ratio was calculated as follow:

FCR = (Feed consumption (g) /rat/12 weeks)/ (body weight gain (g) /rat/12 weeks)

Blood Sampling:

After 12 weeks of experimentation, fasted overnight rats were anaesthetized and euthanized. Blood samples were collected in sterilized plain tubes. Samples were left for 15 min. to clot and kept in the fridge for 3 h then centrifuged at 3000 rpm for 20 min. to obtain sera. The obtained sera were stored at - 20 ºC for liver enzyme and lipid profile assays.

Serum Estradiol (E2) Level:

Serum levels of E2 of both control and FIP treated rats were determined using enzyme-linked immunosorbent assay (ELISA) kit (CALBIOTECH Co., USA). The assay steps were followed according to the manufacturer's pamphlet.

Serum Lipid Profile:

Serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL), triglycerides (TG) and low-density lipoproteins were estimated calorimetrically by kits obtained from Biodiagnostic Co., Egypt.

Serum Liver Enzymes:

The activity of liver enzymes as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was measured by a colorimetric method using Diamond Diagnostic Kits (Egypt).

Glucose Estimation:

After overnight fasting, blood glucose levels of the experimental rats were determined via glucometer (Accu-Chek Active, Germany).

Insulin Estimation:

Serum insulin levels were estimated using commercial rat specific ELISA kits (Abnova, Germany) according to the manufacturer's pamphlet.

Homeostasis Model Assessment-Estimated Insulin Resistance (HOMA-IR) Calculation:

According to Matthews et al. (1985), HOMA-IR was calculated by the following formula:

HOMA-IR = fasting insulin (U/L) × fasting glucose (mg/dL)/405

Tissue Sampling:

Livers were dissected and obtained, rinsed with cold physiological saline (Nacl 0.85%), blotted with filter paper for drying and weighed. The weight of the liver was estimated. Liver for each rat was fixed in 10 % neutral buffered formalin for histopathological investigations. Abdominal fat was excised from each rat. Abdominal fats for each rat were fixed in 10 % neutral buffered formalin for histopathological and morphometric examination.

Histopathology:

Formalin fixed liver and fat sections of all rats at all groups were dehydrated in ascending ethyl alcohol concentrations of (70-100%) and then processed using standard procedures for Hematoxylin and Eosin (H&E) stain as illustrated by Bancroft *et al.* (2008) for histopathology.

Morphometric Examination for Fat Cells' Diameter:

The diameters of the fat cells were measured by selecting seven fields/ animal in all groups using image J program by the aid of calibrated micrometer (AbdelRazek *et al.*, 2013).

Statistical Analysis:

All values were expressed as mean ± standard error of the mean. The differences among groups were analyzed using GraphPad Prism (Version 5.01, GraphPad Software, San Diego, USA) using one-way analysis of variance (ANOVA) followed by post hoc which is Tukey's test for inter-group comparisons A $probability < 0.05$ is considered significantly differed.

RESULTS

Body Weight Gain and FCR:

The treatment with FIP produced non-significant variations between groups. The initial body weights of rats were non-significant at the beginning of the experiment. The FCR was significantly (P<0.05) increased in FIP treated rats than control and the administration of cat claw significantly (P<0.05) ameliorated this increase nearly around control values (Table 1).

Table (1): Effect of *Uncaria tomentosa* on final body weight gain and food conversion ratio (FCR) on fipronil intoxicated rats.

	Control	Uncaria	Fipronil	Fipronil +Uncaria
Initial weight (g)	75.00±1.34[a]	74.00±0.59[a]	73.75±1.42[a]	74.25±0.82[a]
Final weight gain (g)	96.75±0.82[a]	103.3±1.01[a]	99.00±2.79[a]	97.25±2.60[a]
FCR	1.50±0.08[a]	1.26±0.05[a]	1.85±0.07[b]	1.46±0.05[a]

Different superscripts within the same raw indicate significant difference at (P<0.05)

Serum Estradiol (E2) level:

Serum estradiol level was significantly (P<0.05) reduced in FIP treated rats than control. Treatment with Uncaria elvated the level of estradiol (P<0.05) than FIP group (Table 2).

Table (2): Effect of *Uncaria tomentosa* on serum estradiol, lipid profile, liver enzymes, HOMA-IR and fat cell diameter in fipronil intoxicated rats.

	Control	Uncaria	Fipronil	Fipronil+ Uncaria
Estradiol (ng/mL)	30.36± 1.17[a]	31.03±1.45[a]	19.52±0.47[b]	27.77±1.10[a]
HDL (mg/dL)	71.33±4.10[a]	75.33±3.28[a]	56.67±1.76[b]	67.67±2.03[c]
LDL (mg/dL)	117.7±1.62[a]	104.5±5.58[a]	131.4±13.96[b]	135.5±2.07[ab]
TG (mg/dL)	89.67±0.58[ab]	71.33±2.73[b]	102.7±7.22[a]	93.00±4.84[c]
Cholesterol (mg/dL)	82.33±6.17[a]	70.33±4.81[a]	87.00 ±2.52[a]	70.00±2.08[a]
HOMA-IR	0.30 ±0.01[a]	0.27±0.01[a]	0.38±0.03[b]	0.31±0.01[c]
ALT (U/L)	31.48±1.53a	26.42±0.66a	'74.01±4.21[b]	44.78 ±2.44[c]
AST (U/L)	46.35±2.12[a]	43.84 ±1.39[a]	123.2±5.81[b]	79.43±1.69[c]
Fat cells diameter (µm)	238.5±4.49[a]	230.2±3.45[a]	249.5±1.99[b]	238.4±2.23[c]

Different superscripts within the same raw indicate significant difference at (P<0.05)

Lipid Profiles:

The treatment of rat with FIP for 12 weeks produced significant (P<0.05) decrease in HDL while increased the levels of TG, cholesterol and LD than control and other groups. Dietary treatment of FIP intoxicated rats with cat claw (Uncatia) significantly (P<0.05) reduced the elevated levels of cholesterol and TG than FIP treated group. The level of LDL in fipronil+ uncaria group showed a numerical decrease than FIP group without reaching significant value (Table 2).

HOMA-IR:

Chronic administration of FIP for 12 weeks induced significantly (P<0.05) higher insulin resistance (HOMA-IR) than control and other groups. Co-administration of dietary cat claw with fipronil significantly ameliorated insulin resistance than FIP group (Table 2).

Liver Enzymes:

Rats gavaged FIP exhibited a significant (P<0.05) greater level of liver enzymes (AST and ALT) than control and other groups. The dietary supplementation with cat law with FIP

led to the significant (P<0.05) reduction of liver enzymes than FIP group (Table 2).

Histopathology:

The liver of the control and Uncaria group revealed the normal histological structure of hepatic tissue, normal polyhedral hepatocytes, symmetrical hepatic lobules with centrally located central veins and radiating hepatic lobules. The FIP group showed diffuse vacuolar degeneration of hepatocytes, dilated central veins, multifocal lymphocytic infiltrations and focal necrosis of some hepatocytes. The Uncaria and FIP treated group showed marked protection of hepatocytes, that revealed mild lymphocytic aggregations and mild vacuolar degeneration (Fig. 1).

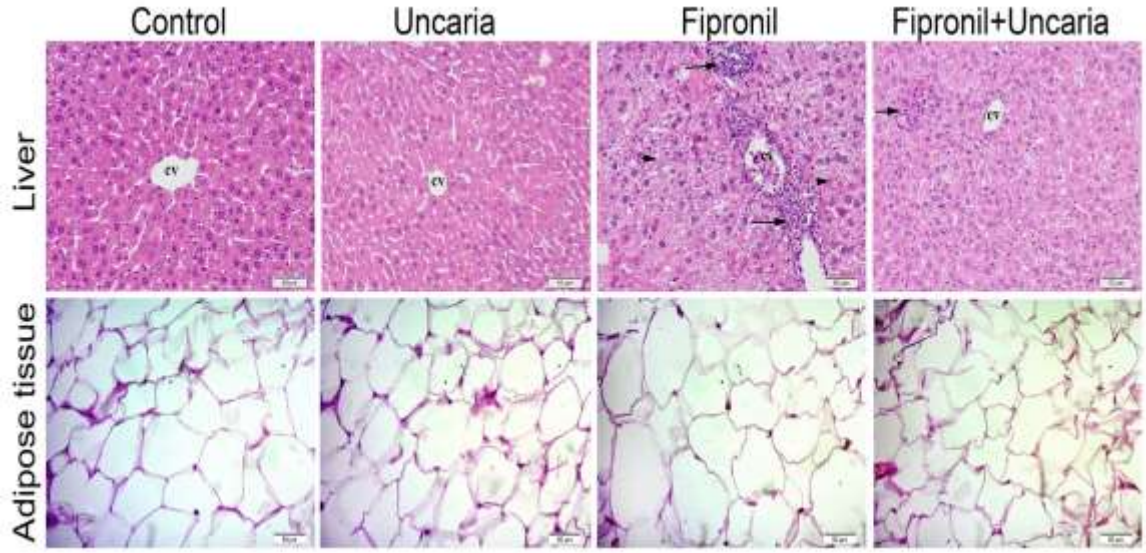

Fig. 1. Rat liver & adipose tissue sections stained by H&E. X 400, liver showing the normal histological structure of liver cells of both control and Uncaria (cat claw) groups. Fibronil group showing diffuse vacuolar degeneration of hepatocytes, focal lymphocytic aggregations (arrows), dilated central vein, and focal hepatic cell necrosis (arrowheads). The treated group with cat claw showing mild vacuolar degeneration with mild focal lymphocytic infiltration (arrows).

Adipose tissue showing large size of adipocytes in fipronil group and nearly similar size in other groups.

The diameters of the fat cells were significantly (P<0.05) increased in FIP treated rats than control and other treated groups. Dietary supplementation with Uncaria significantly (p<0.05) reduced the diameter of fat cells than FIP group however it didn't reach the control diameter (Table 2).

DISCUSSION

FIP is a commonly used insecticide either in home applications or at a commercial level that causes metabolic abnormalities via endocrine disruption (Lu et al., 2015; Mnif et al., 2011). The administration of FIP 1/30 of LD50 for 12 weeks to rats didn't alter body weight gain. Current results were in harmony with those of Badgujar et al. (2016) in mice. The increment of FCR observed in FIP treated group may be due to the oxidative stress that was proven to generated by such insecticide (Badgujar et al., 2015). The oxidative stress is capable of affecting metabolism and gut microbiota adversely thus decreasing the efficiency of converting food into body weight (Kortman et al., 2014; Ranjbar et al., 2016). These results coincided with other results of Gupta et al. (2013) that

may be produced by FIP administration to fish fries. The administration of cat claw that has antioxidant power *(*Bors *et al., 2011*)efficiently normalized FCR in FIP treated rats.

In the hereby study, rats administrated FIP exhibited a significantly lower level of serum estradiol level than control. This decline in estradiol was in agreement with (Ohi *et al.*, 2004; Okazaki *et al.*, 2016). These results confirmed the endocrine disrupting effect of FIP that could be attenuated by cat claw administration. The decrease of estradiol was associated with Lipid profile perturbations that were clear in FIP treated group in the present study. These results concord with previous reports of Badgujar *et al.* (2016). Also, obesity and adipogenesis are common sequellae for estrogen deficiency (Chiang *et al.,* 2016) that were also clear by increasing the diameter of fat cells in FIP group in this study. It seemed that Uncaria was capable for restoring the reduced estrogen level in FIP intoxicated rats thus alleviating lipid profile perturbations as well as fat cells diameter.

The serum hepatic AST and ALT were significantly increased in FIP group. This was attributed to the hepatotoxic and the pro-oxidant effect of FIP on hepatocytes which is the primary target for its metabolism (Guelfi *et al.*, 2015). The oxidative stress induced by FIP could destroy hepatic cell membrane leading to the liberation of its enzyme contents into circulation (Muriel and Gordillo, 2016). The dietary Uncaria administration with FIP declined the liver enzymes level which elevated by FIP suggesting its hepatoprotective power. The protective effect of Uncaria was also evidenced by the histopathological picture in the liver.

The insulin resistance indicated by HOMA-IR was significantly increased in FIP treated rats. This result harmonized with the decreased estradiol level that caused lipid profile abnormalities along with increased fat cells diameter. The decrease in estradiol level could possibly down-regulated the expression of their receptors that play a crucial role in the promotion of pancreatic cells function that produced insulin and enhance its function and receptors (Le Magueresse-Battistoni *et al.,* 2017). Moreover, estradiol receptors influence hepatic function and lipid profile (AbdelRazek et al., 2013).

The hepatic tissue of FIP-treated rats cleared vacuolar changes, inflammation and lymphocytes infiltration with focal necrosis. These results were augmented by the significantly promoted serum AST and ALT as well as estradiol level. Similar findings were obtained by De Oliveira et al. (2012) and Badgujar et al. (2016).

Taking together all data it seemed that FIP had an endocrine disrupting effect appeared by reduced estradiol level that deteriorated lipid profile, hepatic function as well as increased insulin resistance and lipid cells diameters. These effects could be alleviated by cat claw administration that restored all previous parameters as well as reduced FCR.

CONCLUSION

In conclusion, FIP could be considered an endocrine disruptor that deteriorates estradiol level and consequently lipid profile, fat cells diameter, insulin resistance and hepatic integrity. These adverse effects could be alleviated by cat claw administration, so it is recommended to be used for people continuously exposed to FIP.

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ARABIC SUMMARY

مخلب القط يتصدى لخلل الغدد الصماء الناجم عن التعرض المزمن لمبيد الفيبرونيل والمسبب لمقاومة الأنسولين والتلف الكبدي في ذكور الجرذان البيضاء

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تناولت الدراسة الحالية قدرة الاونكاريا (مخلب القط) على مواجهة الخلل الايضى الناجم عن الفيبرونيل. تم تقسيم ٢٠ من ذكور الجرذان البيضاء بشكل عشوائي إلى ٤ مجموعات (٥ جرذان لكل منهما). تلقت جرذان المجموعة الضابطة مياه مقطرة فقط. مجموعة الاونكاريا (مخلب القط) تناولت علف يحتوى على ٥ جرام/ كجم من نبات مخلب القط ، و مجموعة فيبرونيل اعطيت ٣,٢٣ ملغم / كغم من الفيبرونيل ، ومجموعة فيبرونيل والاونكاريا و التي تمت معالجتها مع إعطاء ٣,٢٣ ملغم / كجم من الفيبرونيل مع علف يحتوى على ٥ جرام/ كجم من نبات مخلب القط. أعطيت الجرعات كل يوم لمدة ١٢ أسبوعا على التوالى. تم تحديد وزن الجسم ، وتناول الطعام و معامل التحويل الغذائى. تم تجميع عينات الدم لتقييم هرمون الاستراديول وصورة الدهون فى مصل الدم. كذلك لتقدير انزيمات الكبد. تم تحديد مستوى الجلوكوز والأنسولين لحساب معامل هوما لمقاومة الانسولين. تم إستئصال الكبد والدهون الموجودة فى منطقة البطن للفحوص االنسجومرضية. لم يؤثر مبيد الفيبرونيل على وزن الجسم ، إلا أنه تسبب فى ارتفاع معامل التحويل الغذائي مقارنة بالمجموعات الأخرى. انخفض مستوى هرمون الاستراديول بشكل كبير فى مجموعة الفيبرونيل بينما ساهم مخلب القط فى في رفع مستوى هذا الانخفاض. أظهرت الجرذان المعالجة بالفيبرونيل زيادة كبيرة في نسبة الكوليسترول ، البروتينات الدهنية منخفضة الكثافة (LDL) ، الدهون الثلاثية (TG) وأنزيمات الكبد (AST ، و ALT) من ذلك عنها في المجموعات الأخرى في حين انخفضت البروتينات الدهنية عالية الكثافة (HDL). نجم عن السمية بالفيبرونيل زيادة كبيرة في مقاومة الانسولين (معامل هوما لمقاومة الانسولين) التي تم تحسينها من قبل مخلب القط. وكشف فحص القطاعات النسجومرضية للكبد عن وجود اضمحلال فى خلايا الكبد ، مع وجود تجمعات من الخلايا الليمفاويه ونخر بؤري بالكبد. علاوة على ذلك ، زاد مبيد الفيبرونيل من قطر الخلايا الدهنية. قاوم نبات مخلب القط فى الدراسة الحالية مقاومة الانسولين و تلف الكبد والسمنة الناجمة عن العلاج المزمن بمبيد الفيبرونيل و لذا نخلص انه يمكن لمخلب القط أن يحمي بفعالية من الاضطرابات الأيضيه الناجمه عن التعرض لمبيد الفيبرونيل.