The Effect of Leaf Extracts (Hawthorn and Carica Papaya) and Their Combination on Insulin Resistance in Rats

تأثير مستخلصات أوراق (الزعرور والبابايا) وخليطهما على مقاومة الأنسولين لدى الفئران

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المجلة العلمية لكلية التربية النوعية – جامعة دمياط

عدد (١١) – يونيو ٢٠٢٥

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ABSTRACT

Hawthorn and papaya leaves are widely known for their therapeutic benefits and traditional use in treating infections, inflammation, and various health conditions. Given their abundance of bioactive compounds, this study aimed to investigate the potential effects of these leaf extracts and assess their possible applications in developing functional foods. Therefore, this study was conducted to evaluate the impact of aqueous extracts of Hawthorn (HLE) and Carica Papaya (PLE) on feed intake, body weight gain%, organ weights relative body weight, markers of glucose metabolism and insulin resistance, liver enzyme activity, kidney functions, lipid profile and antioxidant enzymes of rats with insulin resistance. Forty-eight male albino rats weighing (150 ± 10 grams) used in this study. The rats were divided into two main groups: the first main group (6 rats) fed on a basal diet as a control negative group. The second main group (42 rats) was fed on a basal diet supplemented with a 60% fructose-enriched diet. Then, classified into seven other subgroups. **Subgroup (1)** was fed a high-fructose diet (HFD) and tap water as a positive control group. **Subgroup (2)** was fed on HFD and received 2.5% HLE. **Subgroup (3)** was fed on HFD and received 5% HLE. **Subgroup (4)** was fed on HFD and received 2.5% PLE. **Subgroup (5)** was fed on HFD and received 5% PLE. **Subgroup (6)** was fed on HFD and received 2.5% (H+P) LE. **Subgroup (7)** was fed on HFD and received 5% (H+P) LE. Sensory evaluation for cookies supplemented with Hawthorn and Carica Papaya leaves was also done. Simultaneous treatment of rats suffering from insulin resistance with two levels of aqueous extracts of Hawthorn and Carica Papaya and their combination along with fructose led to a decrease in feed intake, body weight gain%, and FER. A significant improvement in levels of fasting plasma glucose (FPG), fasting plasma insulin (FPI), HOMA-IR, HbA1C %, triglycerides, total cholesterol, low- and very low-density lipoprotein cholesterol, kidney functions (uric acid, urea nitrogen, and creatinine), liver enzyme activity (AST and ALT), and MDA enzyme activity. The antioxidant enzyme activities (SOD, GPX, and CAT) and HDL-c rose in comparison to the positive control group. In addition, histological examination of the liver and pancreas of rats in groups treated with different levels of the hawthorn and papaya leaf extracts and their combination showed a noticeable improvement in the tissue structure of these organs. Additionally, cookies were produced with proportions of 2.5 and 5 of Hawthorn, C. papaya leaves powder, and their combination. Sensory evaluation indicated that all cookie samples had an acceptance greater than 75%. Based on these findings, incorporating hawthorn and papaya leaf mixtures—at concentrations of up to 5%—into functional foods may offer substantial nutritional and health benefits for individuals with insulin resistance.

Key words: Hawthorn - Carica Papaya –Insulin Resistance

Introduction

In prediabetic conditions, insulin levels increase to meet normal insulin requirements, leading to chronic hyperinsulinemia, hyperglycemia-induced β-cell failure, and eventually to T2DM **(Vas *et al.*, 2017).** Insulin resistance (IR) is a hallmark of the pathophysiology of prediabetes and metabolic syndrome. IR is defined physiologically as an inability of some type of tissue to respond to normal insulin levels, and thus, higher than normal levels of insulin are required to maintain the normal functions of insulin. Insulin resistance (IR) is a significant factor in the development and progression of metabolic-related diseases like dyslipidemia, T2DM, obesity hypertension, nonalcoholic fatty liver disease (NAFLD), cardiovascular and cerebrovascular disorders, and cancer **(James *et al.*, 2021; Sharma *et al.*, 2021& Zhao *et al.*,2023).** The pathogenesis of IR depends on multiple factors, including age, genetic predisposition, obesity, oxidative stress, modern lifestyle and an increase of consumption of high-sugar diets especially fructose, among others. Recent findings that the increased in the consumption of fructose may be an important contributor to the metabolic syndrome, typically resulting in hyperinsulinemia, insulin resistance, hypertension, hypertriglyceridemia, hyperuricemia, hepatic steatosis, vascular compromise, peripheral insulin resistance, and increased visceral adiposity, and there may also be increased food intake and body weight gain, and leads to increased lipid biosynthesis, because fructose is a lipogenic carbohydrate **(Rutledge and Adeli 2007; Dornas *et al.*, 2015; Ramos *et al.*, 2017; &Uchendu *et al.*, 2021).** Fructose, found in the diet in corn syrup, sucrose, soft drinks, and fruit and fruit-derived products. Fructose is primarily used as a food sweetener, added to foods and beverages to sweeten them. It is also used in the manufacture of medicines, sweets, pies, pastries, canned fruits, and other food products. and its consumption in the form of soft drinks is a public health concern **(Tappy *et al.*, 2010 & Dekker *et al.*, 2010)**. IR is progressively increasing worldwide, and its prevalence has now exceeded 50% of the general population and in overweight children. Asymptomatic or poorly symptomatic, it can last for many years before manifesting itself as diabetes, therefore leading to enormous social and healthcare costs **(Fazio *et al.*, 2024).** Prediabetes is the main risk factor for DM. Analogically to the increase of DM prevalence, the prevalence of prediabetes also increases **(Brannick *et al.*, 2016).** There are 463 million diabetes patients; that is 9.3% of the world's population. It is estimated

that, in 2045, there will be 700 million patients; the prevalence of metabolic disease is now viewed as a global health emergency **(Guerra *et al.*, 2021).**

Glucose levels that are between optimal and indicative of DM can also induce the development of chronic complications. The proper diagnosis of insulin resistance and intensive preventive management are important to public health, as early diagnosis of the disorder could be the basis for early therapeutic interventions that could prevent progression of complications or even cause their resolution **(Baranowska-Jurkun *et al.*, 2020 & Iqbal *et al.*, 2024).** Historical reports show that some plants can be an alternative to standard pharmacotherapy or, at least, help with treatment or have a preventative effect, due to its content of biologically active compounds with specific pharmacological properties, which do not cause undesirable side effects (**Przeor, 2022)**. Papaya leaves have emerged as one of the most useful parts with a plethora of health-promoting compounds and activities, as exhibited antimicrobial activity, inhibiting E. coli, S. aureus, and B. subtilis, and various pharmacological activities like antidiabetic, anti-inflammatory, antihypertensive, hepatoprotective, antinephrotoxicity. Also, PL demonstrates strong nutritional and antioxidant properties, supporting their inclusion in functional food **(Raj and Shankar, 2023 &Choudhary *et al.*, 2025)**. **Choudhary *et al.*, 2025** demonstrated that Papaya leaves contained 25.75% crude protein, 41.49% carbohydrates, and high levels of flavonoids (21.00 mg QE/g), phenolics (8.85 mg GAE/g), and tannins (430 mg TAE/g). Additionally, mineral analysis showed abundant Na, Mg, Ca, K, and Fe (361.2, 789.2,1079, 4071, and 228.2 mg/kg, respectively). Additionally, **Ugbogu *et al.* (2023); Malathi *et al* .(2024)** stated that papaya leaves contain vitamins (especially vitamins C and A), minerals, fiber, and bioactive compounds such as papain, alkaloids, flavonoids, phenolic compounds, glucosinolates, and carpaine. These active ingredients regularly can help manage blood sugar levels and improve insulin sensitivity. Thus, all parts of papaya spp. can be applied as potential anti-diabetic properties and could be developed into functional foods or nutraceuticals. On the other hand, Hawthorn (Crataegus) is widely distributed in the world. It has been used for food and medicine for thousands of years. Hawthorn also has been used in Chinese herbs for centuries to possess the therapeutic effects of tonifying the spleen and regulating blood glucose and lipid metabolism because it contains a lot of biologically active substances, such as flavonoids, phenolics, terpenoids, and pectin **(Li *et al.*, 2011; Rocchetti *et al.*, 2020 & Dai *et al.*, 2021). Liu *et al.***

(2021) suggested that the SIRT1/AMPK/NF-κB signaling pathway was a critical mechanism of hawthorn polyphenols for reducing inflammation and further to alleviate hyperglycemic, insulin resistance responses and ameliorate aortic injury in T2DM rats. Also, **Wang *et al.* (2011)** have found that the increase of postprandial glucose was inhibited by hawthorn flavonoids in sucrose loaded rats. Additionally, **Xu *et al.* (2021)** stated that Vitexin is a natural flavonoid from hawthorn and has been demonstrated to improve high-fat diet triggered insulin resistance. For all the aforementioned reasons, incorporating hawthorn or papaya leaves as raw materials in food products will be highly beneficial to a diverse range of consumers. Therefore, the present study was carried out to investigate the potential effects of different ratios of hawthorn and papaya leaves and their combination on biochemical parameters in experimental rats with insulin resistance. In addition to studying the possibility of adding different ratios of Hawthorn and Carica Papaya leaves and their combination in making cookies.

Materials and Methods

Materials

- Hawthorn (Crataegus) leaves were purchased from the local market of medicinal plants in Cairo, Egypt, and was scientifically identified by Institute of Food Technology, Giza, Egypt.
- Carica papaya leaves were sourced from a farm located in New Damietta, Egypt.
- All ingredients used in cookies formulation (wheat flour, baking powder, salt, sugar, skim milk powder and corn oil) were obtained from the local market from Damietta Governorate, Egypt.
- Casein, vitamins, minerals, choline chloride, salt mixture, cellulose and fructose were obtained from El-Gomhoriya Company for Trading Drugs, Chemicals and Medical instruments, Cairo, Egypt.

Animals: 48 rats used in this study, adult male albino rats *(Sprague Dawley strain)* weighing (150±10g) were obtained from the Medical Experimental Research Center, Faculty of Medicine, Mansoura University

Chemicals: All chemicals, reagents and solvents were of analytical grade and purchased from Al-Gomhoryia Company for Trading Drugs, Chemicals and Medical Instruments, Cairo, Egypt.

Methods

Hawthorn Leaves Aqueous Extraction (HLE)

The hawthorn leaves were sorted to remove foreign materials, cleaned thoroughly, and ground using an electric grinder (Moulinex LM2411EG) into a

fine powder that could pass through a 20-mesh sieve. The powder was then packaged in polyethylene bags and stored at 4°C until used. The fresh aqueous extracts were prepared as needed by blending the dried hawthorn leaf powder (at concentrations of 2.5% and 5%) with 100 mL of ordinary tap water for 12 hours. This mixture was then administered directly into the oral cavity using a syringe.

Papaya Leaves Aqueous Extraction (PLE)

The papaya leaves aqueous extract was prepared according to **Peter *et al.* (2014)** with some modifications. Papaya leaves were thoroughly washed in water 2-3 times to remove adhering dust and impurities. They were then blanched for 2 minutes by immersing them in boiling water, cooled, and dried at 50°C in an air oven until they became brittle to the touch. Subsequently, the dried leaves were powdered with the use of an electric grinder, Moulinex (LM2411EG) and sifted through a sieve. Then placed into compact plastic envelopes and stored at 4°C until used. The fresh aqueous extracts were prepared as needed by blending the dried papaya leaf powder (at concentrations of 2.5% and 5%) with 100 mL of ordinary tap water for 12 hours. This mixture was then administered directly into the oral cavity using a syringe.

Chemical analysis

Hawthorn and Carica papaya leaf powder were analyzed for ash, crude fiber, fat, and crude protein, as determined as described in **A.O.A.C. (2005),** while total carbohydrates were calculated by the differences. The total phenolic content of Hawthorn and Papaya leaf powder was determined according to the method described by **Singleton *et al.* (1999).**

Experimental design

All biological experiments performed complied with the rulings of the Institute of Laboratory Animal Resources, Commission on Life Sciences and National Research Council **(NRC, 2011).** Forty-eight male albino rats weighing 155 ± 5 gm will be kept in individual stainless-steel cages under hygienic conditions and fed one week on a basal diet for adaptation, according to **Reeves *et al.* (1993).** Meanwhile, salt and vitamin mixtures followed those of **Hegested *et al.* (1941)** and **Campbell (1963),** respectively. Overall, the rats were healthy and exhibited normal fasting blood glucose levels when tested prior to treatment. The average fasting blood glucose level for rats was measured at 110.7 mg/dL. After a period of adaptation to the basal diet (one week), the rats were divided into two main groups. The first main group (6 rats) was fed a basal diet containing starch as the source of carbohydrate and tap drinking water ad libitum as a negative control group, while the second main group (42 rats) was fed with a 60% fructose-enriched diet as the source of carbohydrate for 15 days to induce insulin resistance according to the method described by Suganthi et al. (2005). Blood pressure, glucose tolerance tests (both fasting and two hours after

a meal), and HbA1c levels had been assessed prior to and following the 15-day period to ensure the occurrence of insulin resistance in rats. This group was divided into seven subgroups as follows: **Subgroup (1)** was fed a high-fructose diet (HFD) and tap water as a positive control group. **Subgroup (2)** was fed on HFD and received 2.5% HLE. **Subgroup (3)** was fed on HFD and received 5% HLE. **Subgroup (4)** was fed on HFD and received 2.5% PLE. **Subgroup (5)** was fed on HFD and received 5% PLE. **Subgroup (6)** was fed on HFD and received 2.5% (H+P) LE. **Subgroup (7)** was fed on HFD and received 5% (H+P)LE. Treatment was initiated on the 16th day and continued for the next 30 days. The experimental groups were maintained for a total experimental period of 45 days.

During the experiment period (45 days), the diets consumed as well as body weights were recorded twice weekly to determine feed intake and body weight gain. At the end of the experiment, the animals were fasted overnight, then the rats were anesthetized and sacrificed, and blood samples were collected from the aorta.

The blood samples were centrifuged, and serum was separated to estimate some biochemical parameters, i.e. fasting plasma glucose, fasting plasma insulin and HbA1c according to the method described by **Matthews *et al.* (1985); Nathan *et al.* (1984); American Diabetes Association (2010).**

Total cholesterol, triglycerides and HDL-C were determined in the serum according to the method described by **Allain *et al.* (1974)**; **Fossati and principe (1982); Lopes – Virella *et al.* (1977)** respectively. Serum LDL-C and VLDL-C were determined in the serum according to **Friedewald *et al.* (1972)**. Uric acid, urea nitrogen and creatinine were determined in the serum according to the method described by **Fossati *et al.* (1980), Patton and Crouch (1977); Bohmer (1971)**, respectively. Aspartate amine transaminase (AST), Alanine amine transaminases (ALT) andalkaline phosphatase (ALP) activities were measured according to the method described by **Reitman and Frankel (1957); Bergmeyer *et al.* (1974)**, respectively. Serum glucose was determined by **Trinder (1969)**. Catalase, Glutathione Peroxidase (GPX) and Superoxide dismutase (SOD) were determined in the serum according to the method described by **Aebi (1974); Mc Cord and Fridovich (1969)**, respectively. HOMA-IR was calculated to reflect insulin resistance according to **Pitea *et al.* (2009)** by the equation: HOMA-IR = Fasting Plasma Glucose (mg/dL) ×Fasting Plasma Insulin (µIU/mL)/405.

Histological examination

Liver and pancreas were removed from each rat by careful dissection, washed with saline solution, dried with filter paper, and weighed to calculate organs to body weight percentage. The liver and pancreas in each group were examined histopathologically, according to **Sheehan and Hrapchak (1980).**

Formulation and preparation of cookies

The cookies were prepared with slight modification by using the method **(AACC, 2000).** The control and the other experimental formulations were prepared in Table (1). In a large mixing bowl, the butter and powder sugar were mixed by an electric mixer on medium speed for 30 seconds, then add the beat eggs and flavor vanilla until mixed. Add flour and baking powder until dough combined. Refrigerate dough at least 1 hour. The dough was sheeted to a uniform thickness of 5 mm and cut into circular shapes of 60 mm diameter. Baking was carried out at 180 ºC for 15 min. Cookies were then removed from the oven and allowed to cool down to room temperature. Cookies samples were stored in airtight containers before sensory evaluation. The other experimental formulations were prepared by adding powder from HL, PL at 2.5, 5, and a mixture of them.

Table (1). Formulation of cookies

Ingredients (g)	Control	1	2	3	4	5	6
wheat flour	100	97.5	95	97.5	95	95	90
Hawthorn leaves powder	-	2.5	5	-	-	1.25	2.5
Papaya leaves powder	-	-	-	2.5	5	1.25	2.5
Butter	50	50	50	50	50	50	50
Sugar	40	40	40	40	40	40	40
Egg	30	30	30	30	30	30	30
Baking powder	1	1	1	1	1	1	1
Vanilla	1	1	1	1	1	1	1

Sensory evaluation

Sensory evaluation was participated by invited ten panelists of staff members from the Home Economics Department, Faculty of Specific Education, Damietta University, Damietta, Egypt. Samples of the cookies wereprepared one day before the evaluation, cooled for 1-2h at room temperature. The evaluation was carried out according to the method of **(AbdEl – latif, 1990).**

Statistical Analysis

The data were statistically analyzed by SPSS computer software SPSS 2000. The results were expressed as mean ± standard deviation (SD) and tested for significance using One Way analysis of variance ANOVA test, according to **Armitage and Berry (1987).**

RESULTS AND DISCUSSION

Chemical composition of Hawthorn and Papaya leaves

The chemical composition of hawthorn and papaya leaf powder was presented in Table 2. Hawthorn leaf powder comprised 12.31% protein, 10.87% fat, 7.22% ash, 11.63% crude fiber, and 69.60% total carbohydrates. These results were similar to those of **Saad and Zahran (2024).** The table also showed the chemical composition of Papaya leaf powder, which comprised 29.04% protein, 9.51% fat, 11.73% ash, 27.54% crude fiber, and 49.72% total carbohydrates. These results were in harmony with those of **Chaijan *et al.* (2024)** The total phenolic content in Hawthorn and Papaya leaf powder, expressed as milligrams of gallic acid equivalent (mg GAE) of dry weight, recorded 326.17 and 147.41 mg GAE/g, respectively. These results were in harmony with those of **Kabra and Patel (2018); Dekić *et al.* (2020).**

Table (2): Gross chemical composition of Hawthorn and Papaya leaf (on dry weight basis)

Components (g/100g)	Hawthorn leaf	Papaya leaf
Crude Protein	12.31±0.84	29.04±1.46
Fat	10.87±1.00	9.51±1.50
Ash	7.22±0.25	11.73±0.49
Total carbohydrates*	69.60	49.72
Crude fiber	11.63±0.31	27.54±0.41
Total Phenolic (mg GAE)	326.17±0.46	147.41±0.35

Each value represents the mean ± SD.
* Total carbohydrates and available carbohydrates were calculated by differences

Nutritional Parameters

As shown in the table (3), the results indicated that the positive control group had the highest body weight gain (BWG%), feed efficiency ratio (FER), and mean feed intake (FI) compared to the negative control group. However, the groups treated with the aqueous extract of hawthorn, Carica papaya, and their combination showed a significant reduction in BWG%, FER%, and FI as compared to the positive control group. The lowest BWG%, FER, and FI were recorded for the groups treated with a mixture of aqueous extract of hawthorn and papaya leaf, followed by groups treated with aqueous extract of papaya leaf, compared to the positive group. The best improvement was for the group treated with a mixture of aqueous extract of hawthorn and papaya leaf 5% (H+P) LE. The results also showed that there were no significant differences in body weight and feed efficiency between the group treated with 5% (H+P) LE and the negative control group.

On the other hand, the mean value ± SD of liver, pancreas, and kidney weight/body weight % increased significantly ($p < 0.05$) in the positive control group as compared to healthy rats fed on a basal diet. While the group of rats with insulin resistance that was treated with 5% (H+P) LE recorded the highest decrease in the mean values of the liver, pancreas, and kidney weight/body weight % as compared to the positive control group.

Table (3): Effect of Hawthorn and Papaya leaf extracts and their combination on BWG%, FI, FER and Organs weight/body weight% of rats with insulin resistance.

Parameters / Group	B.W.G%	FI g/day/rat	FER	Organs weight/body weight %		
				liver	Pancreas	kidney
NC	40.05±3.3^{e}	25.00	2.4±.2 ^{e}	5.9±.1 ^{e}	0.38±.03 ^{c}	1.3±.1 ^{d}
PC	105.79±7.6^{a}	26.75	6.3±.3 ^{a}	7.6±.1 ^{a}	0.53±.04 ^{a}	2.2±.1 ^{a}
2.5% HLE	92.50±2.0^{b}	26.50	5.5±.2 ^{b}	7.4±.3 ^{ab}	0.51±.04 ^{a}	2.0±.1 ^{ab}
5% HLE	86.95±8.7^{b}	26.17	5.2±.4 ^{b}	6.6±.2^{d}	0.45±.01 ^{b}	1.9±.2 ^{b}
2.5% PLE	63.97±4.3^{c}	25.12	3.9±.2 ^{c}	7.1±.1^{bc}	0.51±.03 ^{a}	1.8±.1 ^{bc}
5% PLE	49.57±2.3^{d}	25.83	2.9±.1 ^{d}	6.9±.3^{cd}	0.41±.03 ^{bc}	1.7±.1 ^{bc}
2.5 %(H+P) LE	48.52±5.7^{d}	24.13	2.9±.3 ^{d}	6.7±.2^{d}	0.40±.03 ^{bc}	1.5±.1^{cd}
5% (H+P) LE	38.15±3.7^{e}	24.00	2.4±.2 ^{e}	6.1±.1 ^{e}	0.41±.01 ^{bc}	1.5±.2^{cd}

FI: feed intake, **BWG:** body weight gain, **H**: Hawthorn, **P:** Papaya, **FER:** feed efficiency ratio.
Values in each column which have different litters are significant different ($p \leq 0.05$).

Assessing markers of glucose metabolism and insulin resistance

Important indicators for assessing glucose metabolism and insulin resistance include fasting plasma glucose (FPG), insulin levels, HOMA-IR (Homeostatic Model Assessment for Insulin Resistance), and HbA1c percentage. These indicators differ in their specificity and informational value. After fasting, FPG calculates the blood glucose level as of right now, whereas HbA1c reflects the average blood glucose levels over the previous two to three months. Insulin levels, measured after fasting, indicate how much insulin the body is producing; Insulin resistance occurs when the body's cells become less responsive to the hormone insulin, which helps glucose enter cells for energy. As a result, the pancreas produces more insulin to compensate, leading to hyperinsulinemia. HOMA-IR is a formula that estimates insulin resistance based on fasting insulin levels and FPG. Additionally, insulin resistance is commonly linked to elevated blood pressure levels. People with insulin resistance often exhibit higher systolic and diastolic blood pressure readings. Grasping this connection is essential for managing cardiovascular health and preventing type 2 diabetes. Data presented in table (4) revealed that the rats fed with HF had an increase in Fasting plasma glucose (FPG) and Fasting Plasma Insulin (FPI)

concentrations of about 256% and 152%, respectively as compared to the negative control group. Also, indicators of insulin resistance were significantly ($p \leq 0.05$) increased in the mean value±SD of HOMA-IR and HbA1c in the HF group rats, which recorded 9.5±1.9 and 8.9±1.0, respectively, as compared to the normal control rats. The intervention with aqueous extracts of hawthorn leaf, papaya leaf, or their combination led to a significant ($p \leq 0.05$) decrease in the same indicators in all groups of rats when compared to the positive control group. From the previous results, it could be observed the highest decrease was recorded for the groups treated with the mixture of hawthorn and papaya leaf extracts. Especially with the high level of 5%, followed by the papaya leaf extracts alone as compared to other treated groups.

Our results are consistent with previous studies which found that consumption of high-fructose diets markedly induces an increase in glycemia associated with hyperinsulinemia and, consequently, a reduction of insulin sensitivity **(Suwannaphet *et al.*,2010)**. According to **Ifegwu *et al.* (2019)** reported that Carica papaya leaves exert insulin-like effect on peripheral tissues by promoting glucose uptake metabolism. C. papaya has also been an antioxidant activity, immunomodulatory, hypoglycemia, hypolipidemic and hepatoprotective. Also, **Roy *et al.* (2022)** revealed that treatment with the extract of C. papaya-controlled blood glucose levels, improved lipid profiles, and enhanced insulin receptor (IR) and glucose transporter type 4 (GLUT4) levels in skeletal muscle. These findings suggest that C. papaya may ameliorate insulin resistance and associated lipid dysfunction. Additionally, **Zhu *et al.* (2013); Aierken *et al.* (2017) & Gheitasi *et al.* (2022)** showed that hawthorn extracts decreased blood glucose level and regulation of insulin secretion, insulin resistance, and improvement of histopathological changes in pancreatic beta cells. It also shows therapeutic and protective effects against diabetic-related complications in various organs. Also**, Liu *et al.* (2021)** indicated that Hawthorn polyphenol extract (HPE) significantly reduced insulin resistance in T2D rats by upregulating the phosphorylation of glucose absorption protein (GLUT4) and insulin resistance-associated proteins, p-IRS1, p-AKT, and p-PI3K, in the rat liver ($p \leq 0.01$).

As presented in the same table (4), mean blood pressure (BP) ratios were measured; they were significantly increased for the positive control group in comparison with the negative control group. This is due to high insulin levels stimulating the sympathetic nervous system, leading to vasoconstriction and

increased heart rate, which elevate blood pressure. Treating insulin-resistant rats with aqueous extracts of hawthorn leaf, papaya leaf, or their combination had lower mean values than that of the PC group. The greatest reduction was observed in the groups treated with the mixture of H and P LE, particularly at the higher concentration of 5%, followed by the group treated with papaya leaf extract alone, as compared to other treated groups. Recent research shows that Hawthorn has lowered blood pressure and acts as a vasodilator, increasing blood supply to the heart and improving the circulation to the extremities by decreasing arterial resistance **(Kim and Choi, 2013).** Also, **Pratiwi *et al. (*2020)** indicated that consumption of papaya leaf jelly could reduce systolic and diastolic blood pressure in prediabetic women papaya leaves have compounds that have a positive effect on blood pressure. Magnesium contained in papaya leaves had a function to regulate the pressure and reactivity of blood vessels by altering the response of vasoconstrictors and vasodilatators.

Table (4) Effect of Hawthorn and Papaya leaf extracts and their combination in assessing markers of glucose metabolism and insulin resistance in rats with insulin resistance

Parameters / Group	FPG (mg/dl)	FPI (uIU/ml)	HOMA-IR (calculated)	HbA1C %	Mean BP (mm Hg)
NC	88.9±2.6 ^{f}	4.8±.5 ^{f}	1.1±.1 ^{e}	2.3±.2 ^{e}	104.4±3.0 ^{d}
PC	316.5±8.7 ^{a}	12.1±2.7 ^{a}	9.5±1.9 ^{a}	8.9±1.0 ^{a}	152.0±6.6 ^{a}
2.5% HLE	276.5±5.5 ^{b}	9.9±1.0 ^{b}	6.4±0.6 ^{b}	7.8±0.4 ^{b}	145.4±6.0 ^{a}
5% HLE	264.9±7.8 ^{b}	7.7±.4 ^{cd}	5.3±0.3 ^{b}	7.2±0.4 ^{b}	131.6±4.2 ^{b}
2.5% PLE	240.7±8.7 ^{c}	8.5±0.7 ^{bc}	5.1±0.6 ^{b}	5.4±0.5 ^{c}	143.6±3.7 ^{a}
5% PLE	172.3±15.4 ^{d}	6.0±0.5 ^{def}	2.6±0.2 ^{cd}	4.8±0.3 ^{c}	129.6±8.1 ^{b}
2.5 %(H+P) LE	185.7±9.0 ^{d}	7.0±0.7 ^{cde}	3.2±0.4 ^{c}	3.7±0.4 ^{d}	117.4±2.4 ^{c}
5%(H+P) LE	134.9±4.2 ^{e}	5.3±0.4 ^{ef}	1.7±0.2 ^{de}	3.2±0.2 ^{d}	102.9±11.4 ^{d}

FPG: Fasting plasma glucose, **FPI:** Fasting Plasma Insulin HOMA-**IR** : Homeostatic Model Assessment for Insulin Resistance, **BP:** blood pressure

Values in each column which have different litters are significant different ($p \leq 0.05$).

Serum lipid fractions

High fructose consumption has an impact on lipid profiles and the development of insulin resistance. Insulin resistance affects lipid levels in experimental rats. Fructose metabolism in the liver leads to an increase in de novo lipogenesis, resulting in higher triglyceride synthesis. These triglycerides are packaged into VLDL particles, leading to elevated serum TG and VLDL levels **(Hieronimus *et al.*, 2019).** In this study, the effects of fructose diets induced insulin resistance on lipid profile in rats were identified as shown in table (5). The rats with insulin resistance induced by fructose diets showed an increase in the mean values of TC (83.2±6.4), TG (115.6±8.7), LDL (73.9±3.5), and VLDL (23.1±1.7), while it caused a decrease in the mean value of HDL

(23.2±2.3) compared to the negative control group. Dyslipidemia is evident in the positive control group, with increased VLDL, LDL, TG, and cholesterol levels and decreased HDL levels, as shown in Table 5. On the other hand, groups of rats with insulin resistance (IR) that were treated with leaves from aqueous extract of hawthorn, Carica papaya, and their combination showed a significant improvement in blood lipid profile through decreasing the TC, TG, LDL, and VLDL, while the opposite direction was observed for the HDL levels. The group of rats that received a mixture of hawthorn and papaya leaf extracts, particularly at the higher concentration of 5%, showed greater improvements in serum lipid level disturbances caused by insulin resistance, followed by the groups treated with papaya leaf extract, in comparison to the other treatment groups. This is in accordance with the previous findings done by researchers, which demonstrate a reduction in blood lipid and cholesterol levels as result of hawthorn consumption. These lipid lowering effects are related to the catechins, triterpene saponins, and quercetin contained in hawthorn **(Zhu, 2024).** Also, **Aierken *et al.* (2017)** demonstrated that hawthorn extract administration led to significant reductions in serum triglyceride (TG) and total cholesterol (TC) levels compared to the untreated T2DM control group. **Lien *et al.*, (2023)** stated that the lipid-lowering effects of hawthorn are attributed to its rich polyphenolic content, including flavonoids and phenolic acids, which exhibit antioxidant properties. These compounds may enhance lipid metabolism by reducing oxidative stress and modulating lipid-regulating enzymes, thereby improving lipid profiles in metabolic disorder models. This hypolipidemic action can also be ascribed to the lipid metabolism modulation caused by phenolics such as chlorogenic acid and flavonoids such as quercetin, leading to a decrease in the total cholesterol, triglycerides, and LDL **(Zeni *et al.*,2017).**

Moreover, **Sheneni *et al.* (2018)** stated that papaya leaf has anti-hyperlipidemic effects. Carica papaya leaf was shown to be effective in significantly lowering total cholesterol, triglycerides and low-density lipoprotein levels; thus, it can be used in the treatment and/or prevention of cardiovascular diseases. Additionally, **Vigasini, (2015**) showed that the aqueous extract of papaya leaves showed a significant reduction in the total cholesterol (TC), low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) and Triglyceride (TG) levels was observed in the experimental group. Therefore, it can be concluded that fresh papaya leaves aqueous preparation can be used as a safe, cost effective, natural supplement for lowering elevated blood lipids. This preparation has the potential to bring about weight reduction thus lowering the risk for heart disease. Collectively, these studies suggest that aqueous extracts of hawthorn and Carica papaya alone or in combined doses possess hypoglycemic and hypolipidemic properties, improving lipid profiles by reducing TC, TG, and LDL-C levels, and increasing HDL-C concentrations in animal models with insulin-resistant.

Table (5) Effect Hawthorn and Papaya leaf extracts and their combination on lipid fractions in rats with insulin resistance

Parameters / Group	Cholesterol (mg/dl)	TG (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	VLDL-c (mg/dl)
NC	30.1±3.5 e	60.6±4.1 e	53.8±2.7 a	16.3±2.0 e	12.1±.8 e
PC	83.2±6.4 a	115.6±8.7 a	23.2±2.3 e	73.9±3.5 a	23.1±1.7 a
2.5% HLE	68.5±5.8 b	111.7±6.4 ab	28.8±2.5 de	42.4±2.8 b	22.3±1.3 b
5% HLE	66.3±6.6 b	101.5±9.2 bc	31.3±2.5 cd	33.6±2.9 c	20.3±1.8 bc
2.5% PLE	56.9±2.2 c	95.0±8.2 c	32.5±1.2 cd	33.7±2.0 c	19.0±1.6 c
5% PLE	43.5±2.8 d	79.5±8.3 d	36.0±4.8 c	29.5±1.4 c	15.9±1.7 d
2.5 %(H+P) LE	36.2±3.0 de	76.4±5.1 d	43.3±3.4 b	21.5±1.7 d	15.3±1.0 d
5%(H+P) LE	32.2±3.3 e	67.7±4.9 de	46.2±7.0 b	19.0±1.1 de	13.4±.9 de

Values in each column which have different litters are significant different (p≤0.05).
TC: Total Cholesterol, **TG:** Triglyceride, **LDL-c:** Low Density Lipoprotein Cholesterol, **HDL-c**: High Density Lipoprotein Cholesterol, **VLDL-c:** Very Low-Density Lipoprotein Cholesterol, **HLE:** Hawthorn leaf Extract**, PLE:** Papaya leaf Extract

Liver Enzymes Activity and kidney function

Insulin resistance in rats—typically induced by high-fat or high-sugar diets—leads to hepatic lipid accumulation, oxidative stress, and chronic inflammation. These processes disrupt insulin signaling (via impaired IRS-1/PI3K/Akt pathways) and cause hepatocyte injury. As liver cells become stressed or damaged, cytoplasmic enzymes like ALT and AST leak into the bloodstream, resulting in elevated hepatic enzyme levels. Thus, insulin resistance is not only a metabolic disorder but also a key contributor to liver dysfunction and early non-alcoholic fatty liver disease (NAFLD), as reflected in rising liver enzyme biomarkers in both experimental rat models and human metabolic syndrome **(Han *et al.*, 2010; Zhao *et al.*, 2020).** From the data presented in table (6), feeding rats a high-fructose diet (HFD) to induce insulin resistance increased ALT and AST enzymes in the positive control group compared to the negative control group. The mean values of AST & ALT enzyme increased significantly ($p \leq 0.05$) in the positive control group, as compared to the negative control group (279.8±18.6 & 202.0±14.4 vs. 25.9±3.1 & 32.8±2.7u/l), respectively. Meanwhile, a significant decrease ($p \leq .5$) in the mean values of ALT and AST enzymes was observed in the groups treated with aqueous extract of hawthorn leaf, papaya leaf, and their combination compared to the positive control group. The reduction was most pronounced with the aqueous extract of the combination of hawthorn leaf and papaya leaf, especially with the high level of 5%, followed by the papaya leaf extracts. The results in the same table (6) revealed that serum uric acid, urea nitrogen and creatinine increased significantly ($p<0.05$) in the PC group that were fed on HFD, as compared to NC group fed on basal diet. Rat groups treated with aqueous

extracts of hawthorn leaf, papaya leaf, and their combination exhibited gradual improvements in the mean values of serum uric acid, urea nitrogen, and creatinine compared to the PC group. The most significant improvement was observed with the mixture of hawthorn and papaya leaf extracts, followed by the papaya leaf extracts. These findings were corroborated by **Qi *et al.* (2019)**, who found that supplementation with Hawthorn leaf extract was effective in decreasing the creatinine, urea, and MDA levels compared to the positive control group. Also, **Saad and Zahran, (2024)** revealed that rats fed on a basal diet plus 10% hawthorn leaves recorded the best treatment for decreasing alkaline phosphatase (ALP), ALT, AST enzymes, and total protein, and the study recommends adding hawthorn leaf powder to the diets of patients with liver disorders. These results also are consistent with the findings of **Idehen *et al.* (2024)** reported that diabetic rats treated with aqueous Carica papaya showed a substantial decrease ($p<0.05$) in the biomarkers ALT, AST, and ALP Compared to rats that were not treated. Also, the aqueous extract of Carica papaya leaves improved the hepatic morphological disruption caused by induced diabetes, which in turn improved the hepatic histoarchitecture. Additionally, **Anis, (2024) & Gheith and El-Mahmoudy, (2018)** reported that Carica papaya extract, particularly from leaves, holds therapeutic potential for promoting liver and kidney health. Also, observed that an aqueous extract of Carica papaya seeds demonstrated effective nephroprotective activity in albino Wistar rats. This was evidenced by a reduction in biochemical parameters and an improvement in kidney architecture among rats with kidney injury. These effects are likely attributed to its antioxidant properties characteristic of alkaloids, flavonoids, and saponins.

Table (6) Effect of Hawthorn and Papaya leaf extracts and their combination on liver enzyme activity and kidney function in rats with insulin resistance

Parameters / Group	ALT (U/L)	AST (U/L)	Creatinine (mg/dl)	Uric acid (mg/dl)	Urea (mg/dl)
NC	25.9±3.1 ^{f}	32.8±2.7^{e}	0.6±.2 ^{f}	1.5±.3^{d}	33.9±2.3 ^{c}
PC	279.8±18.6 ^{a}	202.0±14.4 ^{a}	3.0±.3 ^{a}	2.8±.2 ^{a}	51.4±2.9 ^{a}
2.5% HLE	211.6±13.7 ^{b}	190.3±11.6 ^{a}	1.9±.1 ^{b}	2.0±.2 ^{bc}	45.7±2.3^{b}
5% HLE	203.2±9.3 ^{b}	171.9±6.8 ^{b}	1.8±.1 ^{bc}	1.6±.2 ^{d}	37.1±3.0 ^{c}
2.5% PLE	172.6±6.3 ^{c}	132.4±12.8 ^{c}	1.9±.2 ^{b}	2.3±.1 ^{b}	47.1±4.1 ^{ab}
5% PLE	158.5±14.2 ^{c}	116.1±11.4 ^{c}	1.5±.2^{cd}	1.9±.1^{c}	44.3±3.5^{b}
2.5 %(H+P) LE	97.2±3.5 ^{d}	50.9±4.2 ^{d}	1.3±.1de	1.8±.1^{cd}	36.7±3.2 ^{c}
5%(H+P) LE	56.2±3.0 ^{e}	42.7±2.5 ^{de}	1.1±.1^{e}	1.5±.1^{d}	34.7±2.6 ^{c}

ALT: alanine amino transferase, **AST:** aspartate amino transferase.
Values in each column which have different litters are significant different ($p\leq0.05$).

Antioxidant enzyme activities

As shown in table (7), rats fed with a high-fructose diet had a significant reduction in the activities of antioxidant enzymes (SOD, GPx, and CAT) by about CAT (81%), SOD (48%), and GPx (77%) when compared to the NC group. While all treated groups with aqueous extracts of hawthorn leaf, papaya leaf, and their combination exhibited gradual improvements in CAT, SOD, and GSE activity when compared to the positive control group. The best results for antioxidant enzyme activity were recorded for the groups that were treated with a mixture of hawthorn and papaya leaf extract (2.5% (H+P) LE and 5% (H+P) LE). Concerning Malondialdehyde (MDA) which is commonly used as a marker of oxidative stress in various biological samples, particularly in the context of disease, the highest mean value was achieved in the positive control group (147.0 nmol/L), whereas the lowest one was observed in the case of the negative control group (18.2 nmol/L). MDA plays a very negative role and is able to alter the structure and function of the cell membrane **(Nair and Nair, 2013)**. The formation of MDA and increasing its levels can lead to inhibitory actions, oxidative mechanisms, high cytotoxicity, and tumor development, as it can act as a co-carcinogenic agent **(Koc *et al.* 2003).** All rat groups treated with aqueous extract of hawthorn leaf and papaya leaf and their combination showed a significant reduction in the mean values of MDA as compared to positive control group. Moreover, **Shahein *et al.*(2022)** reported that the consumption of yogurt fortified with the aqueous extract from Hawthorn leaves by rats experiencing oxidative stress resulted in a significant decrease ($p \leq 0.05$) in the triglyceride, total cholesterol, low-density lipoprotein, aspartate aminotransferase, alanine aminotransferase, creatinine, urea, and malondialdehyde levels and a remarkable increase ($p \leq 0.05$) in the high-density lipoprotein, total protein, and albumin levels as well as in the total antioxidant potentials of serum compared to the positive control group, indicating that the extract from Hawthorn leaves can play a preventive role against oxidative stress. Additionally, **Gheitasi *et al.(*2022)** indicated that hawthorn extracts appear both therapeutic and protective effects against diabetic-related complications in various organs through molecular mechanisms, such as decreasing triglyceride, cholesterol, very low density lipoprotein and increasing the antioxidant activity of superoxide dismutase, catalase, glutathione peroxidase, total antioxidant capacity, decreasing malondialdehyde level, and attenuating tumor necrosis factor alpha, interleukin 6 and sirtuin 1/AMP-activated protein kinase (AMPK)/nuclear factor kappa B (NF-κB) pathway and increasing the phosphorylation of glucose transporter 4, insulin receptor substrate 1, AKT and

phosphoinositide 3-kinases, and attenuating blood sugar and regulation of insulin secretion, insulin resistance, and improvement of histopathological changes in pancreatic beta cells. **Saad *et al.* (2024)** and **Orororo *et al.* (2024)** reported that the carica papaya extract improved antioxidant enzymes (CAT and SOD). According to these results, liver and kidney damage can be prevented by the protective actions of Carica papaya leaf extract. Additionally, **Jimoh *et al.* (2023)** showed that the aqueous leaf extract of Carica papaya-treated rats had a significant fall in the plasma glucose level ($p<0.0001$); lower MDA and higher NO, BDNF, NGF, SOD and GSH levels compared to diabetic untreated ($p<0.0001$). Carica papaya leaf extract reduces plasma glucose, mechanical and thermal hyperalgesia, oxidative stress, and nerve damage in streptozocin-induced diabetic peripheral neuropathy in male Wistar rats.

Table (7) Effect of Effect of Hawthorn and Papaya leaf extracts and their combination on antioxidants enzymes activity in rats with insulin resistance

Parameters / Group	MDA (nmol/L)	SOD activity (% inhibition)	Gpx activity (U/ml)	Catalase (nM/ml/min)
NC	18.2±1.3 ^{f}	63.4±3.1^{a}	3.5±.2 ^{a}	1.6±.2 ^{a}
PC	147.0±3.8 ^{a}	32.7±2.9 ^{f}	.8±.06 ^{g}	0.3±.02 ^{f}
2.5% HLE	88.6±5.7 ^{c}	40.5±4.1^{e}	1.3±.1 ^{f}	0.6±.04de
5% HLE	80.3±4.5 ^{c}	50.8±2.3 ^{bc}	1.9±.1 ^{d}	0.9±.1 ^{c}
2.5% PLE	115.9±6.5 ^{b}	37.7±2.0^{ef}	1.2±.1 ^{f}	0.5±.1^{e}
5% PLE	113.5±8.7 ^{b}	43.5±6.9^{de}	1.6±.2 ^{e}	0.7±.1 ^{cd}
2.5 %(H+P) LE	60.1±3.4 ^{d}	48.2±4.0^{cd}	2.3±.2 ^{c}	1.1±.1 ^{b}
5%(H+P) LE	40.4±3.1 ^{e}	56.2±3.4 ^{b}	2.7±.1 ^{b}	1.3±.1 ^{b}

Values in each column which have different litters are significant different ($p\leq0.05$). **SOD:** Super Oxide dismutase, **GPX:** Glutathione Peroxidase, **CAT**: Catalase, **MDA:** Malondialdehyde.

Histopathological Examination

Photo (1) & (2) showed the histopathological examination of liver and pancreas tissue. Microscopically, the liver and pancreas of rats from the control negative group showed the normal histological structure of both hepatocytes and pancreatic islets in **(Photo 1A & 2A, respectively)**. While significant changes were observed in the liver and pancreas of the positive control group, like increase vacuolation in the cytoplasm of hepatocytes and degeneration of islets of Langerhans **(Photos 1B & 2B respectively),** as compared to the negative group. Meanwhile, rat groups treated with aqueous extracts of hawthorn leaf and papaya leaf and their combination showed gradual improvements in both liver tissue **(Photos 1C, 1D, 1E,1F,1G&1H)** and pancreas tissue **(Photos 2C, 2D, 2E, 2F, 2G & 2H).** The high improvement in liver and pancreas cells that looked almost normal was seen in the two groups that got the combined hawthorn and papaya leaf extract, especially at the higher dose of 5%.

Photo (1): Effect of Hawthorn, Papaya leaf extracts and their combination on histological examination of liver tissue

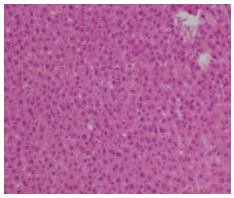
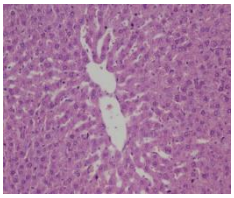
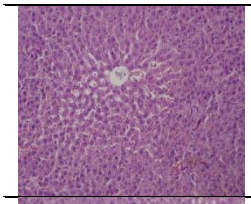
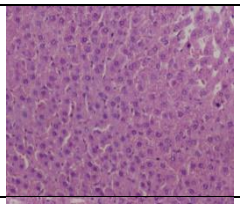
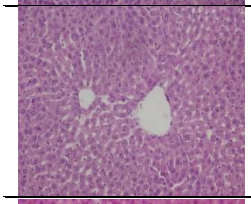
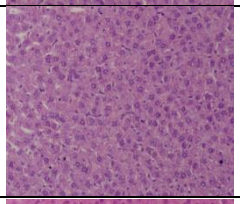
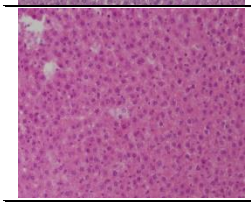
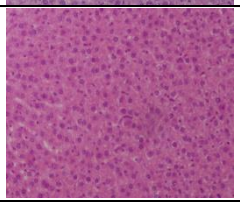
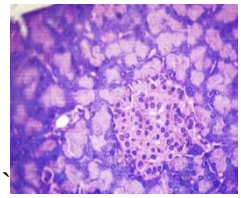
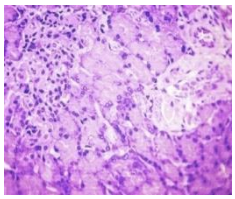
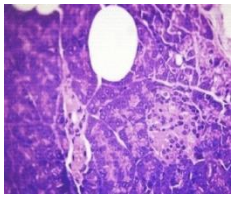
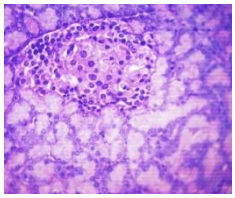
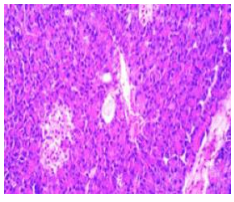
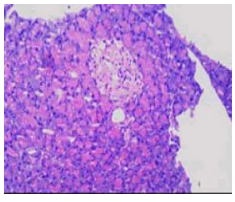
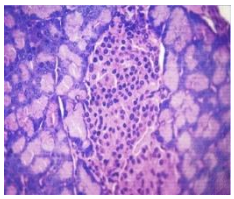
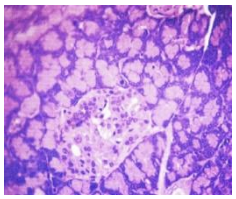
	**Photo (1A):** Control-Normal hepatocytes with normal radial arrangements around hepatic cords (H&E, x400).		**Photo(1B):** Positive control showing increase vacuolation in the cytoplasm of hepatocytes appeared as indistinct clear vacuoles indicate glycogen infiltration in diabetes (H&E, .x400)
	**Photo(1C):** Livers of rats with insulin resistance that were administered 2.5% HLE. Showed slight enhancement in hepatocytes and hepatic architecture (H&E, x400)		**Photo(1D):** Livers of rats with insulin resistance that were administered 5% HLE. Showed slight enhancement in hepatocytes and hepatic architecture. (H&E, x400)
	**Photo(1E):** Livers of rats with insulin resistance that were administered 2.5% PLE. Showed moderate enhancement in hepatocytes and hepatic architecture (H&E, x400)		**Photo(1F):** Livers of rats with insulin resistance that were administered 5% PLE. Showed moderate enhancement in hepatocytes and hepatic architecture. (H&E, x400)
	**Photo(1G):** Liver of rats with insulin resistance that were administered 2.5%(H+P) LE. Showed enhancement in hepatocytes and hepatic architecture (H&E, x400).		**Photo(1H):** Liver of rats with insulin resistance that were administered 5%(H+P) LE. Showed the best enhancement in hepatocytes and hepatic architecture (H&E, x400).

Photo (2): Effect of Hawthorn, Papaya leaf extracts and their combination on histological examination of pancreas tissue

	**Photo(2A):** Control-Normal histological structure of pancreatic islets (H&E, x400).		**Photo(2B):** Control-Positive showing significant degeneration of islets of Langerhans .(H&E, x400)
	**Photo(1C):** Pancreas of rats with insulin resistance that were administered 2.5% HLE. Exhibited slight improvement in pancreatic architecture (H&E, x400)		**Photo(1D):** Livers of rats with insulin resistance that were administered 5% HLE. Exhibited slight improvement in pancreatic architecture (H&E, x400)
	**Photo(1E):** Livers of rats with insulin resistance that were administered 2.5% PLE. Exhibited moderate improvement in pancreatic architecture (H&E, x400)		**Photo(1F):** Livers of rats with insulin resistance that were administered 5% PLE. Exhibited moderate improvement in pancreatic architecture (H&E, x400)

	**Photo(1G):** Liver of rats with insulin resistance that were administered 2.5%(H+P) LE. Showed improvement in pancreatic architecture (H&E, x400).		**Photo(1H):** Liver of rats with insulin resistance that were administered 5%(H+P)LE. Showed the best enhancement in pancreatic architecture (H&E, x400).

Sensory evaluation

The average scores obtained by the cookie's product in the sensory evaluation are presented in table (8). It was found that the color of all cookies with different amounts of Hawthorn, C. papaya leaves, and their mix was significantly darker ($p \leq 0.5$) compared to the control cookies that had no supplements. Also, data showed a significant decrease ($p \leq 0.5$) in the odor of the cookies supplemented with different levels of Hawthorn, C. papaya leaves, and their combination as compared with the control. The mean values of the texture and taste of supplemented cookies showed nonsignificant differences ($p \leq 0.5$) among all supplemented cookies with 2.5% and 5% from Hawthorn, C. papaya leaves, and their combination as compared with each other and the control. On the other hand, the general acceptance of cookies supplemented by 2.5% HLP, 2.5%PLP and 2.5% from their combination were the most liked among all the judges. Statical results for the total score indicated that all cookie samples obtained a score higher than 75%.

Table (8): Sensory evaluation of cookies supplemented with Hawthorn, Papaya leaf powder and their combination

Groups	Color	Odor	Texture	Taste	General acceptability	Total
Control	19.64 ±0.505^{a}	19.82 ±0.405^{a}	19.53 ±0.508^{a}	19.82 ±0.405^{a}	19.91 ±0.752^{a}	98.71 ±0.859^{a}
2.5% HLP	18.86 ±0.595^{ab}	18.85 ±0.866^{ab}	18.87 ±0.882^{ab}	18.63 ±0.546^{ab}	18.82 ±0.405^{ab}	94.03 ±4.943^{ab}
5% HLP	17.65 ±1.677^{cd}	17.64 ±1.375^{cd}	18.14 ±1.743^{abc}	17.16 ±1.751^{abc}	17.04 ±1.839^{bcd}	87.63 ±4.989^{bc}
2.5% PLP	18.21 ±1.167^{b}	18.47 ±1.501^{abc}	18.35 ±1.396^{ab}	18.24 ±0.846^{ab}	18.15 ±0.220^{ab}	91.42 ±7.299^{ab}
5% PLP	16.65 ±1.866^{e}	16.77 ±1.603^{d}	17.07 ±1.793^{bcd}	17.46 ±1.748^{bcd}	16.27 ±2.005^{cd}	84.22 ±2.624^{cd}
2.5%(H+P) LP	17.41 ±1.797^{cd}	17.50 ±1.549^{cd}	17.68 ±1.230^{bcd}	17.12 ±1.405^{bc}	17.85 ±1.757^{abc}	86.75 ±3.935^{bcd}
5% (H+P) LP	16.78 ±1.935^{de}	16.82 ±1.524^{d}	16.60 ±1.371^{cd}	16.97 ±1.102^{bcd}	16.79 ±1.033^{bcd}	83.96 ±3.008^{bcd}

Values in each column which have different litters are significant different ($p \leq 0.05$).
H LP: Hawthorn leaf powder, **PLP:** Papaya leaf powder

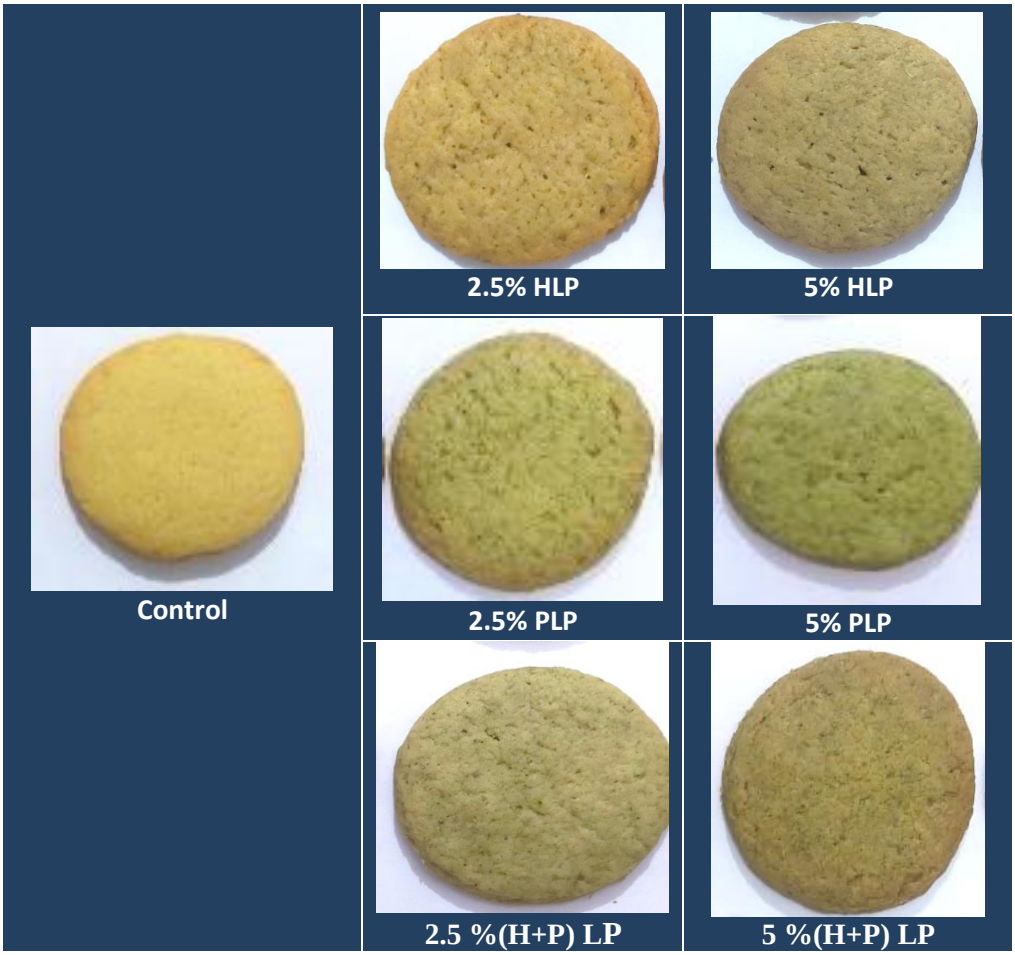


Photo (3): Cookies supplemented with Hawthorn, C. Papaya leaf powder and their combination.

Conclusion

The present study demonstrated that hawthorn and papaya leaf extracts are rich sources of bioactive compounds with significant therapeutic potential. In experimental models of insulin resistance, rats treated with mixtures of hawthorn and papaya leaf extracts showed a marked reduction in body weight gain. These treatments also led to notable improvements in glucose metabolism, insulin resistance indices, lipid profiles, liver enzyme activities, and kidney function parameters. Furthermore, the extracts exhibited antioxidant properties, effectively reducing oxidative stress and supporting the integrity of hepatic and renal functions. Based on these findings, incorporating hawthorn and papaya leaf mixtures—at concentrations of up to 5%—into functional foods may offer substantial nutritional and health benefits for individuals with insulin resistance.

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تأثير مستخلصات أوراق (الزعرور والبابايا) وخليطهما على مقاومة الأنسولين لدى الفئران

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الملخص

تعرف أوراق الزعرور والبابايا بفوائدها العلاجية واستخداماتها التقليدية في علاج العدوى والالتهابات ومختلف الحالات الصحية. ونظرًا لغناها بالمركبات النشطة بيولوجيًا، هدفت الدراسة إلى دراسة التأثيرات المحتملة لمستخلصات هذه الأوراق في علاج مقاومة الأنسولين لدي حيوانات التجارب، وإمكانية استخدامها في إنتاج أغذية وظيفية. تم إجراء هذه الدراسة لتقييم تأثير المستخلصات المائية لأوراق الزعرور (HLE) وأوراق البابايا (PLE) على استهلاك العلف، نسبة زيادة وزن الجسم، أوزان الأعضاء نسبةً إلى وزن الجسم، مؤشرات التمثيل الغذائي للجلوكوز ومقاومة الإنسولين، نشاط إنزيمات الكبد، وظائف الكلى، ملامح الدهون، وإنزيمات مضادات الأكسدة لدى فئران تعاني من مقاومة الإنسولين. استخدم في هذه الدراسة ٤٨ فأرًا من ذكور الألبينو بوزن (١٥٠ ± ١٠ جم). وقُسّمت الفئران إلى مجموعتين رئيسيتين: المجموعة الأولى (٦ فئران) تغذت على النظام الغذائي الأساسي كمجموعة ضابطة سالبة. أما المجموعة الثانية (٤٢ فأرًا) فتغذت على النظام الغذائي الأساسي المدعّم بنظام غذائي غني بالفركتوز بنسبة ٦٠%، ثم قُسّمت إلى سبع مجموعات فرعية. المجموعة الفرعية (١) تغذت على نظام غذائي عالي الفركتوز كمجموعة ضابطة موجبة. المجموعة الفرعية (٢) تناولت ٢,٥% HLE ، المجموعة (٣) تناولت ٥% HLE ، المجموعة (٤) تناولت ٢,٥ % PLE ، المجموعة (٥) تناولت ٥% PLE ، المجموعة (٦) تناولت ٢,٥% HLE+PLE، وأخيرًا المجموعة (٧) تناولت ٥% HLE+PLE. كما تم إجراء تقييم حسي لعينات من البسكويت المدعم بأوراق الزعرور والبابايا. أظهرت النتائج أن المعالجة المتزامنة للفئران المصابة بمقاومة الإنسولين باستخدام مستويين من المستخلصات المائية لأوراق الزعرور والبابايا ومزيجهما إلى جانب الفركتوز، أدت إلى انخفاض في استهلاك العلف، ونسبة زيادة الوزن، ونسبة كفاءة التغذية (FER). كما لوحظ تحسن ملحوظ في مستويات الجلوكوز في الدم أثناء الصيام(FPG) ، والإنسولين في البلازما أثناء الصيام(FPI) ، ومؤشر مقاومة الإنسولين(HOMA-IR) ، والهيموغلوبين السكري (HbA1c %)، والدهون الثلاثية، والكوليسترول الكلي، وكوليسترول البروتينات الدهنية منخفضة الكثافة ومنخفضة الكثافة جدًا، ووظائف الكلى (حمض اليوريك، واليوريا، والكرياتينين)، ونشاط إنزيمات الكبد (AST وALT)، وإنزيم MDA، كما زادت أنشطة إنزيمات مضادات الأكسدة (SOD ، GPX، وCAT)، بالإضافة إلى ارتفاع مستوى HDL-c مقارنة بالمجموعة الضابطة الموجبة. وأظهرت الفحوصات النسيجية للكبد والبنكرياس في الفئران المعالجة بمستويات مختلفة من مستخلصات أوراق الزعرور والبابايا ومزيجهما تحسنًا ملحوظًا في البنية النسيجية لهذه الأعضاء. بالإضافة إلى ذلك، تم إنتاج عينات من البسكويت مدعمة بنسبة ٢,٥% و٥% من مسحوق أوراق الزعرور والبابايا ومزيجهما. وأظهر التقييم الحسي أن جميع عينات البسكويت حصلت على نسبة قبول تجاوزت ٧٥%. واستنادًا إلى هذه النتائج، فإن إدخال مزيج أوراق الزعرور والبابايا بتركيزات تصل إلى ٥% في الأغذية الوظيفية قد يوفر فوائد غذائية وصحية كبيرة للأفراد الذين يعانون من مقاومة الإنسولين.

الكلمات الرئيسية: الزعرور - البابايا - مقاومة الأنسولين