Journal of
Babol University of Medical Sciences
JBUMS
e-ISSN: 2251-7170 p-ISSN: 1561-4107

The Effect of Insect Extract on Liver Tissue and Function in Diabetic Mice

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Article Type
Research Paper

ABSTRACT

Background and Objective: The world is currently turning to treating diseases with alternative medicine to reduce the effects of chemical drugs. This study's objective is to evaluate the physiological and histological changes that take place in the liver of STZ-induced diabetic mice and then evaluate their treatment with Gryllus bimaculatus (GB) extract compared to Metformin.

Methods: This experimental study was conducted on 60 male albino mice weighing 20 to 27 g. 40 mice randomly received 50 µg/kg body weight streptozocin (STZ) through intraperitoneal (IP) administration, whereas 20 mice were not injected and were designated as the control group. Diabetic mice were divided into four groups (n=10): high concentration of insect extract group (HEG), low concentration of insect extract group (LEG), Metformin group (MG), and without treatment as positive control group (+CG). The healthy group was also divided into two groups: one group consumed insect extract (ECG) and the other one served as negative control group (-CG). After one month, mice were scarified and their blood was collected and used to determine fasting blood glucose (FBG), insulin (INS), alkaline phosphatase (ALP) and alanine transaminase (ALT).

Findings: FBG, INS, ALP and ALT in experimental groups showed a significant difference compared to the control group and Metformin group. The LEG group exhibited the closest value of all above parameters to control group (80.5±5.2, 7.2±3.6, 53.8±7.4 and 37.0±5.9 U/L, respectively). This was also shown in histological examination of liver sections in which liver of LEG group was normal compared to MG group, which still had fatty changes of liver cells.

Conclusion: The results of the study showed that low concentration of insect extract could be a suitable treatment for DM and liver disorder compared to metformin.

Keywords: *Diabetes Mellitus, Alkaline Phosphatase, Alanine Transaminase, Insect Extract.*

Received:
Jan 6th 2025
Revised:
Mar 10th 2025
Accepted:
Mar 16th 2025

Cite this article: Ali Rahmat R, Abdul Azeez Shafeeq M, Jouda J. The Effect of Insect Extract on Liver Tissue and Function in Diabetic Mice. *Journal of Babol University of Medical Sciences*. 2026; 28: e24.

Introduction

Diabetes mellitus, known as hyperglycemia, is a metabolic disorder syndrome distinguished by excessively elevated blood glucose levels (1)**.** Diabetes type 1 and type 2 are prevalent forms of illness marked by high blood sugar levels brought on by insufficient insulin action and secretion (2). Given that the liver utilizes glucose as fuel and can hold onto glucose, the liver is a key component in regulating the way that carbs are metabolized (3)**.** The liver converts non-carbohydrate sources of glucose into glycogen (4). This role increases the liver's vulnerability to illnesses in people with metabolic disorders, particularly diabetes mellitus (5). In type 2 diabetes mellitus (T2DM), insulin resistance impairs the ability of insulin to suppress hepatic glycogenolysis and gluconeogenesis, thereby increasing overall hepatic glucose production (6).

Hyperinsulinemia, particularly when combined with hyperglycemia and increased free fatty acid (FFA) flux, up-regulates lipogenic transcription factors in the liver (7). When the hepatic supply of fatty acids exceeds the capacity of the mitochondrial oxidation system, fatty acids accumulate within hepatocytes, leading to hepatic steatosis (8). In patients with type 2 diabetes mellitus (T2DM), these metabolic derangements ultimately contribute to the development of non-alcoholic fatty liver disease (NAFLD) and associated liver enzyme abnormalities (9). Among these enzymes, alanine aminotransferase (ALT) has been most consistently linked to hepatic fat content and is therefore widely used as a surrogate marker for NAFLD (10). In diabetic patients, the combination of chronic hyperglycemia and fatty liver inflicts ongoing injury to hepatocytes (11).

Gryllus bimaculatus (GB) is a nocturnal, cold-blooded insect belonging to the order Orthoptera and the family *Gryllidae* (commonly known as field crickets) (12). As an edible insect species (12), GB has a long history of use as a food source (13). Previous research has described this species as a nutrient-dense resource, highlighting its high levels of total proteins, essential amino acids, omega-3 and omega-6 fatty acids, and various minerals (14). Furthermore, GB contains appreciable amounts of dietary fiber, additional minerals, and polyphenolic compounds (15). GB and its derivatives have been officially recognized as therapeutic resources by the Korea Institute of Oriental Medicine (16). According to recent research, GB has been documented to exert protective effects against multiple pathological conditions, including inflammation, oxidative stress, alcohol-induced liver injury, type 1 diabetes mellitus (T1DM), and insulin resistance (17). In addition, toxicological studies have reported that oral administration of an aqueous extract of GB does not induce any toxicity in rats (18). Traditional literature has further demonstrated beneficial outcomes of GB in the context of edema and hepatic damage (19). However, there has been limited recent research investigating the effects of GB on the liver. Therefore, the present study aimed to evaluate the physiological and histological changes occurring in the livers of mice with experimentally induced T2DM, following treatment with a hot water extract of GB administered at different concentrations, in comparison with metformin, which serves as the conventional standard of care for T2DM.

Methods

This study, conducted as a clinical trial, was approved by the Ethics Committee for the Use of Animals in Research at the College of Science, Al-Mustansiriya University (Reference Number: 150, dated February 2, 2025). A total of 60 male albino mice weighing between 20 and 27 g and aged approximately 8 to 9 weeks were obtained from Mustansiriyah University / Iraqi Center for Cancer Research. The animals were housed in the same environment as the experimental procedures. GB insects were collected from various agricultural fields across Iraq, thoroughly cleaned with 70% alcohol, and allowed to air dry at room temperature for 48 hours. The desiccated GB carcasses were pulverized using an electric grinder. The resulting powder was stored in sealed glass vessels and sterilized in an autoclave at 121°C for 30 minutes. To prepare the aqueous extract, 90 mg of the insect powder was dissolved in 250 mL of distilled water in a volumetric flask. The solution was then placed in a shaking incubator, filtered through Whatman No. 1 filter paper, and centrifuged at 4000 rpm for 6 minutes. The supernatant was subsequently divided into two fractions: 100 mL was diluted with 100 mL of distilled water and placed in a glass container to serve as the low-concentration extract, while the remaining 150 mL was placed in a glass vial without dilution to serve as the high-concentration extract (20). Metformin solution was prepared by dissolving 57 mg of metformin (Merck, Germany) in 10 mL of distilled water according to the protocol established by Ali et al. (21).

The 60 male albino mice were housed in an animal facility with climate-controlled settings, including a temperature range of 22–25°C, and had unrestricted access to water and standard laboratory food. Following the protocol established by Rahmat et al. (20), 40 mice were randomly assigned to receive an intraperitoneal (IP) injection of 100 µL of streptozocin (STZ) at a final concentration of 50 µg/kg body weight to induce diabetes mellitus. The remaining 20 mice were not injected and served as the non-diabetic control group. After STZ administration, all mice were food-deprived for 12 hours. Fasting blood glucose (FBG) levels were measured using an On Call Plus glucometer (ACON, USA). Mice exhibiting FBG levels greater than 150 mg/dL were considered diabetic and included in the study. The diabetic mice were divided into four groups (n=10 each) according to their treatment regimen: the high-concentration GB extract group (HEG), the low-concentration GB extract group (LEG), the metformin group (MG), and the positive control group (+CG), which consisted of diabetic mice receiving no treatment. Both the GB extract and metformin were administered orally on a daily basis at a volume of 100 µL per mouse. The non-diabetic mice were divided into two subgroups (n=10 each): the extract-consuming group (ECG), which received a high concentration of GB extract, and the negative control group (-CG), which did not receive any extract. At the end of the experimental period, all mice were sacrificed, and blood samples were collected for biochemical analyses. Fasting blood glucose (FBG) levels were measured using an enzymatic kit (Biosystem), insulin concentrations were determined using an ELISA kit (Cusabio), alkaline phosphatase (ALP) activity was assessed using p-nitrophenyl phosphate as a substrate (Abnova), and alanine transaminase (ALT) activity was measured using an activity assay kit (Gen Way Biotech). Additionally, the liver was removed and preserved in 10% formalin for subsequent histological processing according to the method described by Eltayef et al. (22).

The present study employed statistical analytic techniques to analyze the collected data using Statview software, version 5.0. Comprehensive characterization of each variable was conducted, with data expressed using measures of central tendency (mean) and dispersion (standard deviation), as well as the range (minimum and maximum values). Fisher's test was utilized for multiple comparisons. One-way analysis of variance (ANOVA), specifically the least significant difference (LSD) test, was employed to evaluate the distinctions between the independent groups under investigation. A significance threshold of 0.05 was used, corresponding to a 95% confidence level, to determine statistical significance.

Results

Estimation of FBG and insulin: At week 1 (designated as zero time, prior to any treatment), diabetic mice were not placed on their experimental diet but were instead provided 10% sucrose solution to determine baseline fasting blood glucose (FBG) levels for subsequent comparison after treatment. During the following 4 weeks (the treatment period), all mice were maintained on their respective diets for testing purposes. FBG levels measured at zero time were significantly higher ($p<0.05$) in all mouse groups compared to levels measured after 4 weeks, with the exception of the healthy control groups that were not injected with STZ (-CG and ECG). These healthy groups demonstrated significantly lower FBG levels (95.4±4.5 and 89.0±6.2 mg/dL, respectively) than the STZ-induced diabetes groups (-CG, MCG, HEG, LEG) and remained close to normal physiological levels. This finding indicates that GB extract does not exert any adverse side effects on healthy mice. At the conclusion of the experiment after 4 weeks, FBG levels were significantly higher ($p<0.05$) in the positive control group (+CG; 169.2±6.4 mg/dL) compared to the healthy controls (-CG and ECG). Importantly, FBG levels in the diabetic mice treated with GB extract (HEG: 80.5±5.2 mg/dL; LEG: 94.7±4.0 mg/dL) were closest to those observed in the healthy control groups. These results demonstrate that GB extract contributed to reducing FBG levels over the 4-week treatment period and may serve as an alternative therapeutic option for diabetes.

Regarding insulin levels, the positive control group (+CG) exhibited higher insulin concentrations (24.1±0.6 µIU/mL) compared to healthy control groups (-CG: 6.2±1.1; ECG: 5.5±0.6) and GB extract treatment groups (HEG: 7.9±0.9; LEG: 7.2±3.6) (Table 1).

Table 1. FBG and Insulin levels in all groups

Groups	FBG (mg/dl)		Insulin (µIU/ml)
	Zero time Mean±SE	After 4 weeks Mean±SE	Mean±SE
-CG	95.4 ± 4.5^{a}	75.4 ± 5.3^{Ba}	6.2 ± 1.1^{a}
ECG	89.0 ± 6.2^{a}	70.0 ± 5.8^{Ca}	5.5 ± 0.6^{a}
+CG	170.2 ± 3.6^{b}	169.2 ± 6.4^{e}	24.1 ± 0.6^{b}
MG	178.1 ± 4.4^{b}	102.7 ± 7.2^{d}	7.9 ± 1.3^{a}
HEG	187.0 ± 7.6^{c}	94.7 ± 4.1^{c}	9.1 ± 0.9^{a}
LEG	196.2 ± 7.8^{d}	80.5 ± 5.2^{b}	7.2 ± 3.6^{a}

The small letters clarify the notable variations between mice groups. The large letters clarify the notable variations between time points. The significance value is p<0.05

Estimation of ALP and AST: The levels of alkaline phosphatase (ALP) and aspartate aminotransferase (AST) were significantly increased ($p<0.05$) in the positive control group (+CG), with values of 383.5±43.1 U/L for ALP and 138.5±16.0 U/L for AST, compared to all other experimental groups. These enzyme levels were also significantly elevated in the metformin-treated group (MG) (ALP: 128.5±13.5 U/L; AST: 50.2±9.2 U/L). In contrast, reduced levels were observed in the healthy control group (ECG) (ALP: 57.3±8.6 U/L; AST: 34.7±7.2 U/L) as well as in the groups treated with GB extract (HEG and LEG). Among these, the low-concentration GB extract group (LEG) demonstrated ALP and AST levels closest to normal physiological values (ALP: 53.8±7.4 U/L; AST: 37.0±5.9 U/L). These findings indicate that GB extract effectively reduces the elevation of ALP and AST and presents a potential alternative therapeutic approach compared to metformin (Figure 1).

Histological findings: Histological examination of liver sections from untreated diabetic mice (+CG) revealed a number of pathologic lesions resulting from STZ-induced diabetes, including cellular damage, fatty changes, necrotic hepatocytes, and lymphocyte infiltration between hepatic cells (Figure 2A, B). By contrast, liver sections from the healthy control groups (-CG and ECG) showed normal hepatocyte structure and morphology (Figure 2C, D), confirming that GB extract did not cause any harmful changes in liver tissue. In the diabetic groups treated with GB extract, the LEG group exhibited liver sections with an appearance closest to normal tissue, characterized by the absence of hepatocyte necrosis (Figure 2E). The HEG group also showed improvement, with only a few inflammatory cells present and no evidence of hepatocyte necrosis (Figure 2F). In comparison, the metformin-treated group (MG) displayed fatty changes in hepatocytes (Figure 2G). Collectively, these findings indicate that GB extract is a superior alternative treatment to metformin for ameliorating diabetes-induced liver tissue damage.

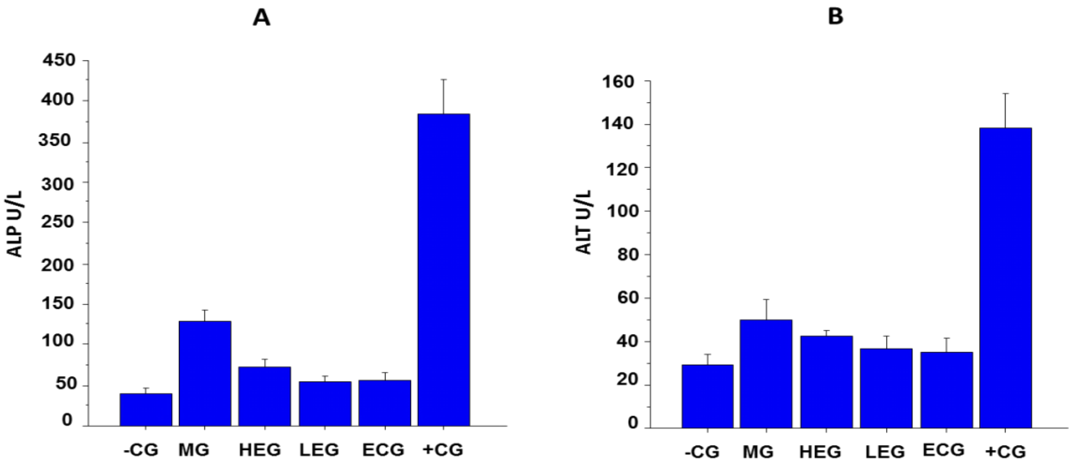
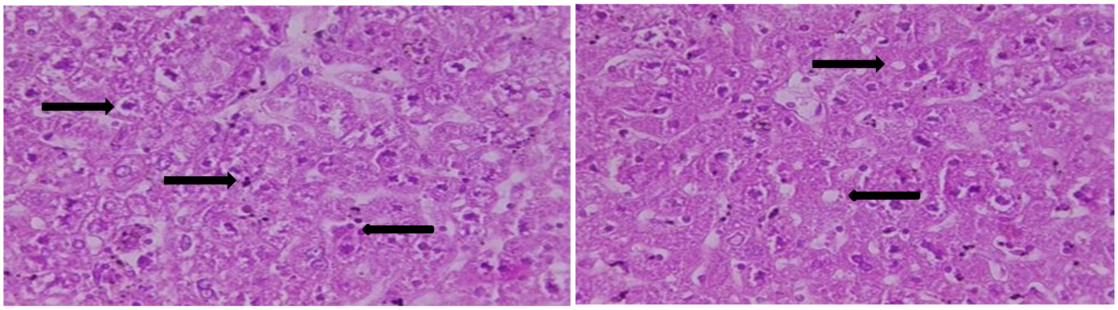
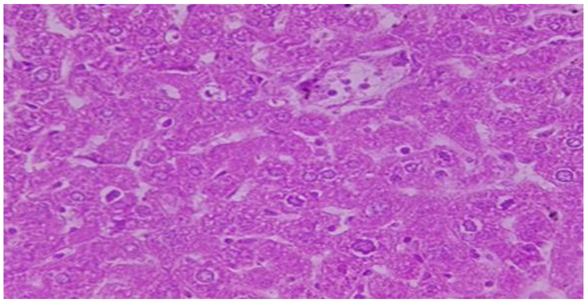


Figure 1. Liver function parameters (ALP and AST) measured in serum from each experimental group after completion of the 4-week treatment period

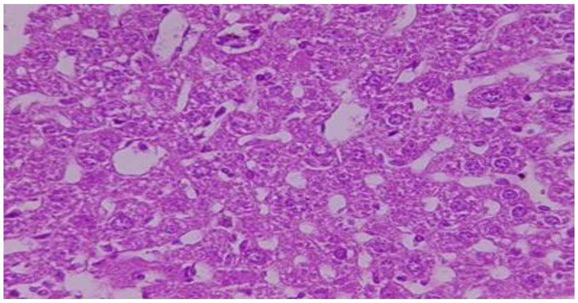


(A) **(B)**

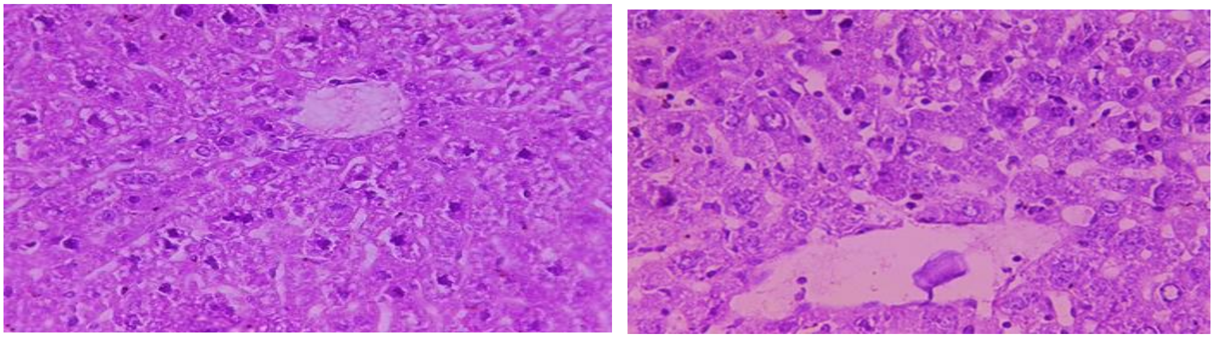
In the positive control group (+CG), liver sections revealed (A) hepatocellular damage, necrosis, and inflammatory cell infiltration within the liver parenchyma, and (B) fatty change with evidence of necrotic cells.



(C): Liver section from the (-CG) group demonstrates normal hepatocyte architecture and cellular morphology.

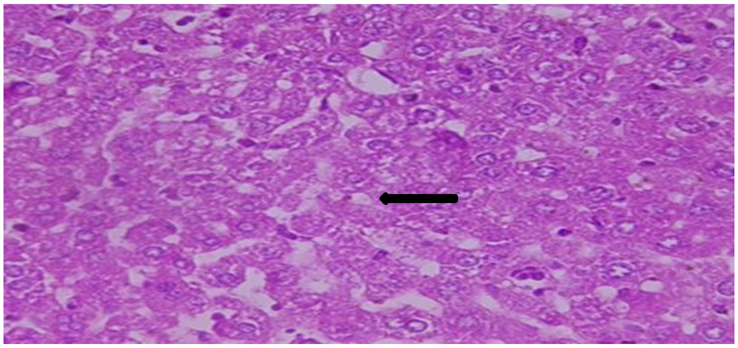


(D): Liver section from the (ECG) group demonstrates normal hepatocyte architecture and cellular morphology.



(E): Liver section from the (LEG) group demonstrates no necrotic hepatocytes, and overall tissue architecture approximates normal histology.

(F): Liver section from the (HEG) group demonstrates sparse inflammatory cell infiltration without any necrotic hepatocytes.



(G): Liver section from the (MG) group demonstrates hepatocellular steatosis.

Figure 2. Longitudinal section of endocrine cells in all experimental groups (↑) (X40) (H & E)

Discussion

In the context of diabetes research, administration of GB extract significantly decreased fasting blood glucose (FBG) and insulin levels in the experimental animal groups compared to the metformin-treated group. According to a study conducted by Ashok et al. (23), the folic acid content in GB was determined to be substantially higher than that of food sources derived from plants and animals, making crickets a less expensive alternative to commercial supplements (24). In numerous studies, folate supplementation has been demonstrated to lower insulin levels (25) and reduce insulin resistance in a manner dependent on the amount of folate supplementation taken (26). These findings are consistent with those reported by Xie et al. (27). Our previous chemical results (28) showed that GB extracts contain a high concentration of chitosan, which is the most common natural polysaccharide and a significant source of dietary fiber (29). This is relevant because numerous investigations have substantiated the advantageous health consequences of chitosan, a dietary supplement made of non-toxic cellulose that reduces the effects of hyperglycemia, diabetes, dyslipidemia, and inflammation (30). Individuals with type 2 diabetes have been discovered to be more inclined to liver function test abnormalities than non-diabetic healthy individuals (31), and these abnormalities are related to several liver conditions, such as hepatocellular carcinoma, liver cirrhosis, and non-alcoholic fatty liver disease (NAFLD) (32). The liver takes part in the control of glucose homeostasis during the fasting state and is responsible for metabolizing approximately 60-65% of circulating glucose (33). STZ-induced diabetes has been linked to significant changes in indicators of oxidative stress and free radical creation, along with concurrent cellular damage. These represent the primary mechanisms underlying the complications of diabetes, which can adversely affect the liver (5).

Elevated liver enzyme levels do not always refer to hepatitis; they might instead imply that metabolic syndrome is present (34). ALP and AST are significant and commonly measured parameters that represent the fundamental state of liver function and demonstrate the degree of hepatocytic damage (35). In the present study, ALP and AST levels were elevated in diabetic mice, which agrees with the observations of Shrestha et al. (36), who also noted that elevated liver isoenzyme levels in serum suggest cholestasis rather than merely hepatic cell damage (2). This cholestatic pattern could be attributable to the development of fatty liver (37). Collectively, this evidence explains the increase in ALP and ALT levels and the histological hepatic changes observed in STZ-induced diabetic mice compared to the normal control mice group in the present study.

On the other hand, current histological examination revealed that liver sections from the LEG (Figure 2E) and HEG (Figure 2F) groups showed no evidence of necrosis, in contrast to the MG group (Figure 2G), which still demonstrated fatty change of liver cells. The necrotic hepatocytes observed in Figures 2A and 2B are due to alterations in blood vessel permeability and dilatation, as well as an increase in adhesion molecules that enable the migration of defense hepatocytes from the circulation into nearby tissues to eliminate dead hepatocytes (38). Our study's findings align with those of Degirmenci et al. (39), who observed hepatocytes arranged less concentrically, enlarged veins, and liver fibrosis. Furthermore, the liver tissues of healthy mice (ECG) (Figure 2D) and diabetic mice treated with GB extracts (LEG and HEG) (Figure 2E, F) resembled those of normal mice in appearance (Figure 2C). This finding is consistent with what was reported by Ahn et al. (40), who found the liver to be in an improved state when the morphology of liver tissue treated with insect extract was examined. This improvement could be attributed to the presence of certain functional groups, such as carbonyl and hydroxyl groups in epoxy compounds, which possess strong free radical scavenging properties (41). With respect to metformin, Al-Hashem et al. (42) found that metformin inhibits profibrogenic and inflammatory biomarkers in rats; however, it has not been shown to protect the liver histologically. This is consistent with our study, in which liver tissue showed fatty change without significant modification when metformin was used as a treatment, in contrast to the GB extract, which effectively modified liver tissue toward a normal appearance. Conversely, metformin may cause hepatotoxicity, including cholestasis and acute hepatitis (43). This evidence could explain the superior therapeutic effect of GB extract compared to metformin.

The findings of this study demonstrated that hot GB extract, administered at both high and low concentrations, could represent an effective therapeutic option for diabetes mellitus when compared to metformin. However, this result necessitates further research to identify the active components responsible for the observed effects. Additionally, this extract may also serve as a beneficial treatment for liver disorders. Nevertheless, additional studies are required to determine whether this positive effect is specific to liver disorders caused by diabetes mellitus or whether it also applies to liver disorders arising from other causes. Furthermore, the low concentration of GB extract (LEG) appeared to yield better outcomes than the high concentration (HEG), suggesting that lower doses may be more efficacious.

Conflict of Interest: The authors deny any potential conflicts of interest related to the research, authorship, and publication of this article.

Acknowledgment

The authors express their sincere gratitude to the Iraqi Center for Cancer Research and Medical Genetics/ Mustansiriyah University and the International Center for Research and Development for their invaluable assistance in facilitating the work and providing technical support throughout this research.

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