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Effect of Treatment with Cyproheptadine and Artemisia Absinthium on Insulin Level of Zinc-Deficient Diet Rats

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Abstract

The effect of Artemisia absinthium and Cyproheptadine on the insulin levels of rats fed on a diet deficient in zinc was examined in the current study. Thirty-two mature male rats were divided randomly into four groups each of eight animals. Control Group (G1), Zinc Deficiency Group (ZDD) (G2), Zinc Plus Cyproheptadine Group (G3), and Zinc Plus Artemisia absinthium Group (G4). Zinc, Cyproheptadine and Artemisia absinthium were taken orally (containing zinc not more than 1mg/kg diet, 720 µg/kg B. W, 100 mg/kg BW) for 30 days. Insulin level and histopathological study were done. The data showed that feeding rats on a zinc deficient-diet (ZDD) resulted in decrease of insulin level compared to the control group. On the other hand, the Cyproheptadine (CH) and Artemisia absinthium (ART) treatment groups exhibited improvement of insulin level compared to zinc deficiency diet feeding group. In addition, zinc deficient-diet (ZDD) showed mild fatty liver with hepatic steatosis and macrovesicular steatosis. After treatment with cyper and Art, liver of both groups are tissue improved significantly. Treatment with artemisia absinthium (ART) and cyproheptadine (CH) of rats feed on a diet deficient in zinc, increases insulin levels and improve liver tissue histology.

Keywords: Anorexia, Cyproheptadine, Artemisia absinthium, insulin, rats.

Introduction

Anorexia is a significant risk factor for malnutrition, which can result from a variety of factors (Landi et al., 2016). Ten-to-40% of hospitalized adult patients displayed indicators of nutritional deterioration and weight loss at some point during their stay, according to a review (Rathenböck, 2022). Most people have experienced a momentary loss of appetite at least once in their lives (Swami et al., 2022). This is typically not a concerning symptom until it lasts more than a day or two (Chu et al., 2018). Additionally, it could be a sign of a serious underlying illness like cachexia, cancer, or hopelessness (Mattox, 2017). The trace element zinc, known to be essential and found in thousands of enzymes, controls the production,

storage, and release of insulin (Shi et al., 2020). Numerous investigations have revealed that the plasma zinc levels of obese individuals are decreased (Olechnowicz et al., 2018). Likewise, a zinc deficiency may raise the risk of insulin resistance, glucose intolerance, coronary artery disease, diabetes, and other conditions (Bjørklund et al., 2020).

Zinc supplements can help with weight loss efforts and have a positive impact on zinc content growth (Roohani et al., 2013). Given the relevance of zinc's role in controlling the levels of the hormones involved in appetite and the metabolism of macronutrients, in addition to the dearth of studies on the effects of zinc supplementation on the hormones that control appetite and anthropometric measurements (Ozturk et al., 2023).

Numerous phytochemicals, such as total flavonoids and phenolic composites, are present in it, which may contribute to the explanation for its anti-oxidative activities **(Guan et al., 2021).**

Artemisia absinthium is antidiabetic and anti-hyperlipidemic effects in diabetic individuals and rats (Adewumi et al., 2020). Cancer research has studies the support of use appetite stimulants like cyproheptadine hydrochloride (CH) to promote weight gain (Kim et al., 2021). These drugs are also safe for use in children because of their low degree of toxicity and, when required, palatable oral solutions (Thabet et al., 2018).

The use of cyproheptadine hydrochloride (CH), a serotonin and histamine antagonist (Okuma et al., 2013), in treating allergic rhinitis (Bernstein et al., 2016), allergic conjunctivitis (Dupuis et al., 2020), urticaria (Kolkhir et al., 2022), dermatographism (Russell et al., 2022), and mild angioedema in children has been approved by the Food and Drug Administration (FDA) (Frank et al., 2016). CH users have been observed to acquire weight inexplicably (Hertzman et al., 2017). According to earlier studies, this drug successfully boosts appetite in children with anorexia nervosa, asthma, failure to thrive, and short height (Feigelman and Keane, 2017). The preset work investigates the effects of A. absinthium and cyproheptadine (CH) on rats fed on zinc deficiency diet.

Materials and Methods

Male albino rats weighing 150–180 g were used along the study. Rats were obtained from the National Organization for Drug Control and Research's animal shelter **(Dokki, Cairo, Egypt)**. Prior to testing, they were kept in the lab room for at least a week under a 12-hour cycle of alternating light and shade. Animals were given conventional laboratory pellets and unlimited amounts of water. The National Research Centre in Egypt's Ethics Committee (registration number 17/004), the National Institutes of Health's Guide for the Care and Use of Laboratory Animals, and the Canadian Council on Animal Care's recommendations were all followed when doing any animal treatments.

Drugs

Cyproheptadine and Artemisia absinthium were purchased as a white, crystalline powder from Cornell Lab in Al-Maadi, Cairo, Egypt.

Experimental groups

Rats received each of the treatments listed below via oral gavage every day for 30 days. The experimental design as flow:

- Group 1 (G1): received water basal diet according to Nutrient Requirements of the Laboratory Rat (Ahmed-Farid et al., 2017).
- Group 2 (G2): anorexigenic rat model treated with zinc deficient diet Zinc (containing zinc not more than 1mg/kg diet) (Kapała et al., 2024).
- Group 3 (G3): ZDD treated with cyproheptadine (720 µg/kg BW) (Kotanidou et al., 2020).
- Group 4 (G4): ZDD and treated with Artemisia absinthium extract (100 mg/kg BW) (Boudjelal et al., 2020).

Preparation of serum samples for biochemical investigations

Following the decapitation, blood samples were gathered in sterile, dry centrifuge tubes. To measure insulin levels serum was obtained by centrifuging blood samples at 5,000 rpm for 20 minutes at 4°C **(Balaji et al., 2020).**

Insulin Determination

The Ray Bio Rat Insulin ELISA kit is an in vitro

enzyme-linked immunosorbent assay for the quantitative measurement of Rat Insulin in serum, plasma and cell culture supernatants. This assay employs an antibody specific for Insulin coated on a 96-well plate. Standards and samples were pipetted into the wells and Insulin present in a sample was bound to the wells by the immobilized antibody. The wells were washed and biotinylated anti-Rat Insulin antibody was added. After washing away unbound biotinylated antibody, HRP-conjugated streptavidin was pipetted to the wells. The wells were again washed, a TMB substrate solution was added to the wells and color develops in proportion to the amount of Insulin bound. The Stop Solution changes the color from blue to yellow, and the intensity of the color was measured at 450 nm.

Histopathological Analysis

Tissues preparation for histological investigation:

From each rat, liver tissues were carefully dissected and fixed in Bouin's solution for routine histological study. Following fixation, tissues were dehydrated in ascending grades of ethyl alcohols, 70%, 90% and 100% (to prevent shrinkage of tissues and to remove water gradually from the fixed tissues), cleared in xylol (to remove alcohol and to allow the fixed tissues to be miscible with paraffin wax in the following step) and embedded in paraffin wax at 60^0C. Serial transverse sections were then cut at 5-6 microns in thickness using Cambridge Rocking Microtome and affixed to slides. For the general histological investigation, sections were stained in Hematoxyline and Eosin (H&E) then washed, dehydrated, cleared, and mounted with Canada plasma for permanent preparations **(Bancroft and Gamble, 2008).**

Statistical analysis

The results obtained are shown as mean ± SE. The reported values are the averages of eight animals. One-way analysis of variance was used in the statistical analysis, then post-hoc least significant difference analysis (Duncan). Statistical Package for Social Science for Windows was used to do the statistical analysis (Version: 17). Statistics were judged significant at a value of $p< 0.05$.

Results

Insulin level:

The results of Insulin concentration of different experimental groups are illustrated in **Table 1** and **Figure 1.** The mean level of Insulin of control group was 3.57 ± 0.24 (lU\ml). However, in zinc deficiency diet group it was 2.67 ± 0.21 (IU\ml). On other hand, the mean of rats treated with Zinc deficiency diet (ZDD) and Cyproheptadine (CH) was 2.91± 0.29 (IU\ml). Furthermore, the mean level of rats treated with Zinc deficiency diet (ZDD) and Artemisia absinthium (Art) group was 2.17 ± 0.17 (IU\ml). ANOVA test shows extremely significant difference between groups at $P < 0.005$.

Presented data of Insulin showed that Zinc deficiency diet (ZDD) and Artemisia absinthium (Art) groups significantly decreased compared to the control group. In addition, rats treated with Cyproheptadine (CH), didn't differ significantly from control group and near to normal value. In contrast, rats treated with CH, and Art didn't differ compared with ZDD group but mild increased at the end of excrement. In the same manner, treated groups with CH, and Art didn't differ from each, but CH showed the best treatment of all.

Table (1): Statistical analysis of serum insulin levels of different treated groups with the compared control group.

	Insulin(lU\ml)	
	Mean± SE	**ANOVA P-value**
Control (n=8)	3.57 ± 0.24 [a]	
ZDD (n=8)	2.67 ± 0.21 [b c]	
ZDD + CH (n=8)	2.91± 0.29 [a b c]	0.005
ZDD + Art (n=8)	2.17 ± 0.17 [c]	

a, b, c, means having the same superscript letters are significantly different from each other (P<0.05). ZDD=Zinc deficiency diet, CH= Cyproheptadine, Art=Artemisia absinthium. The values in each column signify Mean ± SE. N= number of cases in each group.

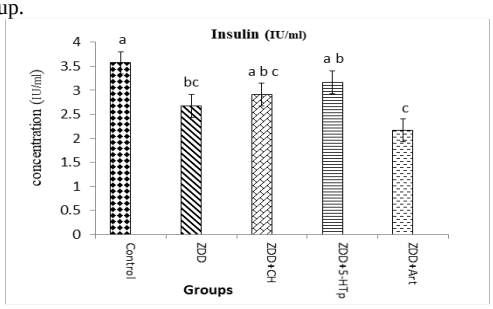


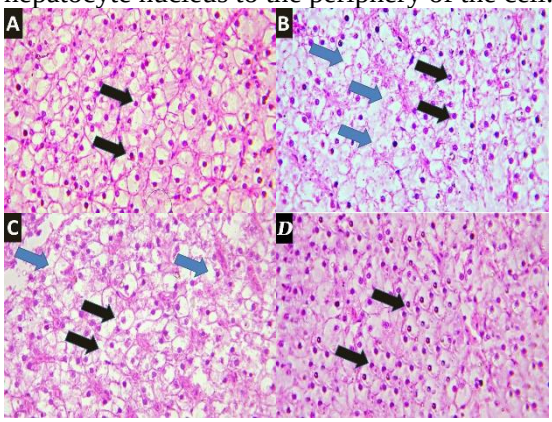
Fig (1): Mean value of Insulin (IU\ml) levels in different treated groups. a, b, c, means having different superscript letters in the same row differ significantly (P<0.05). ZDD=Zinc deficiency diet, CH= Cyproheptadine, Art=Artemisia absinthium.

Histological investigation:

The histopathological examination showed in **Figure 2.** The histopatholog of experimental groups G1, G3, and G4 showed hepatocytes with normal in size, shape, and arrangement (black arrow). They have a distinct nucleus and cytoplasm and no inflammation.

Also there is an absence of inflammatory cells, indicating no ongoing inflammation. There is any evidence of fibrosis or scarring in the liver tissue and no accumulation of fat (steatosis) within hepatocytes.

In contrast, ZDD (G2) showed mild fatty liver with hepatic steatosis (Blue arrow), is a condition characterized by the accumulation of excess fat within liver cells (hepatocytes). Macrovesicular Steatosis: The hallmark feature of fatty liver disease is the presence of large fat droplets (macrovesicular steatosis) within hepatocytes. These fat droplets displace the hepatocyte nucleus to the periphery of the cell.



Fig(2): Histological and histopathological examination of liver rats' control (A), treated with ZDD (B), treated with CH (C) and treated with ART (D) one month ago.

Discussion

Malnutrition is still a significant problem in underdeveloped nations despite international efforts, and it is thought to be the primary risk factor for the illness and death of millions of young children. According to the most recent report from 2013, undernutrition was the cause of 3.1 million child deaths globally, or 45% of all child deaths **(Wali et al., 2021).** Weight loss caused by food restriction or increased physical activity is referred to as anorexia nervosa (AN) **(Casper, 2020).** Body mass index (BMI) values are altered as a result of weight loss, which has an impact on gastrointestinal processes as well as brachial and central nerve impulses **(Investigators et al., 2006).**

The present study is one of the few studies examining the effect of low levels of zinc diet affect hormones and measures that regulate appetite while also raising hunger. Data obtained revealed that the zinc deficiency diet (ZDD)-treated positive group experienced a drop in hunger that resembled a reduction in insulin compared to the control group, which was consistent with a recent study **(Buzzetti et al., 2020).** In a different study, which was published by the journal, zinc supplementation caused obese male rats to lose a large amount of weight **(Abdulmalek et al., 2021).** Two potential explanations for the effect of zinc in weight reduction include the insulin sensitizer activity of zinc and changes in the metabolism of hypothalamic neurotransmitters like insulin **(de Bartolomeis et al., 2023)** the results obtained confirm this. Additionally, collected data on insulin may be distorted for ZDD due to insulin mimicry in cells and the reduction of potentiating insulin receptor signaling **(Krishnan et al., 2018).** The data of, which stated that the Zn deficiency might be expected to lessen insulin stimulated leptin secretion in adipocytes, and ultimately decrease the total level of insulin, agreed with the forfeiture of potentiating insulin receptor signaling depend on ZDD **(Alemany, 2024).** Additionally, insulin insufficiency is linked to excessive lipolysis and an increase in the flow of free fatty acids into the liver. Insulin also has a strong inhibitory effect on lipolysis in adipocytes **(Carpentier and Metabolism, 2021).**

Recent research has shown that zinc, particularly with metabolic syndrome, had positive benefits on insulin level and insulin resistance **(Olechnowicz et al., 2018).** A prospective study revealed that consuming more zinc is linked to a decreased incidence of type 2 diabetes **(Kaur et al., 2014)**, However, among non-obese and obese non-diabetics, there is considerable debate regarding the connections between zinc level and insulin resistance/metabolic risk factors **(Sabán-Ruíz et al., 2014).** Because it can improve insulin's ability to attach to hepatocyte membranes, zinc is known to play a significant role in the stabilization of insulin hexamers and in the pancreatic storage of insulin **(Akbarian et al., 2018).** In fact, the role of zinc during the creation of the insulin receptor may be related to the lower hepatic insulin binding to

hepatocyte membranes during zinc deprivation **(Adulcikas et al., 2019).** Additionally, zinc is a powerful antioxidant, and oxidative stress is thought to be a major factor in the onset and development of insulin resistance and diabetes **(Bjørklund et al., 2020).** According to the study's findings **Witkowska et al. (2021)** an excessive amount of Zn during the growth period of an organism's diet might increase the rate at which nutrients are absorbed by increasing the absorptive surface area of the organism's mucosal intestinal epithelial cells. Zn's increased nutritional uptake stimulates the transport of additional nutrients to adipocytes via insulin, which promotes the development of fat cells **(Olechnowicz et al., 2018).** Additionally, the transportation of extra nutrients worsens the release of leptin from adipocytes and the synthesis of the hormone in the body **(Sáinz et al., 2015).** These effects may be due to increased zinc absorption within cells, which may boost the production of the insulin degrading enzyme (IDE) **(Leissring et al., 2021).**

In this study, it was found that treatment with cyproheptadine leads to an improvement in the symptoms of insulinoma and joint loss compared to the group suffering from zinc deficiency, where the results were (2.91± 0.29), (2.67 ± 0.21) respectively, and This study was supported by a study conducted by **Kim et al. (2021)**, histamine antagonist and appetite stimulant cyproheptadine hydrochloride (CH). The stimulation of growth hormone release brought on by inducing deep sleep and increased calorie intake due to increased desire to eat are two potential factors for this medication's appetite-stimulating effects **(Mukherjee et al., 2022).** By acting as an appetite stimulant and increasing calorie intake, CH most certainly contributes to weight gain **(Harrison et al., 2019).** Two explanations have been offered to explain this phenomenon **(Sandberg and Alvesson, 2021).** According to the first theory, CH directly activates the hypothalamus center for appetite **(Miller, 2019).** This has been demonstrated in animal models, and human 5-HT2 and H1 receptor responses to CH have also been noted **(Potenzieri et al., 2012).** Among children who seem to be underweight, CH therapy may increase their serum levels of insulin-like growth factor-I (IGF-I), accelerating their rate of growth **(Soliman et al., 2019).** One of the main factors affecting general health is the ability to maintain a healthy weight **(Holley et al., 2016).** A number of well-known factors, including hormones like leptin and insulin, affect how homeostatic parameters are regulated **(Chapelot and Charlot, 2019).**

The data obtained from the group treated with Artemisia absinthium indicate a significant improvement in insulin levels and the treatment of anorexia compared to the control group and the zinc loss group. This is due to the therapeutic properties that this plant carries and its antagonistic effect on GABA receptors. The results of this investigation have been validated by the results of previously conducted research. Traditional uses for Artemisia absinthium included sedation, hunger stimulation, analgesia, flavoring, and antiphrastic **(Taraghdari et al., 2015).** The European Medicines Agency's committee on herbal medicinal products acknowledged transient loss of appetite as a therapeutic indication for Artemisia absinthium, with a daily dose of 2.3 g powdered herb in 2-3 doses **(Bommakanti et al., 2023).** This fragrant shrub contains essential oils in amounts as high as 1.7% **(Shaaban et al., 2012).** The main chemical in the essential oil, the monoterpene thujone (40–90%), has been shown to have anti-convulsant effects by blocking GABA receptors **(Al-Harrasi et al., 2022).** An oral dose of an Artemisia absinthium liquid formulation significantly boosted gastric secretions, bile, and pancreatic enzymes in a man **(Palanikumar et al., 2020).**

On the other side, Khandekar et al. (2015) discovered that pancreatic polypeptide reduces people's appetites and food intake.

Along with helping with fat digestion, increasing appetite, and enhancing nutrient absorption, artemisia provides a host of additional advantages for the gut **(Szopa et al., 2020).** Additionally, it replaces the quantity of stomach fluids necessary to reestablish regular digestion and stomach function **(Mulet-Cabero et al., 2020).** Artemisia absinthium was discovered to have significant hypoglycemic action, equivalent to 10 mg/kg, for both normal and diabetic mice **(Hbika et al., 2022).** Rats with diabetes who were fed Artemisia absinthium consumed more food and gained weight **(Batiha et al., 2020).** Elevated triglyceride and total cholesterol levels were demonstrated to sharply decline following Artemisia absinthium administration, although high-density lipoprotein (HDL) levels rose in

diabetic rats. The amount of glycogen in the liver has also dramatically increased **(Bhat et al., 2019).**

Similar outcomes were observed in alloxan-induced diabetic rats, as reported by (Ramadan et al., 2017), where various dosages of ethanolic extraction of A. absinthium caused a significant decline in blood glucose level in a dose-dependent manner (Kauser et al., 2023).

Histopathological analysis of liver rats in the zinc-deficient group's liver were examined, and the results showed mild fatty liver with hepatic steatosis. In patients with chronic liver disease there are insulin resistance **(Pais et al., 2015).** This study suggested that deficiency in serum zinc causes reduced antioxidant activity, increased lipid peroxidation, and liver cell injury in chronic hepatitis. Another research demonstrated decreased serum zinc level in individuals with viral hepatitis compared with the reference group **(Abd Ellatif Afifi et al., 2023).** Examination of the sections of the liver of zinc deficient rats showed the same picture as with H&E examination of marked disruption of liver structure. Most hepatocytes revealed degenerated appearance with extensive intercellular vacuolization in liver parenchyma with multiple spaces between these distorted cells **(Rateb and Kamal, 2022).** The hepatocyte showed condensed cytoplasm with nuclei that appeared greatly distorted, shrunken, very pale, and sometimes with the absence of surrounding cytoplasm **(Rateb and Kamal, 2022).** Others hepatocytes were markedly disfigured, degenerated with absent nuclei **(Chen et al., 2023).** Likewise, treatment with Cyproheptadine and Artemisia absinthium for 30 days liver tissue was normal in size, shape, and arrangement. They have a distinct nucleus and cytoplasm, no inflammation compared with liver tissue of the control group due to their antioxidative and hepatoprotective effects.

Conclusions

An improvement in insulin concentrations and liver histology after treatment of rats given a zinc-deficient diet for a month with Cyproheptadine and Artemisia absinthium.

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الملخص العربي

عنوان البحث: تأثير العلاج بالسيبروهيبتادين والأرطماسيا أبسنثيوم على مستوى الأنسولين لدى فئران النظام الغذائي التي تعاني من نقص الزنك

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تم فحص تأثير Artemisia absinthium و Cyproheptadine على مستويات الأنسولين لدى الفئران التي تتغذى على نظام غذائي ناقص في الزنك في الدراسة الحالية. تم تقسيم اثنين وثلاثين فئرانًا ناضجة من الذكور عشوائيًا إلى أربع مجموعات تضم كل منها ثمانية حيوانات. مجموعة التحكم ((G1، مجموعة نقص الزنك (ZDD) (G2)، مجموعة Zinc Plus Cyproheptadine (G3)، ومجموعة Zinc Plus Artemisia absinthium (G4). تم تناول الزنك والسيبروهيبتادين والأرطماسيا أبسينثيوم عن طريق الفم (يحتوي على الزنك بما لا يزيد عن ١ ملجم/كجم من وزن الجسم، ٧٢٠ ميكروجرام/كجم من وزن الجسم، ١٠٠ ملجم/كجم من وزن الجسم) لمدة ٣٠ يومًا. تم إجراء مستوى الأنسولين والدراسة النسيجية. أظهرت البيانات أن تغذية الفئران على نظام غذائي يعاني من نقص الزنك ((ZDDأدى إلى انخفاض مستوى الأنسولين مقارنة بالمجموعة الضابطة، من ناحية أخرى، أظهرت مجموعات علاج سيبروهيبتادين ((CHوالأرطماسيا أبسنثيوم ((ARTتحسنًا في مستوى الأنسولين. مقارنة بمجموعة التغذية التي تعاني من نقص الزنك. بالإضافة إلى ذلك، أظهر النظام الغذائي الذي يعاني من نقص الزنك ((ZDDكبدًا دهنيًا خفيفًا مع تنكس دهني كبدي، تنكس دهني كبير الحويصلات. بعد العلاج بالسايبر والفن، تحسنت أنسجة الكبد في كلا المجموعتين بشكل ملحوظ. العلاج باستخدام الأرطماسيا أبسنثيوم ((ARTوالسيبروهيبتادين ((CHللفئران التي تتغذى على نظام غذائي يفتقر إلى الزنك، يزيد من مستويات الأنسولين ويحسن أنسجة أنسجة الكبد.