A new stratagem for the synthesis of novel ZnO-Insulin nanoparticles for controlled release of glucose in blood

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ABSTRACT

In this novel research, ZnO–insulin nanoparticles were prepared as glucose level regulator in the blood by sol-gel route adopting micelle template approach. The physicochemical features of the novel nanoparticles were investigated by XRD, FTIR, EDX and HRTEM which reveal noted crystallinity distortion when insulin is present. ZnONPs slight crystallite distortion could aid formulating ZnONPs activity biomedically in presence of protein entities. A homogeneous dispersion of insulin on the surface of ZnONPs was detected by HRTEM could also indicate favorable attachment mutual sites between the ZnO surface and the structural amino acid groups. The hypoglycemic activity effect of ZnONPs, ZnONPs-Insulin (1:1) and ZnONPs-Insulin (1:0.5) drugs was proven and compared to that of insulin in this study. The data showed that ZnONPs-Insulin (1:1) drug was the most potent hypoglycemic agent of them.

INTRODUCTION

Insulin is a hormone that is secreted from pancreas and is of undeniable role in regulating blood-sugar[1]. It comprises of 2 polypeptide chains A (with 21 amino acid residues) and B (with 30 amino acid residues). Both Chains A and B are linked by disulphide bridges [Fig 1]. Insulin is synthesized in the beta cells of pancreases and secreted from the beta cells in response to various stimuli like glucose, arginine, endoplasmic reticulum where it is cleaved into proinsulin by proteolytic enzymes. Various neural, endocrine and pharmacological agents can also exert stimulatory effect[2]. Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of different organs, especially the heart, eyes, kidneys, nerves, and blood vessels. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the pancreatic b-cells which is followed by insulin deficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and

defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia[3].
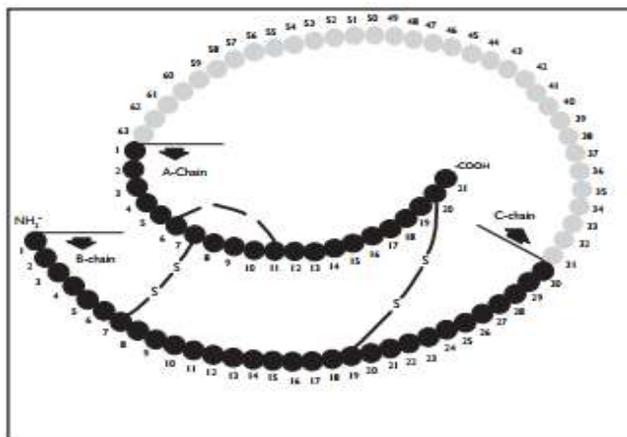
Fig. 1: Insulin hormone

When insulin is used as an external medication, it is derived from either pork (porcine), beef (no longer available in the U.S.), or is genetically made to be identical to human insulin[4].It is generally administered by multiple daily subcutaneous injections. Doses are adjusted according to eating, physical activity, and blood glucose level. This approach and its integration within flexible lifestyles is promoted in "dose adjustment for normal eating" (DAFNE)2 and similar structured training courses[5].

Zinc has an insulin-mimetic activity as it can enhance phosphorylation of serine/threonine protein kinase (Akt) and activate glucose transporter-4 (GLUT4) translocation from the intracellular vesicle to the cell membrane to increase glucose uptake. Additionally, zinc can stimulate the auto-phosphorylation of cytosolic subunit of insulin receptor (IR) increasing insulin sensitivity and initiating insulin signaling. A study used zinc oxide nanoparticles (ZnONPs) and silver nanoparticles (SNPs); separately; to evaluate their efficiency in reducing blood glucose level(BGL) in diabetic rats. ZnONPs and SNPs were significantly found to reduceblood glucose level (BGL) by 75.8% and 68.2%, respectively. Moreover, ZnONPs elevated serum insulin concentration by 79.4%. This determined that both ZnONPs and SNPs have antidiabetic activity even though ZnONP were more potent[6]. Another study investigated the antidiabetic activity and toxic effects of zinc oxide (ZnO) nanoparticles in diabetic rats and compared with zinc sulfate ($ZnSO_4$) with particular emphasis on oxidative stress parameters. ZnO showed greater antidiabetic activity compared with $ZnSO_4$ evidenced by improved glucose disposal,insulin levels, and zinc status in diabetic rats. The net result of the study stated that ZnO nanoparticles acted as a potent antidiabetic agent[7].

In the present work, synthesis of zinc oxide-curcumin and zinc oxide-insulin nanoparticles at low cost and simple route was attempted for the purpose of introducing an effective substrate that endure a useful and novel, effective and safe blood sugar regulator. The physicochemical properties of the prepared nanoparticles were investigated using developed techniques as XRD, HRTEM, EDX and FTIR. The hypoglycemic activities of insulin, ZnONPs and insulin-ZnONPs of ratios (1:1) and (0.5:1) and their pathology effect in rats were investigated to compare the outcomes and determine the most effective hypoglycemic agent

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among the three compounds (ZnONPs, Insulin- ZnONPs(1:1), Insulin- ZnONPs(0.5:1) in comparison to insulin.

MATERIALS AND METHODS

1 Materials and reagents: Insulin, Alloxan monohydrate, Zinc nitrate, CTAP, Ammonium hydroxide, Saline (0.9%) and Nitric acid.

2 Preparation of drug
2.1. Preparation of ZnONPS

20g of zinc nitrate was dissolved in an appropriate amount of distilled water and 10 ml template (1g CTAB dissolved in 10 ml distilled water) just above the critical micelle concentration was added with constant stirring for one hour. Drops of ammonium hydroxide were added slightly till white sol is completely detected revealing the formation of zinc hydroxide followed by vigorous stirring for 2 hours. The white sol was left for 2 days to allow condensation of sol particles into solid gel. The wet gel was filtered and washed with distilled water several times and dried at $100°C$ for 24 hours. Finally, the xero gel articles were calcined in muffle furnace at $500°C$ for three hours.

2.2. Preparation of Insulin-ZnONP compounds

1g of the prepared ZnONPs was dissolved in a slightly acidic solution (few drops of nitric acid in distilled water) and then 1m of insulin was added and stirring and filtration were allowed to obtain Insulin-ZnONPs of the ratio 1:1 .To get Insulin-ZnONPs of the ratio 0.5:1 the same method was performed but instead of adding 1 ml insulin, 0.5 ml insulin was added.

2.3. The biological assessment
Animals

35 male Albino rats weighing from 201 to 248 g (75-90 days old) were used for inducing diabetes. The animals were acclimatized to their new surroundings for 1 week prior to the experimental procedures.

Ethics

All the experiments involving laboratory animals were approved by the National Nutrition Institute (NNI) and all procedures of the current experiment were performed at the animal housing department of the Medical Research Center (MRC), Faculty of medicine, Ain Shams University, Cairo.

Experimental and grouping

The animals were divided into 5 groups C- group is a healthy normal which didn't receive a disease or medicine, c+ which was injected with Alloxan monohydrate to be diseased without having any kinds of drugs. Group 1 which was diseased and had insulin daily as a treatment, groups 2,3,4 were diseased and had ZnONPs, Insulin-ZnONPs (0.5:1) and Insulin-ZnONPs (1:1) for curing. All of the groups except c- group (kept as a control) were fasted and injected by alloxan monohydrate dissolved in sterile normal saline at a dose of 120 mg/Kg body weight, intraperitoneally to induce diabetes. Since alloxan monohydrate is capable of producing fatal hypoglycemia as a result of massive pancreatic insulin release. Rats were treated with 20%

glucose solution 2 hours after injection of alloxan monohydrate. The rats were then kept for the next 24 hours on 5% glucose solution bottles in their cages to prevent hypoglycemia. After 7 days rats with fasting blood glucose level more than 175 mg/dl were considered to be diabetic and selected for studies. The experiment took 45 days, the control group (normal) c-, the c+ group is the diabetic group which didn't have any medication, group 1 which subcutaneously injected by insulin regularly at a daily dose of 2u/kg body weight per rat. Groups 2, 3 and 4 which were administered ZnONPs, Insulin-ZnONPs (0.5:1) and Insulin-ZnONPs (1:1) orally and regularly at a daily dose of 10mg/kg body weight per rat[8-10].

Oral glucose tolerance (OGTT) test for rats were performed according to the standard method {20}[8]. The OGTT was carried out via estimating glucose of blood samples from tail vein by using glucometer (Accuchek active, Roche Diagnostics, Mannheim, Germany) at 0, 60, 120 and 180 minutes. At first, the rats were fasted, and blood samples were collected from the tail veins of all of the rats then an oral glucose dose of 0.3mg/kg body weight per rat was administered then the four medically treated groups had their medication. Later on, blood samples were collected from all rats after 60, 120 and 180 minutes respectively, in order to know the effect of medication on glucose by time. Besides HBA1c analysis was performed to all of the rats last taken blood samples. The livers and pancreases were collected to identify the pathology of organs.

RESULTS AND DISCUSSION
I- Physicochemical Characterization
1. FT-IR

FT-IR spectrum of ZnONPs-insulin are represented in Figur (2). The figure illustrates various peaks at 433, 455, 521 and 605 cm^{-1} which are referred to crystalline ZnO nanoparticles. On careful examining the same Figure, one can notice various bands at 1046, 1333, 1384, 1449, 1506 and 3330 cm^{-1} that assigned to the existence of insulin on ZnO surface.

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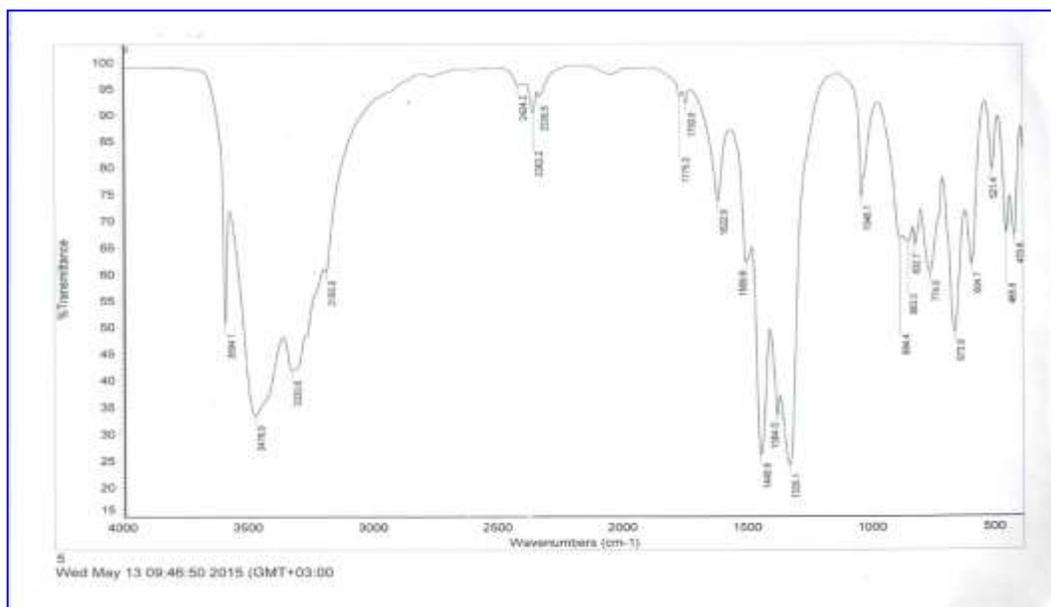
Fig. 2: FT-IR of ZnNPs-insulin

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2. XRD analysis

XRD is considered here in as a powerful tool to explore the crystalline phases and size of ZnO nanocrystallites. Figure (3) depicts the XRD pattern of ZnONPs and ZnONPs-insulin which illustrates several sharp crystalline peaks at 2θ = 31.7, 34.4, 36.2, 47.5, 56.6, 62.8, 66.3, 67.9, and 69.1, marked by their miller indices [(100), (002), (101), (102), (110), (103), (200), (112) and (201)]. These crystalline features have been pointed out the existence of ZnO nanoparticles with Wurtzite structure (JCPDS no. 36-1451). While, as noted, the diffraction pattern of ZnO-insulin nanoparticles resembles that of pure ZnONPs; however, the diffraction peaks seemed slightly broadened which indicate reduction in crystallite size.
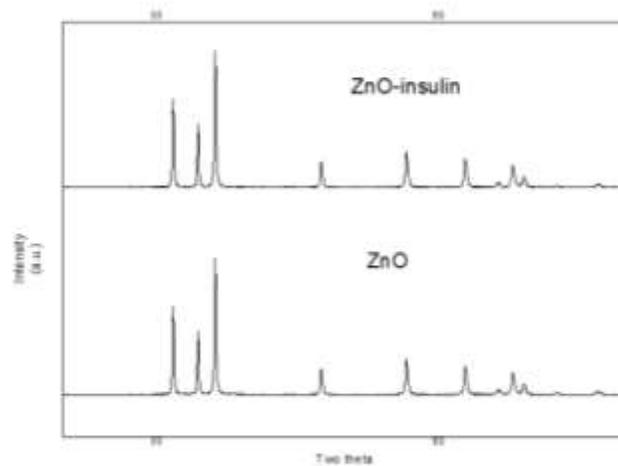
Fig. 3: XRD of ZnONPs and ZnONPs-insulin

3. SEM and EDX

The morphology of the synthesized nanoparticles was investigated by scanning electron microscope (SEM). The micrograph of ZnONPs reveals the existence of spongy-like structure that exhibits large number of porous centers on its surface as represented in Figure (4). The EDX spectrum of prepared sample shows that the sample contains only Zn and O revealing the absence of any impurities in the sample (Fig. 5).
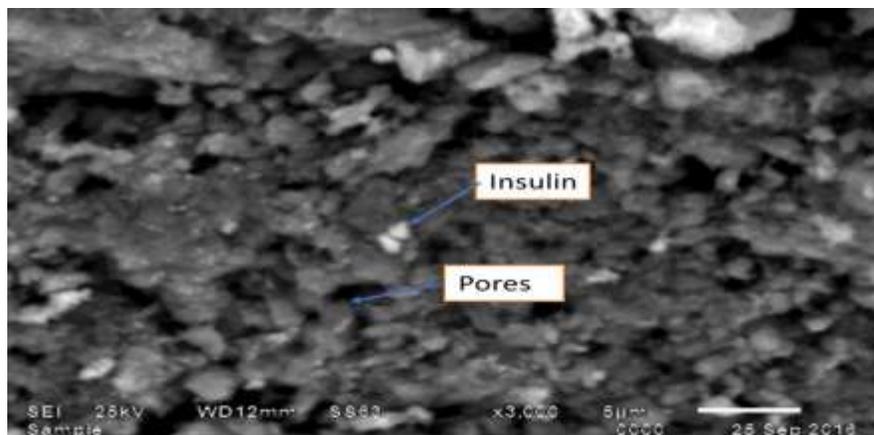
Fig. 4: SEM of ZnONPs-insulin nanoparticles

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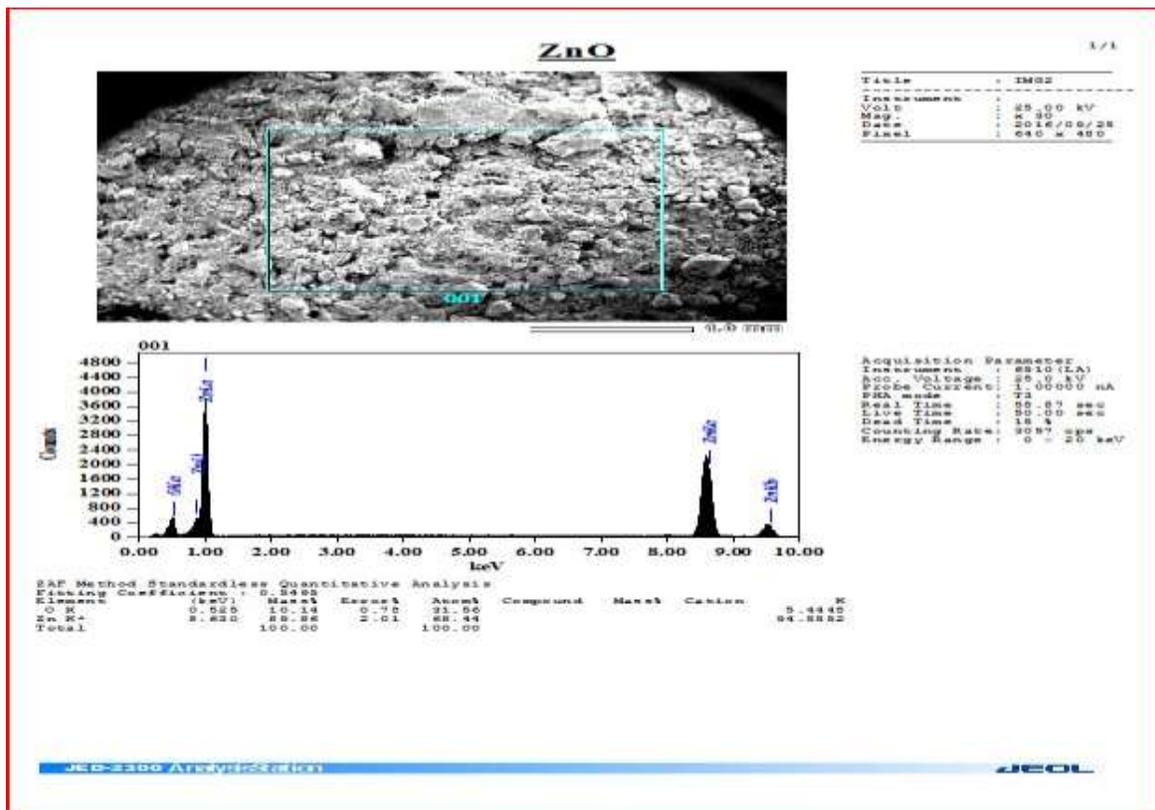
Fig.5: EDX of ZnO-insulin nanoparticles

4. HRTEM

HRTEM image of ZnONPs particles, Figure (6), illustrates the existence of homogeneous nanoparticles of dimensions between 23-63 nm in pure ZnONPs. It is clearly observed that the existence of hexagonal ZnO nanoparticles with perfect crystalline dimensions. On careful examining the figure, one can notice the distribution of insulin as spherical drops on the external surface of ZnONPs crystallites. This result suggests the better dispersion of insulin on ZnONPs surface.
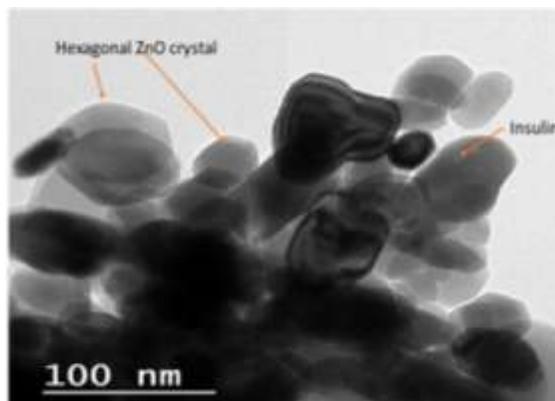
Fig. 6: HRTEM of ZnO-insulin nanoparticles

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3.2Biochemical analysis
3.2.1 Oral glucose tolerance test(OGTT):
On the last day of the experiment, OGTT was performed for rats according to the standard method[12]. The rats were fasted overnight and the first blood samples(at zero minute) were withdrawn. Then an oral glucose dose of 0.3mg/kg body weigh per rat was administered for all groups. The four medically treated groups had their drugs once. Later on, blood samples were collected from all rats after 60, 120 and 180 minutes respectively, in order to know the effect of the drug on glucose level by time. The OGTT Blood samples were collected from the rats in fluoride tubes for estimating blood glucose level using blood glucose kits and UV-VIS spectrophotometer[13].

Glycated Haemoglobin (HBA1C) test:
After sacrificing of animals, blood samples were collected in EDTA tubes for estimating HBA1C level using HBA1C kits and UV-VIS spectrophotometer[14].

Statistical analysis:
The data analyses were carried out using SPSS for Windows 15.0 (SPSS, Chicago, IL, USA).

RESULTS AND DISCUSSION

OGTT measures the body ability to use glucose, the body's main source of energy(15). The results of the OGTT test are illustrated in table 1 and figure 7, the blood glucose level means of G1, G2, G3, G4, G5, G6 groups at overnight fasting were 108.8± 0.5 mg/dl, 235.2± 16.9 mg/dl, 109.2± 5.3 mg/dl, 120.2± 5.9, 104.8± 6.2 mg/dl and 75.6± 2.9 mg/dl. One hour later, all of the groups received the glucose dose and their blood glucose level means raised to 135.4± 2.3 mg/dl, 376.6± 20.3 mg/dl, 132.6± 5.7 mg/dl, 190.9± 8.4 mg/dl, 135.5± 4.5 mg/dl and 135.6± 8.7 mg/dl. After receiving the glucose dose immediately, all groups had their drugs except groups G1 and G2. Two hours later, the blood glucose level means became 109.9± 4.2 mg/dl, 325.8± 20.8 mg/dl, 125.3± 3.6 mg/dl, 148.7± 10 mg/dl, 158.2± 1.9 mg/dl and 137.7± 11.6 mg/dl. Three hours later, the groups means were 98.6± 1.8 mg/dl, 245.6± 16.7 mg/dl, 114.6± 3.1 mg/dl, 126.8± 7 mg/dl, 133.6± 1.2 mg/dl and 116.3 ± 5.4 mg/dl. Fig.7 represents the relation between the glucose level mean and time for each group for the OGTT experiment. All means of groups G2, G3, G4, G5 and G6 were significantly high when compared to the corresponding means of G1 while all means of groups G3, G4, G5 and G6 were significantly low when compared to G2. The data showed that the hypoglycemic effect of ZnO is very clear in group G4 as well as in groups G5 and G6 which were treated with ZnO-Insulin drugs.

Table (2) shows the HBA1C means of all groups. HBA1c is the most important indicator of diabetic progression and is often used in clinical medicine to monitor long-term blood glucose control in diabetics[16]. The results show that HBA1C means were 3.7 ± 0.04%, 12.7 ± 0.35%, 4 ± 0.43%, 4.2 ± 0.06%, 3.5 ± 0.14%, 3.4 ± 0.17% for G1,G2,G3,G4,G5 andG6. The HBA1C mean values of groups G2, G3, G4, G5 and G6 were significantly high when compared to that of G1 while the HBA1C mean values of groups G3, G4, G5, G6 were significantly low when compared to that of G2. The HBA1C means of experimental rat groups are also clarified in figure 8. It is obvious that HBA1C mean value of the positive control group (G2) is very high indicating that it is still diabetic while the values of the normal group (G1) and the groups treated

with ZnONPs and ZnONPs-Insulin drugs (G4, G5 & G6) are approximately equal. Accordingly, the hypoglycemic activity of ZnONPs alone and in combination with insulin is emphasized.

This study agrees with Rinku and kishore (2014) who reportedthe antidiabetic effect of ZnONPs in types 1 and 2 diabetic rats[17]. It also agrees with Kalakotla *et al.* (2017) who emphasized that green synthesized ZnONPs had more potent anti-hyperglycemic activity compared to those of green synthesized cerium oxide nanoparticles and Momordica charantia[18]. The hypoglycemic effect of ZnONPs in alloxan-induced diabetic rats was also proved by Hassan *et al.* (2016)[19].

Zinc has been regarded to be an effective metal which improves glucose utilization through its potent influence on enhancement of hepatic glycogenesis through actions on the insulin signaling pathway. In addition, improved glucose could be as a result of several possible mechanisms:firstly, ZnONPs treatment might result in inhibition of intestinal alphaglucosidase enzyme and therefore reduce glucose absorption. Secondly, blood glucose levels might be lowered due to the increased glucose uptake in the liver and its subsequent storage (glycogenesis). Thirdly, enhanced glycolysis by ZnONPs could cause an improved glucose disposal. Also, the antidiabetic effects of ZnONPs may be due to that zinc is closely involved in general metabolism of protein, carbohydrate, and lipids[19]. ZnONPs also can act as a drug carrier[20] thus it led to a potent hypoglycemic effect when combined with insulin. This hypoglycemic or antidiabetic activity is attributed to the ability of ZnONPs to enhance the pancreas beta cells for insulin secretion[21]. Moreover, nanoparticles can easily cross through biological membranes because of their ultra-small size and hence can be highly absorbed by the digestive system[7]. In general, the ultra-small size plus the large surface area of nanoparticles have brought them in the utilization via oral therapy[22].

Table 1: Oral Glucose Tolerance Test (OGTT) in all experimental rat groups

Group	Blood glucose level mean(mg/dl) ± SE			
	0 hour	**1 hour**	**2 hours**	**3 hours**
G1(negative control)	108.8 [b] ± 0.5	135.4 [b] ± 2.3	109.9 [b] ± 4.2	98.6 [b] ± 1.8
G2(positive control)	235.2 [ab] ± 16.9	376.6 [ab] ± 20.3	325.8 [ab] ± 20.8	245.6 [ab] ± 16.7
G3(Insulin)	109.2 [b] ± 5.3	132.6 [b] ± 5.7	125.3 [b] ± 3.6	114.6 [b] ± 3.1
G4(ZnONPs)	120.2 [b] ± 5.9	190.9 [ab] ± 8.4	148.7 [ab] ± 10	126.8 [ab] ± 7
G5(Insulin/ZnONPs 0.5:1)	104.8 [b] ± 6.2	135.5 [b] ± 4.5	158.2 [ab] ± 1.9	133.6 [ab] ± 1.2
G6(Insulin/ZnONPs 1:1)	75.6 [ab]±2.9	135.6 [b] ± 8.7	137.7 [b] ± 11.6	116.3 [b] ± 5.4

Each value is mean ± standard error, statistically significant at the mean difference < 0.05
a: significant with negative control,   b: significant with positive control.
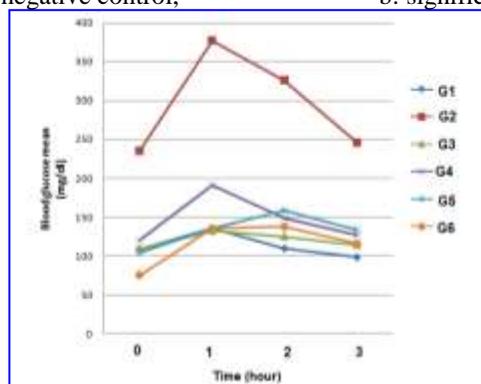
Fig. 7. OGTT in all experimental rat groups. The data correspond to means ± standard error from glucose level to different time periods.

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Table 2: Glycated haemoglobin (HBA1C) means of all experimental rat groups

Group	HBA1C mean(%)± SE
G1(negative control)	3.7^b ± 0.04
G2(positive control)	12.7^a ± 0.35
G3(Insulin)	4^b ± 0.43
G4(ZnONP)	4.2^b ± 0.06
G5(Insulin/ZnONP 0.5:1)	3.5^b ± 0.14
G6(Insulin/ZnONP 1:1)	3.4^b ± 0.17

Each value is mean ± standard error, statistically significant at the mean difference < 0.05
a: significant with negative control, b: significant with positive control.
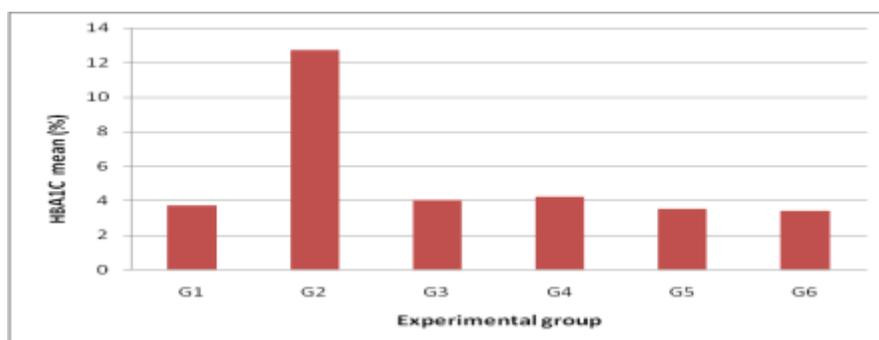
Fig. 8. HBA1C means of all experimental rat groups.

Conclusion

ZnO–insulin nanoparticles were prepared as glucose level regulator in the blood. The physicochemical features of the novel nanoparticles were investigated by XRD, FTIR, EDX and HRTEM which reveal noted crystallinity distortion when insulin is present. ZnO slight crystallite distortion could aid formulating ZnO activity biomedically in presence of protein entities. A homogeneous dispersion of insulin on the surface of ZnO was detected by HRTEM could also indicate favorable attachment mutual sites between the ZnO surface and the structural amino acid groups. The hypoglycemic activity effect of ZnONPs, ZnO-Insulin (1:1) and ZnONPs-NPsInsulin (1:0.5) drugs was proven and compared to that of insulin in this study. The data showed that ZnONP-Insulin (1:1) drug was the most potent hypoglycemic agent of them.

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طريقة حديثة لتحضير مواد نانومترية جديدة لأوكسيد الزنك و الإنسولين من اجل التحكم في إطلاق الجلوكوز في الدم

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المستخلص

لقد تم تحضير جسيمات نانومترية من اكسيد الزنك باستخدام تقنية الصل – جيل كما تم تحضير متراكبين مكونين من اكسيد الزنك و الإنسولين بالنسب 1:1 و 0.5:1 و ذلك لاستخدامهم ا كدواء من أجل خفض مستوي الجلوكوز في الدم . التوصيف الفيزيوكيميائي اثبت المقياس النانومتري للجسيمات و الشكل السداسي البلوري للجسيم وحجمه التقريبي. و قد تم ايضاً تطبيق المتراكبات المحضرة علي فئران التجارب لاثبات تاثيرهم علي مستوي الجلوكوز في الدم ومقرانته مع تأثير الإنسولين بمفرده. وقد اثبتت قدرة المتراكبات العالية علي خفض مستوي الجلوكوز في الدم من خلال التحاليل البيوكيميائية.