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Influence of Castor Oil on Glycated Hemoglobin (HbA1c) on Induced Type 2 Diabetes Mellitus in Rats

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ABSTRACT

Many T2D use CAO as a laxative. We did not find sufficient research to explain CAO's potential effect on the levels of HbA1c in T2D patients. This study will study this effect. Rats (n=80) were divided into eight groups (n=10). Five groups (n=50) were injected with streptozotocin intravenously to induce T2D. One group was given CAO with empagliflozin, and the second was assigned CAO only daily. The third was assigned CAO every two days, with empagliflozin, which was given daily. A fourth was assigned CAO alone daily. Also, the fifth was given empagliflozin alone. In the healthy groups, one group was given CAO, and the other was given empagliflozin. Also, the last healthy group was not assigned any drug. CAO's result on HbA1c in healthy rats was noted to decrease when delivered alone for eight weeks. HbA1c of the diabetic groups showed no significant difference (P-value<0.05) when comparing the rats given CAO with empagliflozin, and the rats were given CAO only. There was also no noticeable effect among the groups of rats given CAO daily and every two days. This study explains that CAO does not lead to a significant difference in HbA1c levels in diabetic rats, even it did for healthy rats, and if given alone, CAO could affect HbA1c levels if given over a long period. Also, CAO has a noticeable impact on experimental rats that co-administered Empagliflozin on HbA1c levels, and that Empagliflozin effect is not significantly affected if taken with CAO.

Keywords: Castor Oil, HbA1c, Type 2 Diabetes Mellitus, Rats, Empagliflozin, Blood Sugar.

INTRODUCTION

Diabetes mellitus is a metabolic disorder generally characterized by a rise in glucose levels that need regular monitoring and effective control. Each single monotherapy pharmacology agent, especially in comparison to lifestyle modifications, magnified the number of patients reaching target levels of HbA1c below 7 percent by 2 to 3 times[1]. Owing to inadequate regulation of diabetes, most patients will need multiple therapies to maintain reasonable long-term glycemic control[2]. Empagliflozin is a potent, highly selective, sodium-glucose cotransporter-2 (SGLT2) inhibitor, is an effective

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and generally well-tolerated antihyperglycemic agent approved for the treatment of adults with type 2 diabetes (T2D)[3]. SGLT2 is the primary carrier taking responsibility for glucose absorption back into circulation from the glomerular filtrate. Empagliflozin is an SGLT2 inhibitor. With the inhibition of SGL T2, empagliflozin decreases the reabsorption and renal level of filtered glucose, thus improving urinary glucose excretion. Empagliflozin/linagliptin (Glyxambi®) is a fixed-dose drug approved once daily in the U.S. in addition to the nutrition and adult exercise T2DM when empagliflozin and linagliptin are both treated appropriately. Using 5 mg linagliptin, Glyxambi® combines 10 mg or 25 mg empagliflozin using different complementary action pathways to improve glycemic control in T2D patients. Empagliflozin removes glucose from the urine by blocking blood glucose reabsorption into the kidney, with linagliptin lowering glucose activity by increasing the pancreas' hormones to create more insulin and decrease the blood glucagon the circulation.

Furthermore, this drug combination is moderately putting down weight and blood pressure without significant safety problems. Empagliflozin/linagliptin's fixed-dose combination generally enhances glycemic control over the individual components when used as an early treatment or as a metformin supplement[4]. Castor Oil (CAO) is known as a potent laxative property. HbA1c test has become the most famous indicator of chronic glycemia in epidemiological trials, clinical studies, and diabetes management[5]. Glycated hemoglobin (HbA1c) analysis in your blood provides evidence of a person's average blood sugar levels over the previous 2 to 3 months, which is predicted to represent the half-life of red blood cells (RBCs)[6]. The HbA1c level, formed via the non-enzymatic adhesion of glucose to hemoglobin, is commonly seen to represent the integrated mean blood sugar during the last 8–12 weeks, the 120-day lifetime of the erythrocyte being defined. HbA1c appears to be in a new stable state 3–4 months after changes in glucose[7]. All previous studies showed a link between the factors of HbA1c and average blood glucose used relatively rare daytime monitoring that is vulnerable to sampling errors and does not track glucose levels nighttime or true 24-hour Glycaemia[5]. ADA recently suggested HbA1c with a cutpoint < 6.5% for the diagnosis of diabetes as an option to plasma glucose fasting (FPG) based on 7.0 mmol / L requirements based[8]. This research's primary purpose is to investigate the effect of CAO on HbA1c levels in hyperglycemic rats treated with the SGLT2 inhibitor "empagliflozin" as an indicator in type 2 diabetes mellitus.

Results and Discussion

HbA1c (Glycated hemoglobin) is suggested for D.M.'s diagnosis as a possible replacement for fasting blood sugar. In this experiment, HbA1c was adopted and considered important as a long-term glycemic regulation predictor with the potential to represent the previous accumulated glycemic history. Accordingly, the HbA1c level of 6.5% or above indicates diabetes. Pre-diabetes is considered normal between 5.7% and 6.4%, and less than 5.7% is health[6].

In this experiment, rats were divided into eight groups, either healthy or diabetic, and treated with CAO for several periods. The results were compared with the corresponding positive and negative controls, as indicated in the experimental section. Comparison between the first group rats (healthy without any given drug) with seventh group rats (healthy rats which given the CAO daily) revealed a significant difference ($P<0.05$) between the two rats groups starting from the ninth week of the experiment until the last week, as can be seen in **Figure 1 and Table 1**. Besides, there is a decrease in values of HbA1c in the Healthy Rats Group, which was given the CAO daily. However, in the Healthy Rats Group, we did not provide any drug and increased the values of HbA1c.

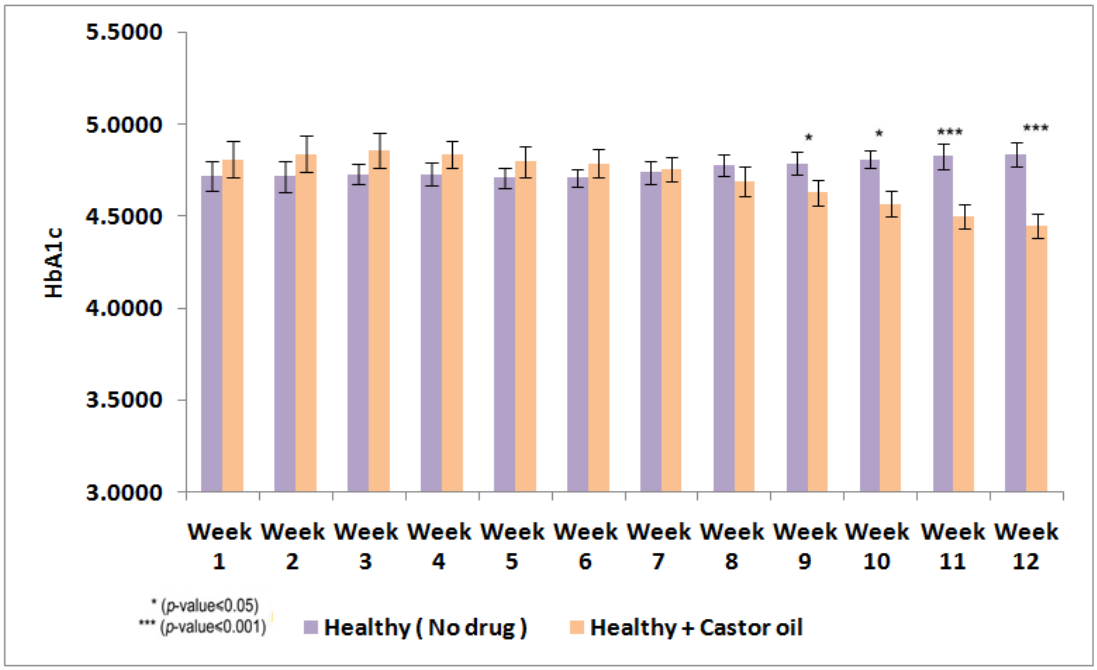

Figure 1: HbA1c % in first and seventh group rats.

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	RAT_H_1 - RAT_H_c_1	-.09000	.29231	.09244	-.29911	.11911	-.974	9	.356
Pair 2	RAT_H_2 - RAT_H_c_2	-.12000	.31903	.10088	-.34822	.10822	-1.189	9	.265
Pair 3	RAT_H_3 - RAT_H_c_3	-.13000	.26687	.08439	-.32091	.06091	-1.540	9	.158
Pair 4	RAT_H_4 - RAT_H_c_4	-.11000	.22336	.07063	-.26978	.04978	-1.557	9	.154
Pair 5	RAT_H_5 - RAT_H_c_5	-.09000	.25144	.07951	-.26987	.08987	-1.132	9	.287
Pair 6	RAT_H_6 - RAT_H_c_6	-.08000	.20440	.06464	-.22622	.06622	-1.238	9	.247
Pair 7	RAT_H_7 - RAT_H_c_7	-.02000	.22509	.07118	-.18102	.14102	-.281	9	.785
Pair 8	RAT_H_8 - RAT_H_c_8	.09000	.25144	.07951	-.08987	.26987	1.132	9	.287
Pair 9	RAT_H_9 - RAT_H_c_9	.16000	.22211	.07024	.00111	.31889	2.278	9	.049
Pair 10	RAT_H_10 - RAT_H_c_10	.24000	.22706	.07180	.07757	.40243	3.343	9	.009
Pair 11	RAT_H_11 - RAT_H_c_11	.33000	.23118	.07311	.16462	.49538	4.514	9	.001
Pair 12	RAT_H_12 - RAT_H_c_12	.39000	.19692	.06227	.24913	.53087	6.263	9	.000

Table 1: Table showing results for healthy rats in Group 1 and compared with healthy Rats in Group 7

There are statistically significant decreases in the HbA1c starting from the ninth week in either healthy and diabetic rats treated with CAO compared to non-treated healthy and diabetic rats' groups, respectively, suggesting that treatment with CAO reduced blood sugar in both types as indicated with the decrease in HbA1c for an extended period, i.e., nine weeks.

These results are confirmed by the results showing no statistical difference between any of the remaining conjugation groups, as apparent in **Table 2**. Also, CAO could lower the HbA1c to a certain degree but does not have Empagliflozin's strength to reduce the HbA1c levels (**Figure 2**). The extent of the decrease in HbA1c in healthy rats treated with Empagliflozin is more significant than that of healthy rats treated with CAO alone, and the effect of treatment started earlier in the Empagliflozin treated rats, i.e., after the fourth week in Empagliflozin treated rats, **Figure 2** and **Table 2**. Another conclusion we can get from these results is that CAO could have the power to decrease HbA1c in healthy rats but to a much lower extent in diabetic rats.

Table 2: Comparisons of the conjugation of Groups of Rats (p-value= 0.05, NS: no statistical difference)

Groups	**Status**	**Comparison result**
Group 1 (healthy)	No drug	With group 4: there is a stat. differences
Group 2 (diabetic)	No drug	With group 8: NS
Group 3 (diabetic)	Empagliflozin only	With group 5: NS
Group 4 (healthy)	Empagliflozin only	
Group 5 (diabetic)	Empagliflozin + CAO	With group 6: NS
Group 6 (diabetic)	Empagliflozin + CAO (every two days)	With group 3: NS
Group 7 (healthy)	CAO only	With group 1: there is stat. differences
Group 8 (diabetic)	CAO only	With group 2: N.S.

However, comparing groups, 1 with 4 (health rats without any treatment with health treated with healthy rats treated with Empagliflozin) revealed the statistically difference ($P<0.05$) starting from week number 4, from which we conclude that the Empagliflozin has a noticeable effect in decreasing HbA1c in Fourth group Rats Compared to the first group rats ensuring that there are no any problems in the injections of the rats, and the study was going very-well **Figure 2**.

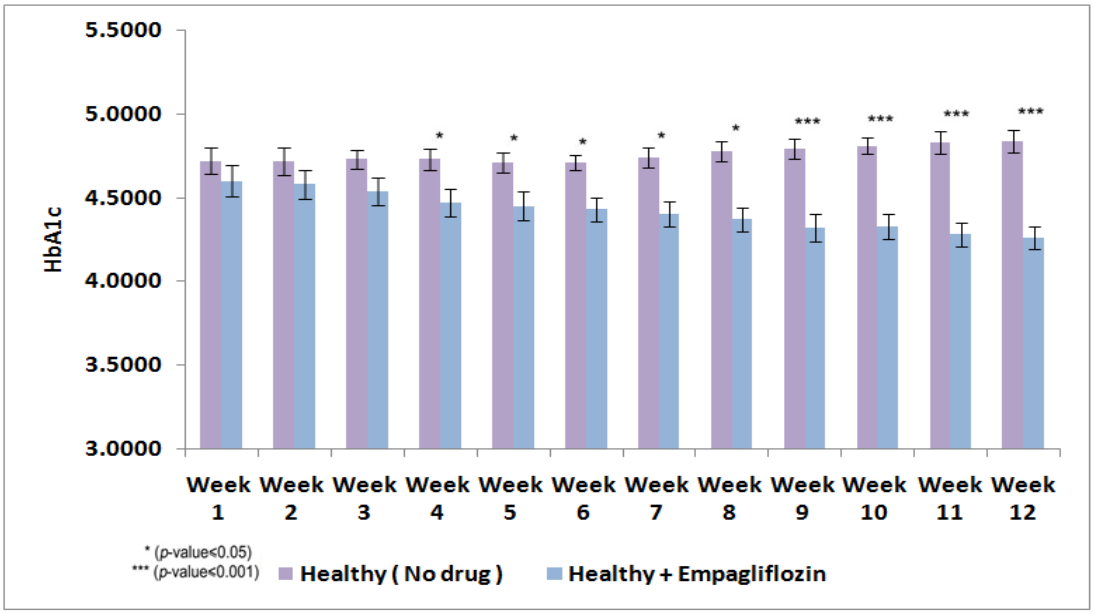

Figure 2: HbA1c % first group rats and fourth group rats

Experimental

Materials

Empagliflozin (Jardiance®) was obtained from the local market and manufactured by Boehringer Ingelheim Pharmaceuticals company (Germany) as a tablet form 10 mg/tablet and used for D.M. type-2 treatment. CAO was obtained from the local market, manufactured by Amman Pharmaceutical Industries (Jordan) as a soluble form of 0.1% as a stimulant laxative agent. Streptozocin 75% α-anomer basis powder, purchased from the local market and manufactured by Sigma Aldrich, known in Merck Germany (B.N: S6130SA), is used to induce type-2 D.M. for medical research.

Instruments

The iCHROMA™ reader is a handheld fluorescent scanner of the first generation that analyzes blood, urine, and other samples and shows the measurement results. More than 30 cartridges can be counted in immunoassay testing, and iCHROMA™ Reader HbA1c is a human blood hemoglobin A1c immunoassay form used for iCHROMA™ Reader. The procedure is used to track glycemic status in D.M. patients regularly. Incubadori Chamber is an incubation chamber for tests HbA1C. Cartridge (kits) for testing chemical composition and measuring test specimens' concentration like the liquid biological sample, use kit for rat hemoglobin A1c (HbA1c). Accu-Chek products were already created to aid you in diabetes management. Explore creative monitoring systems for blood glucose. EDTA tube stands for Ethylenediaminetetra-acetic acid. EDTA works through binding calcium throughout the blood and preventing blood from coagulation. Plastic Capillary Tube, 100% plastic capillary microhematocrit tubes Plain untreated Plastic microhematocrit tubular of Globe Scientific are fully unbreakable. They eliminate the dangers of damage and contamination due to breakage in glass tubes. In the laboratory, micropipettes are used to transfer small amounts of fluid, usually beneath 0.1 uL. The most common micropipettes in pharmaceutical and medicinal discovery labs are 1-10 uL and 20-200 uL. Pipette tips, often with pipette tips, are used for speed processing and cross-contamination with pipette tips and pipettes—those that are available in different styles and components.

Reagents

- Sodium Citrate buffer is used to dissolve Streptozocin.
- Hemolysis Buffer is individually pre-dispensed in a small tube, consisting of a cationic detergent, and stabilized for up to 20 months when positioned at 4-30 ° C.
- Detection Buffer contains HbA1c-peptide fluorescence marked, BSA stabilizer, and sodium azide as a preservative in PBS, is flexible up to 20 months if stored at a temperature of 2-8°C, enables detection buffer to achieve a room temperature (20-30 ° C) before running the test.

Preparation of Solution

Preparation of Streptozocin solution

Streptozocin at dose 45 mg, was prepared by dissolve 45 mg of Streptozocin in 12 mL of Sodium Citrate buffer, and mixing forced in a blender to get homogenous solution 3.75% (w/v), the concentration of Streptozocin, which give (3.75 mg/mL) concentration of solution injected I.P. for each rat[9,10].

Preparation of Empagliflozin solution

Empagliflozin at dose 10 mg (10 mg/70 kg),(0.142 mg/1 kg), (0.035 mg/0.25 kg) was prepared daily, prepared by dissolving 10 mg of Empagliflozin in 100 mL of distilling water and mixing forced in a blender to get a homogenous solution of 0.01%(w/v), the concentration of Empagliflozin, which give (0.035 mg/0.28 mL) concentration of solution orally for each rat[11].

Preparation of CAO solution

CAO at a 60 mL dose, which gives 2 mL of solution orally for each rat[12].

Preparation of sodium citrate buffer solution

Sodium citrate buffer solution prepare by adding distilled water 800 mL in a container, add 24.0g of sodium citrate dehydrate, add 3.5g of citric acid to the solution, adjust the solution to 4.5 pH, storage in 4-10°c.

Study Protocol and preclinical study

The Faculty of Pharmacy and Medical Sciences, University of Petra Appendix No. (3) accepted the study protocol's ethical work. The Wistar Albino rats were supplied and housed at the Faculty of Pharmacy – animal house at Applied Science Private University - Amman.

Animal Handling

Wistar Albino adult male and female laboratory rats were above eight weeks, weighing 250-300 g. The Applied Science Private University animal house was delivered, placed in the air-conditioned room at 20 ° C and subjected to a photographic cycle (12 hours of light / 12 hours of darkness) daily. All the rats weighed and randomized to eight groups for identification purposes were markers on their tails.

Group #1: Was the control - healthy group (No given any drug), which consists of 10 rats given a regular basal diet with water, and this group conducts this study for about 12 weeks under the same environmental conditions.

Group #2: Was the diabetic group (No given any drug), which consists of 10 rats that are not given any drugs, just only given a regular basal diet with water, and this group continued in this study for about 12 weeks under the same environmental conditions.

Group #3: Was the diabetic group (given only Empagliflozin), which consists of 10 rats given only Empagliflozin solution in 0.1mg/mL concentration daily for 12 weeks, delivered using suitable oral gavage and given a regular basal diet with water.

Group #4: Was the healthy group (given only Empagliflozin) which Consists of 10 rats which given only Empagliflozin solution in 0.1mg/mL concentration daily for 12 weeks, delivered by using suitable oral gavage, and given regular basal diet with water

Group #5: Was the diabetic group (given Empagliflozin and CAO, which consists of 10 rats which given Empagliflozin solution in 0.1mg/mL concentration daily for 12 weeks, and given CAO solution in 2 mL/rat concentration daily for 12 weeks, given by using suitable oral gavage, and given a regular basal diet with water.

Group #6: Was the diabetic group (given Empagliflozin and CAO) which consists of 10 rats, which

given Empagliflozin solution in 0.1mg/mL concentration daily for 12 weeks, and given CAO solution in 2 mL/rat concentration every two days for 12 weeks, given by using suitable oral gavage, and given a regular basal diet with water.

Group #7: Was the healthy group (given only CAO), consisting of 10 rats, which was given only CAO solution in 2 mL/rat concentration daily for 12 weeks, given by using suitable oral gavage given a regular basal diet with water.

Group #8: Was the diabetic group (given only CAO), consisting of 10 rats, which was given only CAO solution in 2 mL/rat concentration daily for 12 weeks, given using suitable oral gavage, and given a regular basal diet with water. As summarized in **Table 3**.

Table 3: Groups of the rats

Groups	Status
Group 1 (healthy)	No drug
Group 2 (diabetic)	No drug
Group 3 (diabetic)	Empagliflozin only
Group 4 (healthy)	Empagliflozin only
Group 5 (diabetic)	Empagliflozin + CAO
Group 6 (diabetic)	Empagliflozin + CAO (every two days)
Group 7 (healthy)	CAO only
Group 8 (diabetic)	CAO only

Sample Collection and Processing

A blood sample is drawn through the rat's optical vein by a capillary tube after 12 hours of fasting before sample collecting. The sample was collected at zero time to determine the baseline and then collected weekly until twelve weeks. When sample drawn from rats and putten in tube collector (EDTA, heparin, and NaF), take the sample and measure HbA1c by putting blood sample in Cartridge (kit-Special for rats), and put it in an incubator in the chamber for 12 minutes and finally put in the ichroma™ Reader to read the HbA1c range.

All the experiments were achieved by the University of Petra and Applied Science Private University institutional guideline on animal use, which adopts the Federation of European Laboratory Animal Science Association (FELASA) guideline.

Acknowledgment:

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تأثير زيت الخروع على سكر الدم التراكمي في الجرذان المستحدث فيها داء السكري من النوع الثاني

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ملخص

العديد من مرضى السكري من النوع الثاني يستخدمون زيت الخروع كمليّن للأمعاء. لم نجد أبحاثاً كافية تبحث في التأثير المحتمل لزيت الخروع على مستويات سكر الدم التراكمي في مرضى السكري من النوع الثاني. تهدف هذه الدراسة الى دراسة هذا التأثير. تم تقسيم الفئران (ن = 80) إلى ثماني مجموعات (ن = 10). تم حقن خمس مجموعات (ن = 50) بالستربتوزوتوسين عن طريق الوريد للحث على الإصابة بمرض السكري من النوع الثاني. أعطيت مجموعة واحدة زيت الخروع مع دواء إمباجليفلوزين ، والمجموعة الثانية تم اعطاؤها زيت الخروع فقط يوميًا. أما المجموعة الثالثة ، فتم اعطاؤها كل يومين زيت الخروع، مع دواء إمباجليفلوزين ، والذي كان يُعطى يوميًا. المجموعة الرابعة تم اعطاؤها زيت الخروع فقط وحده يوميا. أيضًا ، تم إعطاء المجموعة الخامسة دواء إمباغليفلوزين وحده. في المجموعات السليمة ، أعطيت إحدى المجموعتين زيت الخروع ، وأعطيت الأخرى دواء إمباغليفلوزين. أيضًا ، لم يتم اعطاء أي دواء للمجموعة الصحية الأخيرة. لوحظ أن نتيجة إعطاء زيت الخروع على مستويات سكر الدم التراكمي في الجرذان السليمة أدى الى انخفاض مستويات سكر الدم التراكمي عند تناوله بمفرده لمدة ثمانية أسابيع. أظهرت نتائج سكر الدم التراكمي لمجموعات الجرذان المصابة بمرض السكري من النوع الثاني عدم وجود فرق احصائي (P-value <0.05) عند مقارنتها مع الجرذان التي أعطيت زيت الخروع مع دواء إمباغليفلوزين او الجرذان التي أعطيت زيت الخروع فقط. لم يكن هناك أيضًا تأثير ملحوظ بين مجموعات الفئران التي أعطيت زيت الخروع يوميًا اوكل يومين. توضح هذه الدراسة أن زيت الخروع لا يؤدي إلى اختلاف كبير في مستويات سكر الدم التراكمي في الجرذان المصابة بداء السكري ، على الرغم من أنها كانت ذات تأثير بالنسبة للفئران السليمة ، وإذا تم إعطاؤه بمفرده ، وانما يمكن أن يؤثر زيت الخروع على مستويات سكر الدم التراكمي إذا تم إعطاؤه لفترة طويلة. أيضًا ، كان لـ زيت الخروع تأثيراً ملحوظاً على الفئران التجريبية التي اعطيت دواء إمباغليفلوزين على مستويات سكر الدم التراكمي وأن تأثير دواء الإمباغليفلوزين لا يتأثر بشكل كبير إذا تم تناوله مع زيت الخروع.

الكلمات الدالة: زيت الخروع، سكر الدم التراكمي ، داء مرض السكري من النوع الثاني، الجرذان، دواء الإمباغليفلوزين.

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