Research Article

Antihyperlipidemic Effects of Resvertrol and its derivative on alloxan Diabetic rabbits

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Abstract

The study has employed an *in vivo* evaluation of resveratrol and its derivative in female rabbits at concentrations (1mg/kg) given orally for 42 days after inducing diabetes mellitus type 2 by alloxan (100mg/1kg body weight). The serum was isolated from heart blood for the biochemical tests, including high density lipoprotein –cholesterol, Triglyceride, Serum Glutamic oxalacetic transminase (SGOT) activity, Serum Glutamic pyruvate Transaminase (SGPT) activity. Statistical analysis showed a significant decrease in Cholesterol, Triglyceride, HDL, SGOT and SGPT of serum blood levels on treated rabbits $p < 0.05$. The results suggest that resveratrol derivative may be helpful in preventing diabetic complications in rabbits. The significant anti-diabetic effect of resveratrol may be due to the presence of phenolics and heterocyclic amide rings as shown in resveratrol derivative or their synergistic properties.

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Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from the defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. The liver and kidney play a major role in the pathogenesis of type 2 diabetes.

Nephrotoxicity is one of the major side effects of drug therapy in clinical practice, frequently leading to acute renal failure [1]. Many natural medicines have been recommended for the treatment of diabetes [2].

Renewed attention to alternative medicines and natural therapies has stimulated new wave of research interest in traditional practices, and there is a need to look for more efficacious agents with lesser side effects. Recently there is a growing interest in resveratrol.

Scientists became interested in exploring potential health benefits of resveratrol in 1992 when its presence was first reported in red wine, leading to a speculation that resveratrol might help explain the " French Paradox" [3]. The potential for resveratrol to treat diabetes mellitus type 2 the has continued to generate scientific interest [4]. Resveratrol (3,5, 4' – trihydroxy stilbene), is a non Flavonoid polyphenol and it has three phenolic hydroxyl groups and shown to have its biological effects [5].

Phenolic and polyphenolic compounds, possess an aromatic ring bearing one or more hydroxyl substituents. These compounds are phytoalexins and have antidiabeteic properties.[6]. Resveratrol may offer benefits in preventing or managing conditions associated with high blood sugar [7]. The derivatives of resveratrol associated with the available oral hypoglycemic agents for the treatment of diabetes mellitus Epsilon-vinifera a resveratrol dimer, ,Piceatanol an active metabolic of resveratrol found in red wine , Piceid a resveratrol glucoside , Trans – diptoindonesin B a resveratrol trimer [8].

These plants produce trans-resveratrol to protect themselves after exposure to ultraviolet radiation, ozone or certain biologic agents. It functions as a ribonucleotide reductase inhibitor [3].The effects of resveratrol are currently a topic of numerous animal and human studies. Its effects on the lifespan of many model organisms remain controversial with uncertain effects in fruit flies, nematode worms and short-lived fish [9].

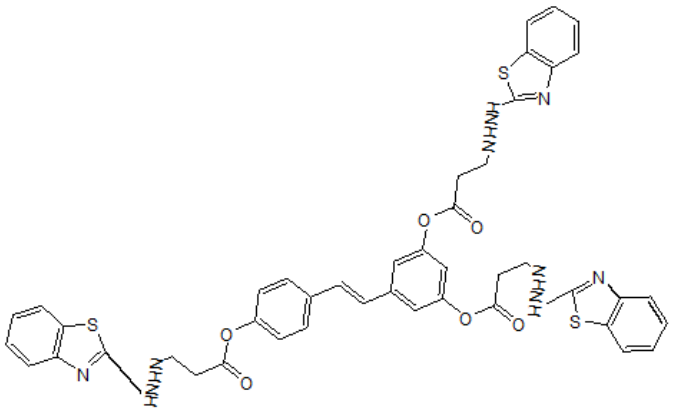
In the only positive human trial, extremely high doses (3–5 g) of resveratrol, in a proprietary formulation designed to enhance its bioavailability, significantly lowered blood sugar. Despite mainstream press alleging resveratrol's anti-aging effects, there is no accepted data to form a scientific basis for the application of these claims to mammals [10]. The aim of this research to study the antihyperlipidemic effect of resveratrol and its derivative on alloxan diabeteic rabbit.

Materials and methods:

Local black grapes cultivated Iraqi were collected from the local market and classified as *Vitis vinifera* by the herbarium of the Biology Department, College of Science, Baghdad University . The grape skin extract was prepared; all steps were done away from direct light and extensive stress that led to oxidation of the plant extract. About 500 grams of fresh skin grapes was shaken with 2.5 litters' 99.9% ethyl acetate in cool dark place for 72 hours. The extract was filtered and the filtrate was dried at 30-40°C by a rotary evaporator to get 1/10 (one tenth) its original volume to be stored at –20°C till the followings steps. The following steps were followed for the isolation of resveratrol:

Preparation of Resveratrol Derivative:

5-(4-(4-(2-(benzo [d] thiazol-2-yl) hydrazinyl) butanoyloxy)styryl)-1,3-phenylene bis(4-(2-(benzo[d]thiazol-2-yl) hydrazinyl)butanoate)



1.6gm (0.003 mole) of compound (2) was dissolved in 50ml of absolute ethanol then 1.58g 0.0096 moles of 2-Mercpto benzothiazole then reflux for 8h. The solvent was removed and the precipitates was filtrated and dried [11].

Purified Resveratrol and its Derivative Dilutions

Pure resveratrol 100 mg was dissolved in 100ml PBS and 0.1ml DMSO as organic solvent for dissolving the substance. The stock was kept in a dark container at –20°C after sterilization with 0.22µm Millipore filter.
Resveratrol derivative 50mg were dissolved in 0.05ml DMSO and complete the volume to 50 ml with PBS. Then it was sterilized and kept in a dark container at –20°C.

Experimental Design:

Induction of diabetes: After 2 weeks of acclimatization ,diabetes was induced in female rabbits with a freshly prepared solution of alloxan monohydrate (5,6-dioxyuracil) in normal saline at a dose 70 mg / kg body weight injected through the marginal vein of ear , because alloxan is capable of producing fatal hypoglycemia as a result of massive pancreatic insulin release , A rabbit was considered to be diabetic if it had a fasting blood sugar where level > 115 mg/dl. Other parameters were also taken and recorded. After the successful induction of experimental diabetes the rabbits were divided into five groups comprising a minimum of six rabbits and treated as follow for six weeks: Animals in first group were received regular standard diet, tap water and severed as control (C).Rabbits in the second group were received alloxan, induced diabetic rabbits. A rabbit was considered to be diabetic(D). Rabbits in the third group were received glbcimaid (0.05mg) orally (D G). Rabbits in the fourth group were received resveratrol 1mg/ml orally (DR). While animals in the fifth group were received resveratrol derivatives 1mg / ml orally (DRD). The experimental protocol was approved by the institutional animal ethics committee of NRI Medical College and General Hospital in accordance with CPCSEA (Committee for the purpose and control and supervision on Experiments on Animals guidelines).

Biochemical Estimation:

The serum cholesterol concentration was estimated according to Young ([11]; high density lipoprotein – cholesterol [11]; serum triglyceride [11]; Serum Glutamic oxalacetic Transaminase (SGOT) activity [11]; Serum Glutamic Pyruvate Transaminase (SGPT)[11].

Statistical Analysis: Data were analyzed by using the SPSS package programmed. Multiple range test was used to detect the significant differences [6].The method which was used to measure the significances at level 0.05 or 0.01 was taken ([12].

Results and Discussion

Table 1 show the level of total cholesterol in resveratrol and its derivative treated group also decreased significantly ($p<0.05$). Resveratrol derivative showed significant value 71mg/dL± 0.57 after 2weeks of treatment and resveratrol failed to reach to normal value after 6 weeks of treatment comparable with control group.

Diabetes mellitus is associated with high levels of circulatory cholesterol and other lipids and this account for the atherosclerosis. Serum total cholesterol (TC) and triglyceride (TG) levels elevated significantly in the diabetic control group in comparison with the control group [13].

The knowledge of the plasma level of lipids (cholesterol and triglycerides) together with lipoproteins of high and low density (HDL and LDL) aids in the detection of many conditions bound to metabolic disorders of high risk. The imbalance in the level of lipoproteins in plasma leads to hyperlipoproteinemias, a group of disorders that affects lipid levels in serum, causing coronary heart disease (CHD) and atherosclerosis, conditions in which the cholesterol levels are important tools in their diagnosis and classification. The abnormally high concentration of serum lipids in diabetics is mainly due to increase in the mobilization of free fatty acids from the peripheral fat depots [14].

In this study, the rise in blood sugar was accompanied by marked increase in cholesterol [15]. Serum total cholesterol levels elevated significantly in the diabetic control group in comparison with the control group after treatment with the extract of *S. mahagoni* seed to the diabetic animals; serum total cholesterol and triglyceride levels were recovered significantly towards the control level [16].

Table 1 The effect of resveratrol and its derivative on serum cholesterol concentration mg/dL of rabbits' groups with weeks

Groups	Treatment periods							
	WK0	**PT**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk5**	**Wk6**
C	70± 0.53 [a] A	70± 0.053 [d] A	66± 0.48[f] A	69± 0.55 [a] A	71± 0.57[f] A	70± 0.53[f] A	73± 0.62[f] A	71± 0.57[f] A
D	70± 0.53 [a] A	300± 8.2[a] A	306± 8.14[a] A	296± 8.2[a] A	299± 8.4[a] A	289± 8.1[a] AB	280± 7.12[a] B	291± 8.15[a] AB
DI	72 ± 0.68 [a] B	275± 4.24 [b] A	250± 8.2[b] B	240± 7.6[b] B	220± 7.35[b] C	220± 7.35[b] C	200± 7.12[b] D	200 ± 7.12[b] D
DR	79± 0.8 [a] E	300± 8.2[a] A	200± 7.12[c] B	160± 507[C] C	160± 5.07[c] C	145± 4.1[c] C	144± 4.1[c] CD	140± 4.0[c] D
DRD	67 ± 0.49 [a] D	299± 822[a] A	75± 0.76[f] A	71± 0.57[g] A	70± 0.53[f] A	68± 0.59[f] A	85± 1.14[f] A	60± 0.56[f] A

Each value represent mean ± SD

Values with non-identical superscripted (a, b, c, d, e& f) are considered as significantly different ($p<0.05$) among the same group of rabbits, Values with non-identical superscripted (A, B, C, D, E& F) are considered as significantly different ($p<0.05$) among the different groups of rabbits, N(number of animals)=3.

C=Control ;D=Diabetic; I=Diabetic after treated with glbcimide;DR= Diabetic after treated with resveratrol; DRD= Diabetic after treated with resveratrol derivative.

Table 2 The effect of resveratrol and its derivative on serum high density lipoprotein (HDL) concentration (mg/dL) of rabbits' groups with weeks.

Groups	Treatment periods							
	WK0	**PT**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk5**	**Wk6**
C	20± 1.01[a] A	20± 1.01 [a] A	25± 1.5 [a] A	24± 1.04 [a] A	24± 1.04 [a] A	21± 1.03 [a] A	20± 1.01 [a] A	25± 1.5 [a] A
D	22± 1.0[a] B	55± 2.5 [e] A	52± 2.48 [d] A	52± 2.48 [d] A	52± 2.48 [d] A	52± 2.48 [d] A	55± 2.5 [e] A	55± 2.5 [e] A
DI	24± 1.04[a] C	52± 2.48 [e] A	50± 2.55 [d] AB	50± 2.55 [d] AB	48± 2.02 [c] AB	48± 2.02 [c] AB	47± 2.06 [c] AB	46± 2.03 [c] B
DR	25± 1.5[a] C	55± 2.5 [e] A	44± 2.9 [d] B	44± 2.1 [d] B	43± 1.55 [d] B	42± 1.9 [d] B	42± 1.9 [d] B	40± 2.02 [c] B
DRD	20± 1.01[a] B	55± 2.5 [e] A	24± 1.08 [cd] B	24± 1.08 [a] B	22± 1.0 [a] B	20± 1.0 [a] B	20± 1.0 [a] B	20± 1.0 [a] B

Each value represent mean + SD

Values with non-identical superscripted (a, b, c, d, e& f) are considered as significantly different ($p<0.05$) among the same group of rabbits, Values with non-identical superscripted (A, B, C, D, E& F) are considered as significantly different ($p<0.05$) among the different groups of rabbits, N(number of animals)=3.

Table 2 shows the diabetic rabbits treated with the resveratrol and its derivative showed significant increase in the levels of Serum HDL ($p<0.05$). Derivative shows significant value after one week of treatment 24mg/dL±1.08. Serum HDL level decreased in the diabetic control group in respect to the control. The levels of the above-mentioned parameters recovered significantly towards the control group after treatment of the extract of *S. mahagoni* seed when compared with the diabetic control group [17]. Low levels of HDL, have been associated with heart disease, insulin resistance and diabetic mellitus [18].

Hyperlipidemia is associated with diabetic state and this may be due to uninhibited action of lipase. Low levels of serum HDL in STZ-induced diabetic state focused the low level of serum insulin and the results are consistent with our previous findings [18]. Almost similar increased in HDL level was also observed by chlorpropamide, a known antidiabetic drug in a dose of 84 mg/kg. The aqueous extract *Phyllantus emblica* Linn also induced hypotriglyceridemia by increasing HDL levels at 0, 1, 2 and 4 hours in diabetic rats ($p<0.05$) [19].

Low HDL cholesterol is used as a risk factor to estimate 10-year risk for coronary heart disease, having several causes: elevated triglycerides overweigh and obesity, physical inactivity, and type 2 diabetes. Other causes are, cigarette smoking, very high carbohydrate intakes (> 60% of calories), and certain drugs as anabolic steroids and progestional agents.

Hyperlipidemia has been reported to accompany hyperglycemia states and there are important coronary risk factors for heart diseases.

Table 3 the results showed significant increase in the level of serum triglyceride which are signs of renal dysfunction in the diabetic rabbits when compared to control rabbits.

The diabetic rabbits treated with the resveratrol and its derivative decrease levels of Serum Triglyceride significantly The results showed significant decrease in the level of serum triglyceride of rabbits treated with resveratrol and its derivative ($p<0.05$).Derivative showed significant value after one week of treatment 88mg/dL±4.2**.**

Serum triglyceride level elevated significantly in the diabetic control group in comparison with the control group after treatment with the extract of *S. mahagoni* seed to the diabetic animals; serum total cholesterol and triglyceride levels were recovered significantly towards the control level [16]. High levels of triglycerides have been associated with heart disease, insulin resistant since insulin inhibits adipose tissue hormone sensitive lipase and reduces lipolysis.

Resveratrol and its derivative may correct the above mentioned disorders by mimicking insulin action. The most exciting results and the additional advantage of these compounds over the existing drugs in this concern is the correction of triglyceride and elevation in HDL concentration level as most of these drugs decreased the blood level of triglyceride.

This correction may be due to the antidiabetic efficacy of these compounds that prevent the reactive oxygen species generation by preventing glucose auto oxidation and by glycation non diabetic and diabetic mellitus [17].

The abnormally high concentration of serum lipids in diabetics is mainly due to increase in the mobilization of free fatty acids from the peripheral fat depots [15]. The effect of aqueous fruit extract of *Phyllanthus emblica* Linn in a dose of 200mg/kg body weight was studied on type-II diabetes. Triglycerides (TG) significantly ($p<0.05$) after its intraperitoneal administration in alloxan-induced diabetic rats [16].

Table 3 The effect of resveratrol and its derivative on serum triglyceride concentration (mg/dL) of rabbits' groups with weeks.

Groups	Treatment periods							
	WK0	**PT**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk5**	**Wk6**
C	68± 3.0 [a] A	80± 3.16 B	88± 3.25 A	88± 3.25 A	85± 4.15 AB	82± 3.45 B	67± 1.26 D	75± 1.22 C
D	70± 3.5 [a] B	210± 5.03 A	52± 2.28 C	52± 2.28 C	52± 2.28 C	52± 2.28 C	55± 2.5 C	55± 2.5 C
DI	76± 3.04 [a] C	200± 2.6 A	175± 2.52 B	175± 2.52 B	175± 2.52 B	180± 5.1 B	177± 3.6 B	175± 2.52 B
DR	85± 4.15 [a] F	200± 2.6 A	160± 3.07 B	150± 2.75 C	150± 2.75 C	130± 1.5 D	120± 2.4 E	115± 2.36 E
DRD	80± 23.16 [a] CD	180± 5.1 A	88± 4.2 B	87± 3.15 B	86± 3.11 B	82± 2.10 BC	75± 2.16 D	68± 2.10 C

Each value represent mean + SD

Values with non-identical superscripted (a, b, c, d, e& f) are considered as significantly different ($p<0.05$) among the same group of rabbits, Values with non-identical superscripted (A, B, C, D, E& F) are considered as significantly different ($p<0.05$) among the different groups of rabbits, N(number of animals)=3.

Table 4 The effect of resveratrol and its derivative on serum GOT concentration U/mL of rabbits' groups with weeks.

Groups	Treatment periods							
	WK0	**PT**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk5**	**Wk6**
C	9± 0.25[a] A	10± 0.25[c] A	10 ± 0.05[h] A	11± 0.05[g] A	11± 0.5[f] A	9± 0.15[e] A	10± 0.25[f] A	12± 1.5[d] A
D	11± 0.05[a] C	55± 2.5[a] A	50± 2.6[a] B	50± 2.6[a] B	50± 2.6[a] B	52± 2.45[a] B	55± 2.5[a] A	55± 2.5[a] A
DI	11± 0.05[a] D	50± 2.6[b] A	40± 2.0[b] B	40± 2.0[b] B	40± 2.0[b] B	38± 1.7[b] B	38± 1.26[b] B	35± 2.5[b] A
DR	11± 0.05[a] E	55± 2.5[a] A	27± 1.0[c] A	25± 1.0[c] A	25± 1.0[c] A	24± 1.1[e] A	22± 1.2[c] A	16± 0.07[c] A
DRD	4± 0.23[a] CD	55± 2.5[a] A	14± 0.72[g] A	12± 0.63[fg] A	10± 0.25[f] A	9± 0.23[e] A	8± 0.22[f] A	7± 0.14[f] A

Each value represent mean ± SD

Values with non-identical superscripted (a, b, c, d, e& f) are considered as significantly different ($p<0.05$) among the same group of rabbits, Values with non-identical superscripted (A, B, C, D, E& F) are considered as significantly different ($p<0.05$) among the different groups of rabbits, N(number of animals)=3.

The group of enzymes called transaminase exists in tissues of many organs. Necrotic activity in these organs causes a release of abnormal quantitaties of enzyme into the blood where they are measured. Since the heart tissue is rich in SGOT increased, serum levels appear in patients after myocardial infarction, as well as in patients with muscle disease, muscular dystrophy and dermatomyositis when compared to control rabbits. The diabetic rabbits treated with the resveratrol and their derivatives showed decrease levels of SGOT significantly ($p<0.05$)as shown in **Table 4**. Resveratrol Derivative shows significant value after three weeks of treatment 12±0.63. The levels of SGOT have been reported to increase in alloxan-induced diabetic rabbits which agree with other researches. In this investigation, resveratrol and their derivatives reduced elevated level of SGOT significantly ($p<0.05$) and thus improving renal and hepatic functions [20]. The concentration of alanine aminotransferase in the plasma of the non-diabetic control rat was 36 ± 3.3 μ/L. In the non-diabetic rats administered (Essential Oil) EO, this value was 37.5 ± 4.5 μ/L but in the diabetic control rats, it was 66 ± 3.65 μ/L. In the diabetic rats administered (Essential Oil) (EO), this valuewas 44 ± 4.5 μ/L. Thus. *Z. multiflora* EO(Essential Oil) had no effects on the alanine aminotransferase level in the healthy rats but in the diabetic rat, the level of alanine aminotransferase reduced to the non diabetic control level ($p = 6.22 \times 10^{-7}$, n=8) [21].

The liver is specially rich in serum Glutamic pyruvate transaminase (SGPT) being the enzyme measurement used primarily as a test for infectious and toxic hepatitis, although high levels of both SGPT may also be found in cases of liver cell damage and acute pancreatitis, suggesting that the obstruction of the biliary tree by the edematous pancreas and the presence of associate hepatic disease may contribute to elevated SGPT level in these patients.

Table 5 showed significant decrease in the level of serum GPT of rabbits treated with resveratrol and their derivatives ($p<0.05$). Resveratrol derivative shows significant value after tow week of treatment 10±0.25.

Diabetes mellitus is associated with high levels of circulatory cholesterol and other lipids and these accounts for the atherosclerosis, arteriosclerosis and severe coronary heart disease which leads to increase levels of transaminases, which are important enzyme signs of heart and liver damage [22].

The levels of SGPT have been reported to increase in alloxan-induced diabetic rats [20]. In this study resveratrol and their derivatives significantly ($p<0.05$) reduced elevated levels of SGPT, thus improving renal and hepatic functions. This observation is consistent with earlier report on hepatoprotective potentials of leaf extracts of *V. amygdalina* in mice [23].

Previous work of on, the effects of *Cynodon dactylon*, [25], on the effects of *omordi cacharantia*, [26] and on the effects of *Chinese propolis* and *Brazilian propolis* in diabetic rats indicated that SGPT, while insulin increased significantly $p<0.05$. [27].

The effects of Oral administration of an aqueous extract of *A. squamosa* leaves (300 mg/kg body weight) of rats for 30 days were examined in the plasma, liver and kidney tissues of control and experimental groups. It shows significant decrease in diabetic rats on blood aspartate aminotransferase level ($p<0.05$) [28].

Table 5 The effect of resveratrol and its derivative on Serum Glutamic Pyruvate Transaminase (SGPT) concentration U/mL of rabbits' groups with weeks

Groups	Treatment periods							
	WK0	**PT**	**Wk1**	**Wk2**	**Wk3**	**Wk4**	**Wk5**	**Wk6**
C	7 ± 0.25^{a} A	7 ± 0.25^{c} A	8 ± 22^{f} A	8 ± 0.22^{f} A	8 ± 0.22^{f} A	9 ± 0.23^{d} A	10 ± 0.25^{e} A	10 ± 2.5^{d} A
D	8 ± 0.22^{a} A	40 ± 2.01^{a} A	43 ± 1.5^{a} A	43 ± 1.5^{a} A	42 ± 2.1^{a} A	41 ± 2.05^{a} A	45 ± 2.3^{a} A	44 ± 2.32^{a} A
DI	8 ± 0.22^{a} A	40 ± 2.01^{a} A	40 ± 2.01^{a} A	40 ± 2.0^{a} A	40 ± 2.01^{a} A	40 ± 2.01^{a} A	40 ± 2.01^{b} A	41 ± 2.05^{a} A
DR	8 ± 0.22^{a} A	45 ± 2.3^{a} A	35 ± 1.58^{b} A	34 ± 1.55^{a} A	33 ± 1.53^{b} A	20 ± 0.5^{b} A	20 ± 0.5^{c} A	20 ± 0.5^{b} A
DRD	9 ± 0.23^{a} A	43 ± 1.5^{ab} A	14 ± 0.31^{e} A	10 ± 0.25^{f} A	10 ± 0.25^{f} A	9 ± 0.23^{d} A	8 ± 0.4^{e} A	7 ± 0.14^{d} A

Each value represent mean $\pm$ SD

Values with non-identical superscripted (a, b, c, d, e& f) are considered as significantly different ($p<0.05$) among the same group of rabbits, Values with non-identical superscripted (A, B, C, D, E& F) are considered as significantly different ($p<0.05$) among the different groups of rabbits, N(number of animals)=3.

Conclusion

We could concluded that resveratrol and its derivative are safe and potent hypoglycemic and hypolipidemic agent which is capable of normalizing other biochemical and hematological abnormalities associated with diabetes mellitus type 2. Thus could be prescribed as adjunct to dietary therapy and main therapy for diabetes mellitus type 2. The significant anti-diabetic effect of resveratrol may be due to the presence of phenolics , the presence of heterocyclic amide rings as shown in resveratrol derivative or their synergistic properties.

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