DIABETERTM REDUCES POST MEAL HYPERGLYCEMIA VIA ENHANCEMENT OF GLUCOSE UPTAKE INTO ADIPOCYTES AND MUSCLES CELLS

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ABSTRACT

There are lots of herbal products for diabetes mellitus treatment available in local market. Most of these products are not standardized and lack of efficacy and safety data. DiaBetterTM is one of the herbal products that have been used for diabetes treatment. This study was carried out to determine the efficacy of DiaBetterTM in reducing hyperglycemia and to elucidate the mechanisms by which hyperglycemia is reduced. The results showed that DiaBetterTM significantly reduced post meal hyperglycemia in normal and diabetic rats, and improved glucose tolerance activity in diabetic rats particularly after 4 and 6 hours of administration. Antihyperglycemic mechanisms elucidation revealed that the DiaBetterTM significantly enhanced insulin-stimulated glucose uptake into adipocytes and muscle cells, with the highest magnitude of enhancement were 1.54-fold (p<0.01) and 1.46-fold (p<0.001), respectively. Molecular mechanisms that responsible for this enhancement were the increment of insulin sensitivity at cells membrane. Cytotoxic evaluation was also done and confirmed that DiaBetterTM was toxicologically safe against muscle and adipocytes cells. In conclusion, post-meal antihyperglycemic and glucose tolerance activity of DiaBetter™ was mediated through the enhancement of glucose uptake into adipocytes and muscle cells. Insulin sensitizing activity showed by DiaBetterTM suggests that this product has the potential to ameliorate insulin resistance condition. Therefore, it is suggested that DiaBetterTM can be used as dietary adjunct for the management of type 2 diabetes mellitus which related to insulin resistance.

ABSTRAK

INTRODUCTION

171 million people have been diagnosed with diabetes mellitus in the year of 2000 and this number is expected to rise to 366 million by the year of 2030 (Wild et al., 2004). More than 90% of the cases are Type 2 diabetes which is characterized by variable degree of insulin resistance, impaired of insulin secretion and increased glucose production from liver (Guo and Tabrizchi, 2006). Insulin resistance is a condition in which normal amounts of insulin are inadequate to produce a normal insulin response from the insulin responsive cells; adipocytes and muscle (Cefalu, 2000). It is also associated with hyperinsulinemia, enhanced hepatic gluconeogenesis and impaired insulin-stimulated glucose uptake into muscle cells. Type 2 diabetes is normally treated with oral antidiabetic drugs such as sulfonylureas (SUs), biguanides and thiazolidinediones (TZDs) (Cheng and Fantus, 2005 & Kimmel and Inzucchi, 2005). Although lots of antidiabetic drugs available, diabetes mellitus remains major global health problem (Wild et al., 2004). This could possibly be due to the lack of efficacy of current antidiabetic drugs as well as the undesirable effects. These limitations have fueled the search for new therapeutic agents for treatment of diabetes mellitus. The use of plants as the alternative treatment for diabetes is gaining momentum during the past decade and lots of plant-based products have been developed and available in the market. Despite being widely used, most of these products are not standardized and lack of efficacy and safety data. DiaBetter™ is one of the available local herbal products that have been used for diabetes treatment. This product was manufactured by Aspire Paradise Sdn. Bhd, and consists of several plants namely Petai Cina (Leucaena leucocephala), Belimbing Tanah (Tacca spp), Bunga Mukmin (Gossampinus malabarica), Bуш Kundur (Beninsaca hispicta), Tunjuk Langit (Helminthostachys zeylanica), Mahkota Dewa (Phaleria papuanca), Chrysanthemum, Habbatussauda, and Ganoderma. There are still no pharmacological evidences to support the effectiveness of this product in diabetes treatment. Therefore, this study was carried out to determine the efficacy of DiaBetter™ in reducing hyperglycemia and to elucidate the mechanisms underlie its antihyperglycemic activity.
MATERIALS AND METHODS

Chemicals and reagents

3T3F442A pre-adipocytes and L6 rat myoblasts (CRL-1458) were obtained from Universiti Putra Malaysia. All cell culture media and supplements were purchased from Invitrogen, USA. Sodium deodecyl sulphate (SDS), 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), insulin, dimethylsulphoxide (DMSO), metformin, streptozotocin, CMC and D-glucose were purchased from Sigma Chemical Co. (St. Louise, USA). Ultima Gold™ LLT was purchased from PerkinElmer (USA). 2-Deoxy-[1-3H]-glucose was purchased from GE Healthcare (USA). Rosiglitazone maleate and DiaBetter™ was purchased from a local supplier.

Preparation of DiaBetter™

For in vitro assays, DiaBetter™ syrup was freeze-dried and for in vivo evaluation, DiaBetter™ syrup was used directly at dose of 16.7 ml/kg b.w. as recommended by the manufacturer.

Experimental animals and diabetes induction

Adult normal male Sprague Dawley rats (200-250 g) were used in this study. Animals were bred in house at Animal House of Malaysian Nuclear Agency and were fed using a standard laboratory pellet diet, and water was supplied ad libitum. Diabetes was induced with intravenous injection of streptozotocin (STZ) solution (60 mg/kg b.w.) given under ether anesthesia. Fasting blood glucose was checked 7 days after injection, and rats that had blood glucose levels 13.0 mmol/L or above were considered diabetic and used as the experimental animals (Kesari et al., 2006). A total of 21 rats were used in each experiment. Rats were randomly divided into three groups (7 rats in each group). Group I (control group) was given vehicle, 1% carboxymethylcelulose (CMC). Group II was treated with DiaBetter™ at dose of 16.7 ml/kg b.w. and group III was treated with metformin at dose of 500 mg/kg b.w. (Arun and Nalini, 2002).

Antihyperglycemic test and oral glucose tolerance test (OGTT)

In fasting state, rats were fasted 12-hour prior to test whereas in post meal state, rats were fasted 1-hour prior to test. After fasting period, rats were treated with the DiaBetter™ and metformin orally using intragastric gavage. Blood samples were collected from the tip of rats’ tails before (0 hour) and after 2, 4 and 6 hour of test agents administration for the measurement of blood glucose concentration. For OGTT, Fasting blood glucose was checked in 12 hours fasted (-30 min) followed by oral administration of the test agents orally. 30 minutes later (at 0 hour), rats of all groups were given glucose (1.5 g/kg; 100 mg/ml in distilled water) orally. Blood samples were collected just prior to glucose administration (0 min) and 30, 60, 120 and 180 minutes after glucose administration. Glucose level was determined using an electronic glucometer, Accu Check Advantage from Roche Diagnostic (Indianapolis, USA). Total glycemic responses to OGTT were calculated from respective areas under the glucose curve (AUCGlucose) at the 180 minutes observation period using computer calculator software provided by Thomas Wolever from Department of Nutritional Sciences, University of Toronto, Ontario, Canada (Jalil et al., 2008).
Glucose uptake assay

3T3F442A pre-adipocytes (adipocytes cells) and L6 myoblast (muscle cells) were maintained in DMEM supplemented with 10% (v/v) FBS and 1% (v/v) antibiotic solution (10,000 units/ml penicillin and 10 mg/ml streptomycin) at 37°C humidified with 5% CO₂. The 3T3F442A pre-adipocytes were differentiated into adipocytes spontaneously when confluence and cultured with medium supplemented with 5 μg/ml insulin. L6 myotubes differentiation was induced by reducing the FBS in the complete culture medium from 10% to 2%. Cells were maintained in this medium for 4 to 6 days post-confluence. The extent of differentiation was established by observing multinucleation of cells. In the present experiment, about 85 to 90% of the myoblasts was fused into myotubes. Glucose uptake assay was done according to Liu et al., 2001, with some modifications. Briefly, confluent cells were seeded at a concentration of 2 x 10⁵ cells/well in a 12-well plate and left overnight at 37°C. Then, cells were washed with serum-free DMEM and pre-incubated with this medium for 2 hours at 37°C. After starvation period, cells were washed with the Krebs-Ringer bicarbonate buffer (KRb) and further incubated for 30 minutes at 37°C with DiaBetter™ (62.5-2000 μg/mL) either alone or with 100 nM insulin. Rosiglitazone maleate and metformin were used as positive control for 3T3F432A adipocytes and L6 myotubes, respectively. To initiate glucose uptake reaction, 2-deoxy-[1-3H]-glucose (1 μCi/mL) diluted in 0.1 mM D-glucose solution was added to each well and further incubated for 60 minutes at 37°C. Then, cells were washed with ice-cold KRb buffer and solubilized with 1 ml of 0.1% sodium deodexyl sulphate (SDS) dissolved in phosphate buffer, pH 7.4. The content of each well was transferred into scintillation vials, and 15 mL of scintillation cocktail, Ultima Gold LLT, was added. The radioactivity incorporated into the cells was measured using liquid scintillation counter (Hewlett Packard, USA).

Cell viability assay

The viability of adipocytes and muscle cells the presence of DiaBetter™ was conducted according to the established methods (Mosman, 1983 & Carmichael et al., 1987). The differentiated cells were seeded at concentration of 1.5 x 10⁵ cells/well into 96-wells plate and incubated at 37°C overnight. Cells were further incubated at 37°C for 72 hours in the absence or presence of DiaBetter™ (62.5-2000 μg/mL), metformin (10-1000 μM) and rosiglitazone maleate (62.5-1000 μg/mL). Following incubation, 20 μL of 5 mg/mL of MTT was added to each well and incubated for 4 hours. Subsequently, the media from each well was then gently aspirated and 100 μL of DMSO was added to dissolve the formazan crystals. Plates were shaken for 5 seconds and absorbance was measured at 570 nm using Anthos microplate reader (Beckman Coulter, USA).

Statistical analysis

Results are expressed as mean ± standard deviation for a given number of observations. Statistical analyses were performed using GraphPad Prism Software version 4.0. The data were analyzed using one way Analysis of Variance (ANOVA), followed by Tukey’s post hoc test. The group means were considered significantly different at the level of p<0.05.

RESULTS

Effect of Diabetter™ on fasting hyperglycemia in normal and diabetic rats

Table 1 and 2 shows the effect of Diabetter™ on fasting blood glucose in normal and diabetic rats. Following Diabetter™ treatment, there is no significant difference in blood glucose changes between
pretreatment (0 hour) and post treatments hours for both group of rats. Metformin significantly reduced blood glucose after 4 and 6 hours of treatment in normal rats, and reduced fasting hyperglycemia after 2, 4 and 6 hours of administration in diabetic rats.

**Table 1:** Effect of Diabetter™ on blood glucose level in normal rats at fasting state

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Blood glucose level (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hour</td>
</tr>
<tr>
<td>Control</td>
<td>4.550 ± 0.212</td>
</tr>
<tr>
<td>Diabetter™ (16.7 ml/kg b.w.)</td>
<td>4.625 ± 0.050</td>
</tr>
<tr>
<td>Metformin (500 mg/kg b.w.)</td>
<td>4.350 ± 0.810</td>
</tr>
</tbody>
</table>

*Notes: Values in bracket indicate percentage of blood glucose reduction relative to 0-hour of the respective treatment group. *p<0.05; **p<0.01 compared to 0 hour of the respective treatment group.*

**Table 2:** Effect of Diabetter™ on blood glucose level in diabetic rats at fasting state

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Blood glucose level (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hour</td>
</tr>
<tr>
<td>Control</td>
<td>18.88 ± 2.092</td>
</tr>
<tr>
<td>Diabetter™ (16.7 ml/kg b.w.)</td>
<td>15.33 ± 2.698</td>
</tr>
<tr>
<td>Metformin (500 mg/kg b.w.)</td>
<td>16.72 ± 1.574</td>
</tr>
</tbody>
</table>

*Notes: Values in bracket indicate percentage of blood glucose reduction relative to 0-hour of the respective treatment group. *p<0.05; **p<0.01 compared to 0 hour of the respective treatment group.*

**Post meal antihyperglycaemic activity of Diabetter™ in normal and diabetic rats**

Diabetter™ significantly reduced post meal hyperglycemia after 4 and 6 hours of administration in normal rats (Table 3). Metformin also reduced post meal hyperglycemia of normal rats significantly after 6 hours of administration. In diabetic rats, Diabetter™ and metformin reduced post meal hyperglycemia significantly after 2, 4 and 6 hours of administration (Table 4).

**Table 3:** Effect of Diabetter™ on blood glucose level in normal rats at post meal state

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Blood glucose level (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hour</td>
</tr>
<tr>
<td>Control</td>
<td>6.220 ± 0.723</td>
</tr>
<tr>
<td>Diabetter™ (16.7 ml/kg b.w.)</td>
<td>6.400 ± 0.922</td>
</tr>
<tr>
<td>Metformin (500 mg/kg b.w.)</td>
<td>5.025 ± 0.877</td>
</tr>
</tbody>
</table>

*Notes: Values in bracket indicate percentage of blood glucose reduction relative to 0-hour of the respective treatment group. *p<0.05; **p<0.01 compared to 0 hour of the respective treatment group.*
Table 4: Effect of Diabeter™ on blood glucose level in diabetic rats at post meal state

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Blood glucose level (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hour</td>
</tr>
<tr>
<td>Control</td>
<td>13.14 ± 1.549</td>
</tr>
<tr>
<td>Diabeter™ (16.7 ml/kg b.w.)</td>
<td>22.81 ± 4.724</td>
</tr>
<tr>
<td>(27.93%)</td>
<td>(27.93%)</td>
</tr>
<tr>
<td>Metformin (500 mg/kg b.w.)</td>
<td>23.96 ± 3.601</td>
</tr>
<tr>
<td>(44.16%)</td>
<td>(44.16%)</td>
</tr>
</tbody>
</table>

Notes: Values in bracket indicate percentage of blood glucose reduction relative to 0-hour of the respective treatment group. **p<0.01 compared to 0 hour of the respective treatment group.

Glucose tolerance profile of Diabeter™ in normal and diabetic rats

Diabeter™ showed no effect on glucose tolerance activity in normal rats. However, in diabetic rats, glucose tolerance activity was significantly improved as shown by the attenuation of AUCglucose value (Table 5).

Table 5: Effect of Diabeter™ on glucose tolerance activity in normal rats and diabetic rats

<table>
<thead>
<tr>
<th>Treatment/Dose</th>
<th>AUCglucose value (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal rats</td>
</tr>
<tr>
<td>Control</td>
<td>210.3 ± 151.9</td>
</tr>
<tr>
<td>Diabeter™ (16.7 ml/kg b.w.)</td>
<td>226.9 ± 130.5</td>
</tr>
<tr>
<td>Metformin (500 mg/kg b.w.)</td>
<td>84.42 ± 39.75</td>
</tr>
</tbody>
</table>

Notes: Values in bracket indicate percentage of AUCglucose attenuation relative to control group. *p<0.05 and **p<0.001 compared with control group.

Glucose uptake activity in muscle and adipocytes cells in the presence of DiaBetter™

DiaBetter™ did not affect basal glucose uptake in muscle cells but it significantly enhanced insulin-stimulated glucose uptake at all concentrations evaluated (Figure 1). The magnitude of uptake were 1.46-fold, 1.38-fold, 1.41-fold, 1.44-fold and 1.33-fold (p<0.01), found at concentrations of 62.5, 125, 500, 1000 and 2000 µg/ml, respectively. The enhancement effects exhibited by Diabeter™ at concentrations of 62.5 and 1000 µg/ml were found to be 1.22-fold (p<0.001) and 1.26-fold (p<0.01) higher than that of 100 nM insulin, respectively. Furthermore, the enhancement effects exhibited by such concentrations was also found to be significantly higher than that of its respective basal uptake (1.67-fold and 1.43-fold; p<0.001). Metformin evoked an uptake of 1.62-fold (p<0.001) under basal and 2.26-fold (p<0.001) under insulin-stimulated state.
In adipocytes cells, DiaBetter™ also did not affect basal glucose uptake. However, insulin-stimulated glucose uptake was significantly enhanced by 1.54-fold (p<0.01) at concentration of 62.5 μg/ml. This enhancement was found to be 1.49-fold (p<0.01) higher than that of 100 nM insulin alone (Figure 2). Rosiglitazone maleate (12.5 μg/ml) evoked an uptake of 2.11-fold (p<0.001).

**Figure 1:** Effect of DiaBetter™ on glucose uptake into muscle cells

*Notes:* Values represent the means ± SEM (n=4), α p<0.001 compared with control. α p<0.05, β p<0.01; γ p<0.001 compared to 100 nM insulin. D: DiaBetter™

**Figure 2:** Effect of DiaBetter™ on glucose uptake into adipocytes cells

*Notes:* Values represent the means ± SEM (n=4), α p<0.001; β p<0.01 compared with control. α p<0.001; β p<0.01 compared to 100 nM insulin. D: DiaBetter, R: Rosiglitazone

**Adipocytes and muscle cells viability in the presence of DiaBetter™**

DiaBetter™ did not affect the viability of adipocytes and muscle cells (Figure 3). This is shown by the viability of both cells were more than 50% after 72-hours treatment.
DISCUSSIONS

The present study reports the antihyperglycemic activity of DiaBetter™ in normal and diabetic rats and the mechanisms underlie its antihyperglycemic activity, which was elucidated through glucose uptake assay. In order to challenge antihyperglycemic and glucose uptake activity of DiaBetter™, rosiglitazone maleate and metformin was used as positive control. Rosiglitazone, which is a member of Thiazolidinedione group, is a selective peroxisome proliferator-activated receptor-γ (PPARγ)-agonists. The mechanism by which this agent exerts its antidiabetic activity is through the reduction of insulin resistance and improvement of insulin sensitivity in insulin-responsive cells, resulting in a decrease of hyperglycemia (Boelsterli and Bedoucha, 2002). Metformin belongs to Biguanide group and its main antidiabetic mechanism is through the enhancement of insulin-stimulated glucose uptake into muscle cells and reduction of gluconeogenesis in the liver, resulting in reduction of hyperglycemia (Chehade and Mooradian, 2000).

In this study, DiaBetter™ showed the ability to prevent the occurring of hypoglycemia. This was confirmed by the stable of blood glucose level in normal rats after 6 hours of DiaBetter™ treatment (Table 3.1). Hypoglycemia is characterized by the drop of blood glucose level below the normal range (3.6 - 5.5 mmol/L) and may causes death if not properly controlled (Ryan, 2002). In diabetic rats, fasting hyperglycemia was not reduced as expected even though after 6 hours of DiaBetter™ treatment. This indicates that Diabeter™ at dose of 16.7 ml/kg b.w. is not effective in reducing fasting hyperglycemia event after 6 hours treatment. This could possibly be due to inadequate dose of Diabeter™ or insufficient of treatment duration. Therefore, in order to achieve optimum therapeutic effect, dose of Diabeter™ must be increased and duration of treatment needs to be extended.

Post meal hyperglycemia was reduced significantly in normal and diabetic rats following DiaBetter™ treatment particularly after 4 and 6 hours of administration (Table 3 and 4). The post meal antihyperglycemic activity of DiaBetter™ in normal rats was almost comparable to that of metformin after 6 hours of administration. However, in diabetic rats, even though antihyperglycemic activity of DiaBetter™ is significantly reduced, but this therapeutic activity is less than metformin. Glucose tolerance activity in normal rats was not changed following DiaBetter™ treatment. However, in diabetic rats, the glucose tolerance activity was significantly improved (Table 5). However, this activity was less than standard drug, metformin. This could possibly be due to the fact that DiaBetter™ contains a
mixture of compounds which are bioactive and non-bioactive. There is possibility that amount of bioactive compounds is less than non-bioactive and hence reduced its therapeutic activity.

Glucose uptakes into adipocytes and muscle have been widely accepted as one of the mechanisms by which hyperglycemia is reduced (Patel and Mishra, 2008). These insulin-responsive cells are the major targeted cells for glucose disposal from blood stream (Christopher et al., 1983). Glucose uptake into such cells is mediated by insulin, an anabolic hormone which regulates metabolism of carbohydrate, lipid and protein (Saltiel and Pessin, 2002). Insulin mediates glucose disposal into these cells by binding to the insulin receptor (IR) proteins at the surface of the cells, activating a series of proteins within the cells leading to the translocation of the GLUT4 to the cell surface and permit the entrance of glucose into the cells (Saltiel. and Kuhn, 2001; Watson and Pessin, 2006 & Roffey et al., 2007). Insulin was reported to increase basal glucose uptake into adipocytes and muscle cells (Kang and Kim, 2004; Mitsumoto et al., 1991 & Konrad et al., 2002). The present study was in accord with such reports that 100 nM insulin slightly increased glucose uptake into muscle and adipocytes cells. The same concentration of insulin was also used to stimulate glucose uptake in the presence of DiaBetter™. This concentration of insulin was widely used to stimulate glucose uptake into adipocytes cells (Sakurai et al., 2004 & Elmore et al., 2002).

In this study, DiaBetter™ showed no effect on basal glucose uptake in both adipocytes and muscle cells. However, insulin-stimulated glucose uptake into adipocytes cell was significantly enhanced by DiaBetter™ (62.5 µg/ml) with the magnitude of uptake was 1.54-fold (p<0.01). This suggests that such concentration has the ability to enhance insulin-stimulated glucose uptake into adipocytes cells. Furthermore, this enhancement was found to be 1.49-fold (p<0.01) higher than that of 100 nM insulin indicating that DiaBetter™ possess insulin sensitizing activity while enhancing glucose uptake into adipocytes cells. In L6 muscle cells, all concentrations of DiaBetter™ significantly enhanced insulin-stimulated glucose uptake. The enhancement exhibited by DiaBetter™ at concentrations of 62.5 and 1000 µg/ml were found to be 1.22-fold and 1.20-fold higher than that of 100 nM insulin, respectively. This indicates that these concentrations of DiaBetter™ possess insulin sensitizing activity during enhancing glucose uptake into muscle cells. Furthermore, the insulin-stimulated glucose uptake by these concentrations was also found to be significantly higher than that of its respective basal uptake. This indicates that these concentrations of DiaBetter™ enhances insulin-mediated glucose uptake into muscle cells synergistically with 100 nM insulin. In this study, glucose uptake activity shown by DiaBetter™ is less than rosiglitazone and metformin. This could possibly be due to that DiaBetter™ contains a mixture of compounds which are bioactive and non-bioactive. There is possibility that amount of bioactive compounds is less than non-bioactive and lead to lower glucose uptake activity.

The viability of 3T3F442A adipocytes and L6 myotubes cell in the presence of various concentrations of DiaBetter™ was evaluated using MTT assay. In this assay, the yellow tetrazolium salt, MTT is reduced by the mitochondrial enzymes, succinate dehydrogenase to form insoluble purple formazan crystals which are solubilized by the addition of a detergent. The color produced then can be measured spectrophotometrically at 570 nm. MTT reduction was proportional to cell viability (Mosman, 1983 & Carmichael et al., 1987). Following 72-hours treatment, DiaBetter™ at particular concentrations reduced 3T3F442A adipocytes and L6 myotubes cells, but this reduction was not less than 50%. According to Elmore et al., 2002, the highest concentration of a test agent in cytotoxicity evaluation should be 1000 µg/ml or 1000 µM. If none of the concentrations of test agents exhibited cytotoxic effect in excess of 50% of cell populations, the test agent is considered non-toxic against the tested cell line. In this study, viability of 3T3F442A adipocytes and L6 myotubes was more than 50% after 72-hours treatment indicating that DiaBetter™ is not toxic against such cells.
CONCLUSIONS
This study showed that DiaBetter™ possess post meal antihyperglycemic and glucose tolerance activity in diabetic rats and these activities are mediated through enhancement of glucose uptake into muscle and adipocytes cells. The insulin-sensitizing properties possess by DiaBetter™ indicated that this herbal product has the potential to ameliorate systemic insulin resistance and may be beneficial for type 2 diabetes mellitus related to insulin-resistance.

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REFERENCES


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