PROTECTIVE EFFECT OF PANAX GINSENG AGAINST THIOACETAMIDE CYTOTOXICITY IN LIVER AND KIDNEY OF ALBINO RAT

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ABSTRACT

Thioacetamide (TA) has a deleterious effect on hepatocytes and kidney cells. TA administration is an established technique for generating rat models of liver fibrosis and cirrhosis. Panax ginseng root has an antioxidant and protective effect against many chemical and physical agents. In this study Panax ginseng roots with a dose of 117mg/kg was used for a period of 10 days prior to TA oral administration of 300 mg/kg sublethal dose.

TA highly affected liver and kidney of rats. Previous starvation for 24, 48 and 72 hours immediately to TA administration strongly potentiated the effect of TA on the tissue injury of liver and kidney. The histopathological observations indicated highly disturbed hepatic portal area and marked hyperplasia in liver of rats while the damage of kidney involved areas of internal haemorrhage, disrupted and swollen cells of convoluted tubules and lobulated atrophied glomeruli.

The obtained results showed that pre-treatment with Panax ginseng roots partially improved or modulated the pathological changes induced by TA intoxication in the liver while no significant protective effect in kidney cells has been detected against cellular damages of TA. This work aimed to evaluate the protective effect of Panax ginseng roots against the destructive effect of TA.

Histochemical analysis of total protein showed that administration of TA induced depletion of liver and kidney proteins while pretreatment with ginseng improved the protein contents.

Keywords: Panax ginseng - Thioacetamide -

INTRODUCTION

Thioacetamide (TA) is a model hepatotoxin activated by biotransformation to toxic metabolites thus leading to centrilobular liver necrosis (Hunter et al., 1997& Kucera et al., 2004 and Low et al., 2004). High doses of TA inhibited tissue healing and caused hepatic necrosis (Mangipudy et al., 1995a & 1996), Bussi et al. (2005) reported that liver damage had occurred after the rats were subjected to chronic treatment with TA (300 mg/kg) for two months. Low doses of TA stimulated cell division and tissue healing in liver (Mangipudy, 1995b). Raja et al.(1998) studied TA hepatotoxicity, they found that light microscopic examination of liver sections revealed apoptotic bodies early as 2 hours after TA administration, they also noticed that lower doses of TA seemed to cause cell death via apoptosis and higher doses caused cell death via necrosis. Clawson et al. (1997) observed microscopic foci of hepatic injury in liver of rats treated with TA 48 hours post treatment. These foci were surrounded by a peripheral rim of histologically normal hepatocytes which contained enlarged nuclei.

TA has a deleterious effect on hepatic cells. It can also induce intestinal endotoxemia in which the liver injury is prominent. (Liu et al., 2000). Theocharis et al. (2000) reported that TA administration in rats caused severe hepatic injury. Liver cirrhosis in rats induced by TA was characterized by altered lipid and protein metabolism and an excessive accumulation of extracellular matrix components (Perez et al. 2004). At 24, 36 hours post TA administration, intense nuclear and cytoplasmic staining of hepatocytes were found in vicinity of necrotic area with the peak of hepatocyte proliferate capacity occurring at 48&60 hours post TA administration. TA also induced hepatic fibrosis in mice (Schnur et al., 2005). On the other hand, Cruz et al. (2005) reported that, melatonin prevents experimental liver cirrhosis induced by TA in rats.

A lot of researches studied the protective effect of some materials against TA. toxicity. Kucera et al. (2004) studied the protective effect of adenosyine thionine (SAME) against TA hepatotoxicity, results indicated that (SAME) protected hepatocytes rather by stabilization of mitochondrial and cellular membranes than by direct inhibition of lipid
peroxidation or prevention of glutathione depletion. Administration of Nigella sativa protected rats from the hepatic toxicity of TA (Osman, 2004) where the protein values of the liver of Nigella sativa treated rats were approximately as control values.

_Ginseng_ is a plant of medical importance and it has been used by elderly Asian to boost physical and mental vitality (Kiritikar & Basu, 1987). The biological name is _Panax ginseng_. The most important part of _ginseng_ is the root and its chemical constituents are arabinose, comphor mucilage, resin, starch and saponin (Food & drug administration, 1999).

Panax ginseng is a potent antioxidant since it acts as an active free radical scavenger (Xiaoguang et al., 1998) it reduces tissue damage, reinforces the immune system and helps to keep blood sugar levels under control (Kitts, 2000). It has been reported that _ginseng_ can reduce chromosomal aberration induced by some chemicals (Umnova et al., 1991).

_Panax ginseng_ increases immune functions of lymphocytes in eldest (Lin et al., 1995), promotes the phagocytic activity and enhances the mutagenesis of T&B lymphocytes primed by mitogene (Yang & Fu., 1999). In another study _ginseng_ exerted a stimulating effect on DNA repair synthesis and had an inhibitory effect on cellular transformation (Rhee et al., 1990). Moustafa & Tohamey (2002) reported that TA administration of _Panax ginseng_ roots for a period of 10 days prior to TA administration performed protective effect against TA toxicity and manifested marked improvement in the liver functions and structure of testis and epididymis.

The purpose of this study was to evaluate the potential protective action of _Panax ginseng_ root against thioacetamide TA toxicity particularly on liver and kidney of adult male rats.

**MATERIALS AND METHODS**

Male albino rats (_Rattus norvegicus_) weighting 120-150 g, were used in this study. Rats were kept on a fixed balanced diet (Hegested et al. 1940 & Campbell, 1961), and were divided into 8 groups of 8 animals each for the treated groups. Rats were left as follows:

*Group 1:* control received 0.9% Nacl – Tween 80 for uniform suspension daily for 10 days (35 rats).

*Group 2:* was treated with _Panax ginseng_ (117 mg/kg b.w.). The dose was selected according to (Cui, et al. 1998).

*Group 3:* (TA 24): was treated with (300 mg/kg b.w.) TA daily for 12 weeks and dissected after 24 hours, the dose was selected according to (Bassi et al., 2005).

*Group4:* (G + TA 24): was treated with (300 mg/kg b.w.) TA daily for 12 weeks, and with _Panax ginseng_ (117 mg/kg b.w.). 10 days before TA administration and dissected after 24 hours.

*Group 5:* (TA 48): was treated with (300 mg/kg b.w.) TA daily for 12 weeks and dissected after 48 hours.

*Group 6:* (G + TA 48): was treated with (300 mg/kg b.w.) TA daily for 12 weeks and _Panax ginseng_ (117 mg/kg b.w.) 10 days before TA administration and dissected after 48 hours.

*Group 7:* (TA 72): was treated with (300 mg/kg b.w.) TA daily for 12 weeks and dissected after 72 hours.

*Group 8:* (G + TA 72): was treated with (300 mg/kg b.w.) TA daily for 12 weeks, and _Panax ginseng_ (117 mg/kg b.w.) 10 days before TA administration and dissected after 72 hours.

The dose of 300mg/kg TA was dissolved in saline solution (0.9% Nacl-Tween 80 for uniform suspension). Rats were left 2 days after the end of TA treatment. Ultra pure chemicals were used in this study and obtained from Sigma Chemicals Company. Powder of _Panax_ root (aqueous extract) was used freshly prepared and suspended in distilled water. It was given orally by stomach tube, and was obtained from IPECO Company 10th of Ramadan city, Egypt.

For histopathological studies livers and kidneys were surgically removed from the different groups of rats, then fixed immediately in neutral buffer formol, paraffin sections (5µ) were stained with haematoxylin and eosin (Drury & Wallington, 1980). For histochemical studies, bromophenol stain was used to demonstrate protein (Mazia et al., 1953). The histochemical interpretation was done using computer image analyzing system (Leica Model). Estimation of the optical density of thirty cells in each group was made. The data obtained were statistically analyzed according to Snedecor (1987). Differences between the group means were assessed using _t_-test. _p_< 0.05 was considered significant, and the percentage of change was calculated as follows:

\[
\text{Percentage of change %} = \frac{\text{Data of treated} - \text{Data of control}}{\text{Data of control}} \times 100
\]

**RESULTS**

1.A) Histopathological changes in liver's rats:

The normal histological structure of liver (Group 1) was observed in (Fig. 1) Showing normal appearance of hepatic strands, hepatocytes, sinusoidal spaces and Kupffer cells. Treatment of rats with ginseng (Group 2) showed well developed hepatocytes, central vein with endothelial lining, blood sinusoinds and Kupffer cells (Fig. 2).

Liver sections obtained from rats belonging to Group 3 (TA24) showed highly histopathological changes in the hepatic tissue. These changes were manifested in disturbed hepatic portal area with thickened wall of arteries and veins, also dilated central vein with ruptured endothelial lining and congested hepatic portal vein which was...
surrounded by monocellular infiltration. Irregular wall of bile canaliculi, signs of haemolysis and haemorrhagic area were detected (Fig. 3).

Liver sections of Group 4 (G + TA 24) showed that hepatocytes had normal architecture, however some aggregations of inflammatory cells still surrounded the dilated congested hepatic portal vein. Central vein had also normal structure (Fig. 4). Group 5 (TA 48) showed disturbed portal area with highly affected blood vessels, dilated sinusoidal spaces and marked hyperplasia (Fig. 5).

Group 6 (G + TA 48) displayed normal appearance of hepatocytes in spite of thickened wall of the hepatic portal vein, highly reduced bile canaliculi, moderate cellular infiltration and hyperplasia with intense reaction (Fig. 6).

Group 7 (TA 72). Signs of destruction in hepatocytes, highly elongated hepatic portal vein with condensed cellular infiltration and dilated sinusoidal spaces were detected in (Fig. 7).

Inspected liver sections obtained from group 8 (G+TA 72) showed improvement as proved by the appearance of normal hepatocytes while few were faintly stained with affected nuclei. The central vein appeared normal (Fig. 8).

1.B) Protein content in control and treated liver's rats:

Normal distribution of protein in liver of control rat group (1), and (Fig. 9) reached 172.7±15.38 Pixel. In contrast, in group (2), total protein of liver cells revealed an increase of 5.39 % (Table 1). On the other hand, groups 3 (TA 24), 5 (TA 48), and 7 (TA 72) revealed deep stainability with bromophenol blue particularly importal area and endothelial lining of the central vein with adjacent area around it while some hepatocytes lost their staining ability (Figs. 11&13). Total protein in these groups recorded 138, 140.7 and 148 pixel with a significant decrease reaching 20.093, 18.529 and 14.302 respectively. The other three groups 4 (G+TA 24), 6 (G + TA 48), and 8(G+TA 72) showed signs of increase stainability in some central hepatocytes when compared to the peripheral ones (Fig. 12). Intense reaction for protein was observed in endothelial lining, bile canaliculi, and many hepatocytes while peripheral ones appeared faintly stained (Fig. 14). As shown in table (1) total protein decreased in group 4 and 6 (10.246 and 4.884) and increased in group(8) to reach 179.6 pixel in contrast to control.

2.A) Histopathological changes in kidney’s rats:

Group 1 showed normal structure of rat kidney (Fig. 15). Group (2) illustrated well developed glomerulus Bowman’s capsule, proximal and distal convoluted tubules (Fig. 16). Group(3) (TA 24) revealed area of internal haemorrhage and few disrupted convoluted tubules. Some atrophied glomeruli were also detected (Fig. 17). Similar injury was observed in groups 5 and 7 besides bleeding especially around the small arteries, some swelled cells of convoluted tubules and lobulated atrophied glomeruli (Figs. 19&21).

In group 4 (G + TA 24), some convoluted tubules appeared normal while others were still affected with large haemorrhagic areas and hypertrophied glomeruli (Fig. 18). Group 6 (G + TA 48) revealed internal haemorrhage, hypertrophied glomeruli, thick wall arteries with narrow lumen and elongated nuclei of endothelium while some tubules appeared normal (Fig. 20). In group(8) (G + TA 72), no signs of recovery have been detected where internal haemorrhage, hypertrophied glomeruli, disturbed and faintly stained tubules still existed except for some tubules which appeared normal (Fig. 22).

Table (1): Illustrating statistical analyses of the quantitative measurements (pixel) of the total protein in liver and kidney cells of control and treated white rats strains.

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<th>Control</th>
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Fig. (1): Section in control liver of a rat showing normal appearance of hepatocytes, sinusoidal spaces (S) and Kupffer cells (K). (Hx. & E, X 400)

Fig. (2): Section in liver of a rat treated with ginseng showing well developed hepatocytes, central vein with endothelial lining (→), blood sinusoids (S) and Kupffer cells (K). (Hx & E, X 400).

Fig. (3): Section in liver of rat treated with TA and dissected 24 hours post treatment,

Fig. (4): Section of liver rat group (4) shows that hepatocytes almost have normal architecture, in spite of some aggregation of inflammatory cells still surrounds the dilated and congested hepatic portal vein, thick and irregular wall of the artery(→) (Hx. & E, X 200).

Fig. (5): Section of liver of rat treated with TA and dissected 48 hours post treatment, notice highly dilated sinusoidal spaces, some hepatic cells appeared normal, others contain pyknotic nuclei, the remnant contained karyolitic nuclei (→) and marked hyperplasia could be detected also (Hx. & E, X 200).

Fig. (6): Section of liver of rat treated with TA and ginseng dissected 48 hours post treatment (G 6), shows normal appearance of hepatocytes in spite of thickened wall of the hepatic portal vein, highly reduced bile canaliculi and cellular infiltration (Hx. & E, X 200).
Fig. (7): Section of liver of rat treated with TA and dissected 72 hours post treatment shows signs of destruction in hepatocytes, highly elongated hepatic portal vein with condensed cellular infiltration and haemolysed blood corpuscles with dilated sinusoidal spaces (s). (Hx. & E, X 200).

Fig. (8): Section of liver of rat treated with TA and ginseng 72 hours post treatment shows normal appearance of most hepatocytes, few appeared faintly stained with affected nuclei (→) and the central vein acquired the normal appearance. (Hx. & E, X 400).

Fig. (9): Section of liver of control rat showing moderate +ve bromophenol reaction in hepatocytes. (bromophenol blue x200)

Fig. (10): Section of liver of rat treated with ginseng shows moderate stain ability of protein in hepatocytes with slight increase around the central vein. (bromophenol blue X 200).

Fig. (11): Section of liver of rat treated with TA + ginseng and dissected after 24 hours shows deeply stained portal area (bromophenol blue x200)

Fig. (12): Section in liver of treated rat with TA and ginseng dissected after 48 hours, shows signs of hyperplasia are accompanied by intense stain ability and so WBCs (bromophenol blue X 200)
Fig. (13): Section in liver of rat treated with TA and dissected after 72 hours post treatment, shows poorly stained hepatocytes and moderate staining around the central vein (bromophenol blue x200).

Fig. (14): Section in liver of rat treated with TA and ginseng and dissected after 72 hours post treatment, shows faintly stained peripheral hepatocytes (bromophenol blue x200).

Fig. (15): Section in kidney of control rat showing normal structure of kidney (Hx. & E, X 400).

Fig. (16): Section in kidney of rat treated with ginseng showing well developed glomerulus, Bowman’s capsule proximal and distal convoluted tubules (Hx. & E, X 400).

Fig. (17): Section in kidney of rat treated with TA and dissected 24 hours post treatment showing areas of internal haemorrhage with haemolysed blood corpuscles. Few convoluted tubules are disturbed while the remnants are normal or faintly stained. Some cells of convoluted tubules appeared vacuolated with debris of granulated chromatin (Hx. & E, X 200).

Fig. (18): Section in kidney of rat treated with ginseng and dissected 24 hours after treatment, showing that some convoluted tubules appeared normal while others are still affected with large haemorrhagic area. Most glomeruli appeared hypertrophied (Hx. & E, X 200).

Fig. (19): Section in liver of rat treated with TA and dissected after 72 hours post treatment, shows poorly stained hepatocytes and moderate staining around the central vein (bromophenol blue x200).

Fig. (20): Section in liver of rat treated with TA and ginseng and dissected after 72 hours post treatment, shows faintly stained peripheral hepatocytes (bromophenol blue x200).

Fig. (21): Section in kidney of control rat showing normal structure of kidney (Hx. & E, X 400).

Fig. (22): Section in kidney of rat treated with ginseng showing well developed glomerulus, Bowman’s capsule proximal and distal convoluted tubules (Hx. & E, X 400).

Fig. (19): Section in kidney of rat treated with TA and dissected 48 hours post treatment showing internal bleeding especially around the small arteries, this bleeding occupied the degenerated convoluted tubules. Some glomeruli appeared lobulated, others are atrophied. Some cells of convoluted tubules are swelled and faintly stained (Hx. & E, X 200)

Fig. (20): Section in kidney of rat treated with TA and ginseng 48 hours post treatment showing internal haemorrhage, large degenerated areas contained debris of destructed tubules and some tubules appeared normal, hypertrophied glomeruli, thick wall of arteries with narrow lumen and elongated nuclei of endothelium (Hx. & E, X 200)

Fig. (21): Section in kidney of rat treated with TA and dissected 72 hours post treatment, showing that internal haemorrhage occupied the destructed convoluted tubules (Hx. & E, X 200)

Fig. (22): Section in kidney of rat treated with TA and ginseng 72 hours post treatment showing internal haemorrhage, disturbed tubules with faint staining others appear normal and hypertrophied glomeruli. (Hx. & E, X 200)

Fig. (23): Section in kidney of control rat, showing normal stain ability of protein (bromophenol blue X 200).

Fig. (24): Section in kidney of rat treated with ginseng showing deeply stained glomeruli with less stained Bowman's capsules and convoluted tubules (bromophenol blue X 200).
Fig.(25): Section in kidney of rat treated with TA and dissected 24 hours post treatment showing moderate reaction in the lobulated glomeruli and some arteries while tubules are less stained and the remnant are faintly stained (bromophenol blue X 200)

Fig.(26): Section in kidney of rats treated with TA and *ginseng* and dissected after 24 hours, shows deeply stained artery and bizarre debris of destructed tubules, some of the adjacent tubules are deeply stained and the most of them are faintly stained (bromophenol blue x200)

Fig.(27): Section in kidney of rat treated with TA and dissected 48 hours post treatment showing deeply staining of thick walled artery, basement membrane and brush border of the adjacent tubules (bromophenol blue X 200)

Fig. (28): Section in kidney of rat treated with TA and *ginseng* and dissected 48 hours after treatment, showing decreased reaction in hypertrophied glomeruli and most of convoluted tubules, (bromophenol blue x200)

Fig.(29): Section in kidney of rat treated with TA and dissected 72 hours post treatment, shows very weak reaction inside the tubules and glomeruli. (bromophenol blue x200)

Fig.(30): Section in kidney of rat treated with TA and *ginseng* and dissected 72 hours post treatment, shows weak reaction in most tubules and glomeruli. (bromophenol blue x200)
2.B) Protein content in control and treated kidney's rats:

Groups (1, 2) showed normal distribution of protein in rats kidney in Figs.23& 24 recorded 166.7 and 167.9 Pixel respectively. Groups 3 (TA 24), 5 (TA 48) and 7 (TA 72) revealed moderate reaction in the lobulated glomeruli and in some arteries while tubules were less stained (Figs. 25, 27 &29). Total protein decreased significantly and its depletion reached 39.112, 31.314 and 26.395%, respectively (Table 1). Groups 4 (G+TA 24) and 6 (G + TA 48) revealed deeply stained artery, most of the convoluted tubules appeared faintly stained whereas glomeruli were moderately stained and total protein recorded 131 and 142.9 pixel respectively (Figs. 26 & 28 and Table 1). Group 8 (G+TA72) revealed decreased stainability of hypertrophied glomeruli and convoluted tubules while blood corpuscles were deeply stained, (Fig. 28). A decrease in protein reaction was recorded (138.1 pixel) with a non-significant decrement reaching 7.157% (Table 1).

DISCUSSION

Thioacetamide is well known as hepatotoxic and hepatocarcinogenic agent (Hunter et al., 1997). TA treatment resulted in striking loss of specific liver plasma membrane enzymatic activity which caused cell death (Nikolaev et al., 1986). Ramaiah et al. (1998), found that necrotic hepatocytes following administration of TA (50mg/kg) were started at 12 hours in rats a fact which was concordant with plasma enzyme elevation. TA administration caused hepatic damage creating oxidative and nitrosative stress accompanying perivenous necrosis and lymphocytic infiltration. The significant elevation of total nitrite level in livers of TA treated rats reflected the activation of inducible nitric oxide synthase activity (Karaby et al., 2005). According to the present study, histological lesions in liver and kidney were detected after 24, 47&72 hours post treatment of TA, this was observed by disturbed hepatic portal area including thickened walls of arteries and veins, dilated and congested hepatic portal vein and central vein, irregular wall of bile canaliculi, signs of haemolysis, cellular infiltration, marked hyperplasia, haemorrhagic areas and dilated sinusoidal spaces. However the histological lesions in kidney of rats involved areas of internal haemorrhage especially around small arteries, swelled and disturbed cells of convoluted tubules. Some glomeruli were lobulated and atrophied.

Masumi et al. (1999) observed that the livers taken from rats treated with TA for 12 weeks and studied 4 weeks after the end of the 12 weeks developed many micronodules of various sizes in all lobules. These nodules were separated by areas showing marked proliferation of collagen fibers resulting in the formation of pseudolobules which represented the cirrhotic features of livers.

The present study detected the beginning of the nodular cirrhosis after 48 hours from the end of the TA treatment and marked hyperplasia. Moustafa and Tohamey (2002) attributed the increased serum transaminase, alkaline and acid phosphatase 48 hours and 72 hours after TA administration and the decrease in synthesis of testis glutathione, to the hepatocellular damage induced by TA.
where glutathione was considered as a control to the antioxidant defense system of the cell.

Marked depletion in protein content was observed in livers and kidneys in the present study gradually 24, 48&72 hours post treatment with TA. These results were in agreement with Huang *et al.* (1999) who noticed that TA treatment for 3 weeks reduced the liver specific protein level to below 30% of control.

Panax ginseng inhibited the development of liver cirrhosis in TA treated rats. The mechanism of action was associated with decreased oxidative stress and hepatic necroinflammation (Perez *et al.*, 2004).

In the present study, injection of rats with ginseng prior to TA administration partially improved the picture of liver where hepatocytes and central vein almost acquired the normal appearance, in spite of the disturbance of hepatic portal area which revealed some aggregation of inflammatory cells surrounding the dilated congested hepatic portal vein and atrophied bile canaliculi. This was in agreement with Moustafa and Tohamy (2002) they reported that the administration of panax ginseng for a period of 10 days prior to TA treatment in rats performed protective effect against TA toxicity and manifested marked improvement in liver function and structure of testis and epididymis.

No significant improvement could be seen in the kidneys of rats treated with ginseng prior to administration of TA, except some convoluted tubules which appeared normal. Moreover, internal haemorrhage occupied the destructed convoluted tubules, glomeruli were congested and hypertrophied, also thickened walls of arteries with elongated endothelium nuclei have been detected.

In the present study, improvement in protein content could be detected in the liver of rats treated with ginseng prior to TA administration while kidney showed weak reaction. However, in another study, Morsy (2002) noticed an increase in PAS +ve material in kidney of rats treated with ginseng for 8 weeks.

Panax ginseng was found to exert a stimulatory effect on DNA repair synthesis and had an inhibitory effect on mutagenicity and cellular transformation (Nishino *et al.*, 2001). Moreover it had a promoting action on RNA synthesis in diabetic rats (Yokozawa *et al.*, 1996). Ginseng has a chemopreventive and therapeutic action and could enhance immune function prosperities (Xiaoguang *et al.*, 1998 & Shin *et al.*, 2000). Lee *et al.* (2002) stated that ginseng might reduce cell damage induced by toxic substances and acted to stabilize cell membranes by providing protection against toxic agents induced tissue injury.

Proteins constitute a major part of the living protoplasm of animal cells. The function of protein is not only to supply energy but also to maintain nitrogen balance and furnish certain essential components of the living tissue to the organism, the formation of enzymes, certain hormones and other physiologically important compounds.

The major function of liver is the protein synthesis as production of albumin, plasma transport proteins and clotting factors. Kidneys remove the end product of protein metabolism and are the major sites of production of certain hormones and degrade several polypeptide hormones including insulin, glucagon and parathyroid hormones. Thioacetamide induced a marked reduction of the total protein in livers and kidneys of rats. It was apparent that there is a dose response relationship regarding the proteinic constituents of the cells.

Depletion of proteins observed in livers and kidneys treated with TA could be attributed at least partly to the hyperactivity of the hydrolytic enzymes liberated under TA effect and an excessive accumulation of extracellular matrix components.

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