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Investigating the Cardio-protective Activity of *Agaricus bisporus* in Wistar Rats Induced with Myocardial Infarction

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Myocardial infarction is now recognized as one of the chronic diseases and the leading cause of death across the globe. The use of plants abundant in our environment, especially *Agaricus bisporus*provides a cheap alternative to combat this common foe of mankind. Hence, this study was carried out to evaluate the cardio-protective effect of the leaf extract of *Agaricus bisporus* in isoproterenol-induced myocardial infarction. Fresh sample of *Agaricus bisporus* were purchased from a market at Asaba, Delta State, Nigeria. The samples were thereafter shredded with a knife and oven-dried at 40^{o}C and pulverized and extracted, using Solvent-solvent (ethanol and water)

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(7:3) via maceration for 72 hr. The filtrate was evaporated to dryness to obtain the ethanol extract which was used for further bioassay study. The animals were administered with the extract of *A. bisporus* orally for fourteen consecutive days at a divided dose of 100 mg/kg, 200 mg/kg and 400 mg/kg body weights and thereafter 0.2 ml isoproterenol (ISO) at 150 mg/kg was injected intraperitoneally at an interval of 24 h on the 15th and 16th day. Subsequently, the blood pressures were monitored and blood collected for bioassay studies. Assay of High density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), triglyceride (TG) and total cholesterol (TC) levels as well as activities of lactate dehydrogenase (LDH), were carried out with standard assay kit sourced from Randox laboratories Ltd, United Kingdom with maximum adherence to the manufacturer's instruction. Results showed a significant increase ($P<0.05$) in high density lipoproteins (HDL) levels and lactate dehydrogenase (LDH) activities with a significant decrease ($P>0.05$) in low density lipoproteins (LDL) and triglyceride levels in a dose-dependent manner ($100<200<400$ mg/kg body weight) among the extract treated groups when compared to the untreated control group. Conversely, total cholesterol levels of extract treated groups showed no significant difference when compared with the untreated control group.The findings of this work have shown that extract of *Agaricus bisporus* could help to mitigate cardiovascular diseases and could be used to produce plant based products to combat myocardial infarction, thereby improving general wellbeing.

Keywords: Agaricus bisporus; chronic disease; lactate dehydrogenase; myocardial infarction.

1. INTRODUCTION

Myocardial infarction (MI), sometimes referred to as Heart attacks, are a major cause of death globally, emphasizing the critical need for efficient treatment alternatives. Interest in natural substances with possible health advantages has increased despite the fact that breakthroughs in pharmacological treatments have greatly increased survival rates [1]. However, these medications frequently have side effects and do not entirely restore heart function. Myocardial infarction (MI) is caused by decreased or complete cessation of blood flow to a portion of the myocardium [2]. Myocardial infarction may be "silent" and go unnoticed, or it could be an obvious event, leading to hemodynamic deterioration and sudden death [3].

Most myocardial infarctions are due to underlying coronary artery disease, the leading cause of death in the United States. With coronary artery occlusion, the myocardium is deprived of oxygen. Prolonged deprivation of oxygen supply to the myocardium can lead to myocardial cell death and necrosis [4]. Patients can present with chest pain or pressure that can get to the neck, jaw, shoulder, or arm. In addition to the history and physical exam, myocardial ischemia may be associated with ECG changes and elevated biochemical markers such as cardiac troponins [5].

Agaricus bisporus, or White button mushrooms, are valued for their nutritional and therapeutic qualities. They are abundant in anti-inflammatory and antioxidant compounds [6]. According to earlier studies [6,7], these substances have the ability to alter immune responses and may provide protection against a number of illnesses, including cardiovascular disorders.

Less research has been done on *A. bisporus's* direct contribution to cardiovascular health, particularly in the context of myocardial infarction. This study aims to investigate whether *A. bisporus* can improve cardiac recovery and function after myocardial infarction by delivering various concentrations of *A. bisporus* extract and evaluating cardiac function and tissue pathology.

Observations from this could indicate potential applications outside conventional medicine by providing information on dietary or supplement-based strategies that may reduce myocardial damage and speed cardiac recuperation.

2. MATERIALS AND METHODS

2.1 Sample Collection and Preparation

Fresh sample of *Agaricus bisporus* were purchased from a market at Asaba, Delta State, Nigeria. Identification and authentication of the fungi was carried out at the Department of Botany, Nnamdi Azikiwe University, Awka and a voucher specimen was deposited at the herbarium of the Department for futurereferences. The samples were thereafter shredded with a knife and oven-dried at 40^{o}C in

order to get rid of the moisture as well as preserve the bioactive compounds. The dried sample was pulverized using a laboratory blender and the fine powders obtained was weighed and stored in an air-tight container at room temperature for further use.

2.2 Extraction of Sample Materials

The weighed powdered sample (200.60 g) was then used for the extraction with a solvent combination of ethanol and water (7:3) (2000 ml) for 72 hr via maceration in an unheated medium. The mixture was decanted and filtered using sterile Whatman paper No. 1. The filtrate was there after evaporated to dryness with the aid of a rotary evaporator set at 50 ^{o}C to obtain crude ethanol extract which was carefully preserved for further analysis. The method of Nkafamiya et al. [8] was used to calculate the yield (10.05 g) of the crude extract using the formula below:

$$\text{Percentage yield} = \frac{Mass of crude extract\ (g)}{Mass of powdered sample\ (g)} \times 100$$

2.3 Animal Studies

2.3.1 Procurement of study animals

Wistar albino rats (30) weighing approximately 180 g were purchased from Chris Farm Ltd Mgbakwu, Awka, Anambra State and were brought to the animal house of the Department of Applied Biochemistry, Nnamdi Azikiwe University, Awka. The rats were kept in standard cages with saw dust as bedding, and at standard room temperature as well as standard housing conditions of 12:12 light: dark cycles and fed with standard rat pellets and water *ad libitum*. The animals were allowed to acclimatize to the new environment for seven days.

2.3.2 Dose preparation and treatment

The hydro-ethanolic extract of *A. bisporus* was prepared with distilled water in three divided doses (100, 200, and 400) mg / kg, lisinopril (10 mg/kg) was used as a reference drug and distilled water was used as a vehicle for the untreated group. The animals were administered the extract and drug orally for fourteen consecutive days concurrently prior to the induction with water *per os* and feed *ad libitum*.

2.3.3 Experimental design

The animals were randomly grouped into five, with six animals in each group, and the treatment was as follows: Groups A, B and C animals were designated as *A. bisporus* treatment group and were pre-treated with the ethanol extract at 100 mg/kg, 200 mg/kg and 400 mg/kg, respectively, for 14 days and thereafter 0.2 ml isoproterenol (ISO) at 150 mg/kg was injected intraperitoneally at an interval of 24 h on the 15th and 16th day. Group D animals were designated as isoproterenol control and were administered 0.2 ml of 10 mg lisinopril for 14 days and thereafter 0.2 ml isoproterenol (ISO) at 150 mg/kg was injected intraperitoneally at an interval of 24 h on the 15th and 16th day while group E animals (designated as vehicle control group) were administered 0.2 ml distilled water for 14 days; and on the 15th and 16th day, 0.2 ml isoproterenol (ISO) at 150 mg/kg was injected intraperitoneally at an interval of 24 h.

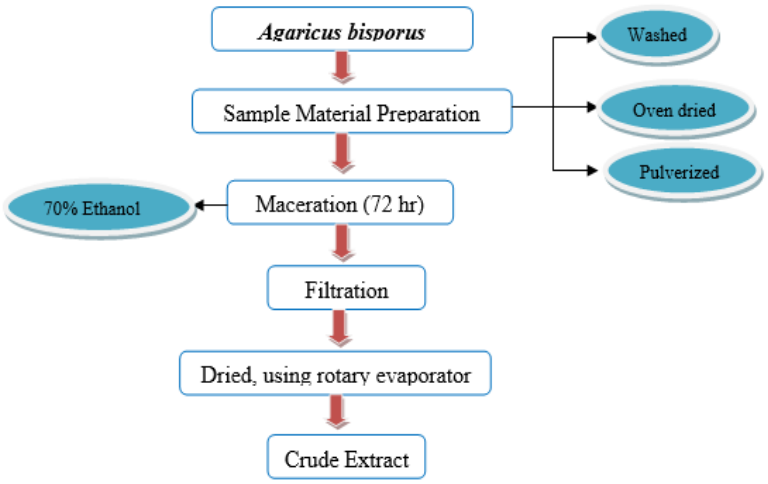

Fig. 1. Procedure for the extraction of *Agaricus bisporus* crude extract

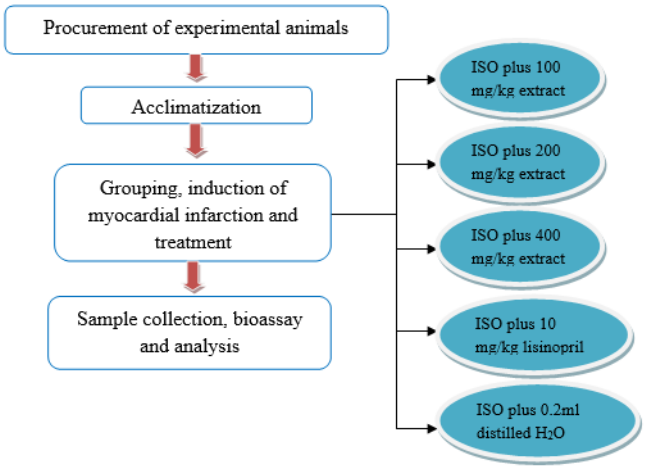

Fig. 2. Experimental design of the study (*In vivo*)

2.3.4 Collection of blood sample

At the end of the experimental period, the animals were anesthetized with chloroform vapor and sacrificed. A 5 ml sterile syringe with needle was used for blood collection through cardiac puncture and the sera obtained were used for bioassay studies.

2.3.5 Biochemical assays

Assay of High density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), triglyceride (TG) and total cholesterol (TC) levels as well as activities of lactate dehydrogenase (LDH), were carried out with standard assay kit sourced from Randox laboratories Ltd, United Kingdom with maximum adherence to the manufacturer's instruction.

2.4 Data Analysis

The results obtained in this research were expressed as Mean ± SEM of triplicate determinations within each group. One-way analysis of variance (ANOVA) was carried out on the results and significance was accepted at $p<0.05$. GraphPad Prism5 Program (GraphPad Software, San Diego, CA, USA) was used for the graphical analyses of the results obtained.

3. RESULTS

The findings from this study are presented in Figs. 3 through 7. The result revealed a

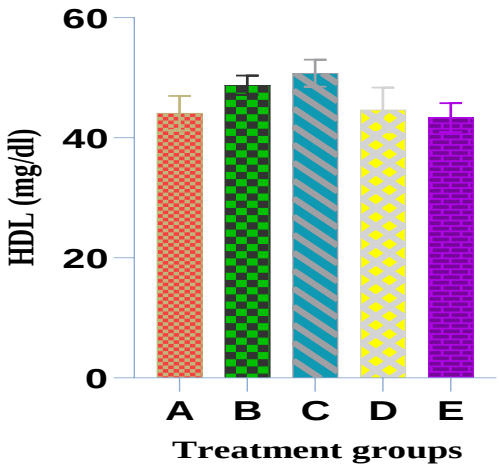

Fig. 3. Effect of oral administration of the leaf extract of *Agaricus bisporus* on lactate high density lipoprotein (HDL) levels in wistar rats induced with acute myocardial infarction

significant increase (P>0.05) in HDL levels levels and lactate dehydrogenase activities (Figs. 3 and 7) but a decrease in LDL levels, triglyceride (Figs. 4 and 5) levels among the group treated with the extract, in a dose-dependent manner when compared to the untreated control group (group D). Conversely, total cholesterol levels (Fig. 6) of extract treated groups showed no significant difference when compared with the untreated control group (group D).

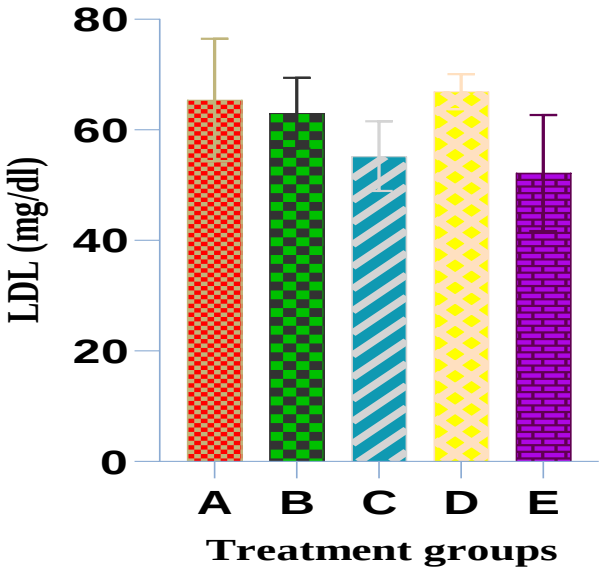

Fig. 4. Effect of oral administration of the leaf extract of *Agaricus bisporus* on low density lipoprotein (LDL) levels in wistar rats induced with acute myocardial infarction

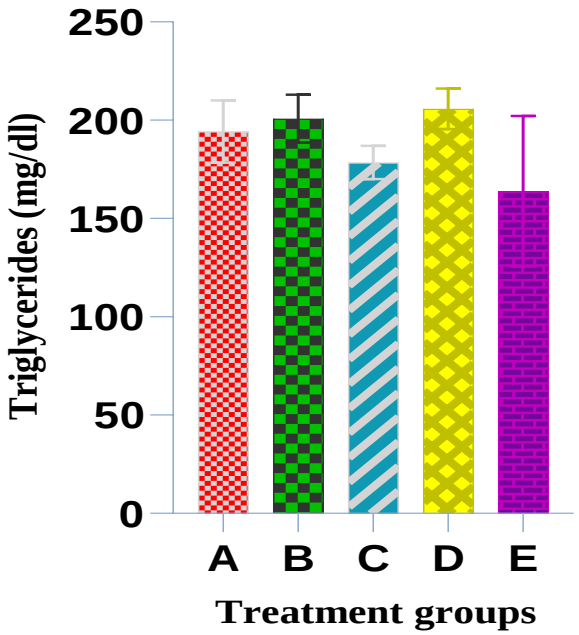

Fig. 5. Effect of oral administration of the leaf extract of *Agaricus bisporus* on triglyceride (TG) levels in wistar rats induced with acute myocardial infarction

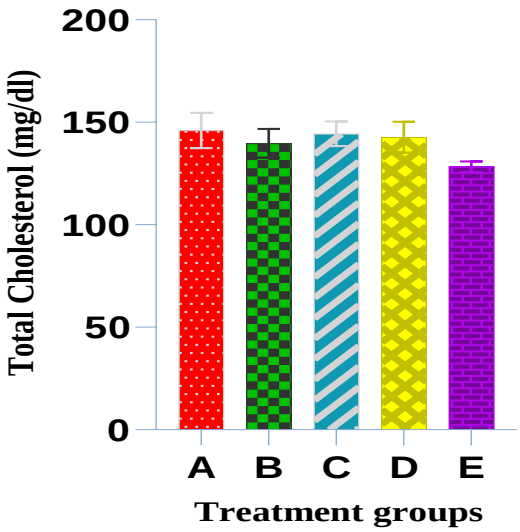

Fig. 6. Effect of oral administration of the leaf extract of *Agaricus bisporus* on total cholesterol (TC) levels in wistar rats induced with acute myocardial infarction

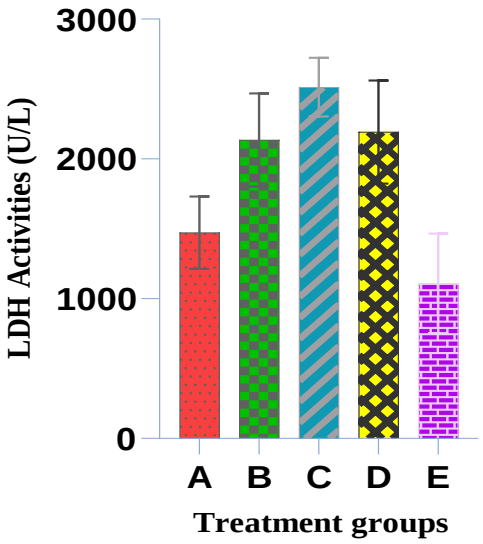

Fig. 7. Effect of oral administration of the leaf extract of *Agaricus bisporus* on lactate dehydrogenase (LDH) activities in wistar rats induced with acute myocardial infarction

4. DISCUSSION

For thousands of years, medicinal compounds have been found in nature. Medicinal substances derived from plants and fungi have been essential for maintaining human health since ancient times. A valuable natural food and medicinal source are mushrooms (*Agaricus bisporus)*. Local indigenes have long recognized the value of edible and wild mushrooms, which are currently being tested for their potential therapeutic use, especially on myocardial infarction.*Agaricus bisporus* possesses cardioprotective efficacy through many pathways, including as antioxidant [4,9], anti-inflammatory [10,11] and lipid-modulating properties [2,12]. These mechanisms work together to enhance the plant's ability to prevent or mitigate myocardial infarction (MI).Using existing data and additional research, this study

was performed to investigate the potential cardioprotective effects of *Agaricus bisporus* leaf extract on myocardial infarction.

Generally, the result of this study revealed that *Agaricus bisporus* leaf extract has the ability to provide cardioprotective effects on myocardial infarction. Five critical biochemical parameters were examined to assess the impact of this treatment: high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), total cholesterol (TC), and lactate dehydrogenase (LDH).

Fig. 3 showed the effect of oral administration of the leaf extract of *Agaricus bisporus* on high density lipoprotein (HDL) levels in wistar rats induced with acute myocardial infarction.The findings of this study showed a significant increase in HDL levels within the *Agaricus bisporus* treated groups in a dose-dependent manner(100<200<400 mg/kg). HDL is widely recognized for its cardiovascular protective roles, largely due to its ability to facilitate reverse cholesterol transport and exert anti-inflammatory effects [13]. The increase in HDL aligns with studies suggesting that certain phytochemicals can enhance HDL functionality and concentration [14,15]. This increase in HDL levels could be attributed to the bioactive compounds in *Agaricus bisporus*, such as polysaccharides and ergosterols, which have been studied for their lipid-modulating activities [10]. A high level of HDL (“good”) cholesterol is often an indicator of a lower risk of cardiovascular disease, such as myocardial infarction. This increase in HDL levels of treated group as seen in Fig. 3 could be due to the inhibition of endothelial lipase; a form of lipase secreted by vascular endothelial cells in tissues with high metabolic rates and vascularization, such as the liver, lung, kidney, and thyroid gland, since endothelial lipase (EL) hydrolyzes phospholipids in high-density lipoprotein (HDL) resulting in reduction in plasma HDL levels [16]. This result of increased HDL by *Agaricus bisporus*being a risk-reducing factor for myocardial infarction also agrees with the findings of Uchiyama et al. [17] and Onwubuya et al. [2].

Low-density lipoprotein (LDL) cholesterol, often termed “bad cholesterol”, is a fat that circulates in the blood, moving cholesterol around the body to where it is needed for cell repair and depositing it inside the artery walls. Elevated low-density lipoprotein (LDL) cholesterol is a causal risk factor for the development of atherosclerosis and drives an increased risk of both myocardial infarction and early death [18]. The reduction in LDL levels in a dose-dependent manner (100>200>400 mg/kg) observed in the extract-treated groups compared to the untreated control (Fig. 4) suggests significant anti-cardiovascular properties of *Agaricus bisporus*. The LDL level reduction could be achieved through the bioactive compounds in *Agaricus bisporus*, such as B—glucans. β-glucans found in dietary sources like oats and mushrooms reduce LDL cholesterol levels through multiple mechanisms, such as the inhibition of cholesterol absorption in the intestine by forming viscous gels and enhance bile acid excretion from the liver, as evidenced in a study by Bell et al. [19]. Additionally, β-glucans upregulate hepatic LDL receptor expression, promoting LDL clearance from the bloodstream, as demonstrated by research conducted by Kim et al. [20]. This is supported by similar findings where LDL-lowering effects of*Agaricus bisporus* wasdemonstrated [12].

Likewise, the decrease in triglyceride levels among the treated groups (Fig. 5) is consistent with previous reports that have emphasized the efficacy of natural extracts in regulating lipid profiles [21]. Elevated triglycerides are independently associated with cardiovascular risk and are a target for pharmacological intervention [22]. The observed triglyceride-lowering effect could be due to the enhancement of lipase activity or inhibition of lipogenesis, a hypothesis supported by studies on similar fungal extracts [23]. Enhancement of lipase activity promotes the hydrolysis of triglycerides into glycerol and free fatty acids, thereby reducing triglyceride levels in the bloodstream. This process helps mitigate myocardial infarction by decreasing the substrate available for lipid accumulation in the coronary arteries, as supported by a research conducted by Bansal et al. [24]. The possibility of triglyceride-lowering effect through inhibition of lipogenesis is by the reduction of the synthesis of fatty acids, which are precursors for triglyceride formation, thus lowering triglyceride levels in the bloodstream. This mechanism mitigates myocardial infarction by decreasing the substrate available for lipid accumulation in the coronary arteries, as supported by researches such as that conducted by Brown and Rosner [25]. These research evidences could portray the cardioprotective effect of *Agaricus bisporus* through the lowering of triglyceride level.

On the contrary, the result in Fig. 6 showed no significant changes in total cholesterol levels of the treated group when compared to the untreated group. The National Heart, Lung, and Blood Institute defines total cholesterol as "the cumulative measurement of cholesterol content in the bloodstream, encompassing both high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol, with the normal range to be less than 200 mg/dL, borderline high as 200 to 239 mg/dL and high at or above 240 mg/dL. The lack of significant changes in total cholesterol levels might suggest that the primary effects of *Agaricus bisporus* extract are more targeted towards specific lipoprotein components rather than a broad spectrum cholesterol-lowering effect. This selective modulation could be particularly advantageous by avoiding the potential negative effects of excessively low cholesterol levels, such as hormonal imbalances and cognitive issues [26,27].

As presented in Fig. 7, there was an increase in lactate dehydrogenase (LDH) activity in the untreated group when compared to the treated group, in a dose-dependent manner (100<200<400 mg/kg). The increase in LDH activity observed in our study suggests an enhancement of cellular metabolism or a response mechanism to myocardial damage. LDH is an indicator of tissue damage and its elevation typically reflects ongoing cellular repair processes. The increase in LDH levels in response to the extract treatment could indicate enhanced turnover and repair of myocardial tissue, possibly facilitated by bioactive components of the extract such as its polysaccharide bioactivity, which could have protective effects against ischemic damage. This polysaccharide bioactive compound, particularly beta-glucans, has been demonstrated to modulate immune responses and cellular metabolism. Beta-glucans have been shown to trigger cellular activity, potentially causing an increase in LDH release as a consequence of enhanced metabolic processes [23,28,29].

5. CONCLUSION

The findings of this research have provided evidence for the cardioprotective efficacy of *Agaricus bisporus* extract against myocardial infarction. This can be drawn from its significant modulation of key biochemical parameters, including increasing high-density lipoprotein (HDL), decreasing low-density lipoprotein (LDL), particularly in the prevention and management of lipid-associated disorders, as well as triglycerides (TG). Cardioprotective effect wasalso achieved by inducing an adaptive response in lactate dehydrogenase (LDH) activity, underscoring its potential as a versatile therapeutic agent for cardiovascular health. Hence, *Agaricus bisporus* could serve as a form of amelioration to cardiovascular diseases, specifically myocardial infarction.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal Ethic committee approval has been collected and preserved by the author(s)

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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