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Frankincense Upregulates the *FMR1* Gene and Alleviates $AlCl_3$-Induced Memory Impairment in Rats

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ABSTRACT

Alzheimer's disease (AD) is a multifactorial disorder that its progress and development are related to various genetic and environmental factors. The disease onset is affected by both genetic and environmental factors such as oxidative stress, inflammation, and mitochondrial dysfunction, and is remarkably related to age progress. Aluminum, a neurotoxic environmental factor, impairs memory performance and can cause neurodegenerative diseases such as AD. On the other hand, the regulatory RNA-binding product of Fragile X mental retardation (*FMR1*) gene exerts a translational inhibitory effect on the expression of amyloid precursor protein (APP), the main culprit in AD development. In the present study, we treated $AlCl_3$-induced Alzheimer's disease model rats with Frankincense and investigated its protective and therapeutic effects on the $AlCl_3$-induced memory disturbance by behavioral and molecular assays. Also, Rivastigmine was used as a standard control. Morris Water Maze (MWM) was used to assay special memory working of the rats and quantitative real-time PCR (qRT-PCR) was applied to investigate the expression profile of the *FMR1* gene in the hippocampus of the treated rats. MWM behavioral tests indicated that both Frankincense and Rivastigmine not only may prevent $AlCl_3$-induced memory impairment but also may alleviate the memory declines induced by $AlCl_3$ in the rats. Expression analysis showed significant upregulation of the *FMR1* gene in response to both Frankincense and Rivastigmin treatments. Further, qRT-PCR results revealed that the $AlCl_3$-induced downregulation of the *FMR1* gene expression could significantly be reversed by both Frankincense and Rivastigmine, though Rivastigmine was more effective than Frankincense. In conclusion, our results highlighted that Frankincense might be effective both in the prevention and treatment of memory impairments, to some extent, by affecting the *FMR1* gene expression.

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Introduction

Alzheimer's disease (AD), as the most common form of dementia, is a progressive neurodegenerative disorder severely manifesting in cognitive abilities especially memory (Beheshti and Aghaie, 2016; Hajipour *et al.*, 2016; Lee *et al.*, 2020; Lin *et al.*, 2020). The disease onset is affected by both genetic and environmental factors such as oxidative stress, inflammation, and mitochondrial dysfunction, and remarkably related to age progress (Hajipour *et al.*, 2016). Early detection of the disease (Fotuhi *et al.*, 2019) and avoiding its promoting environmental factors (Al-Amin *et al.*, 2019; Kumar *et al.*, 2019) might be critical players in saving people from AD development and progress. Among the environmental factors, Aluminum toxicity has been contributed to the increased incidence of AD (Al-Amin *et al.*, 2019; Kumar *et al.*, 2019), where it causes neurodegeneration by oxidative stress induction

and reactive oxygen species (ROS) formation (Wu *et al.*, 2012). Although the precise etiology of the disease is not known, the characteristic features of AD are the formation of hyper-phosphorylated tau protein and its intracellular accumulation into neurofibrillary tangles (NFT) and the accumulation of beta-amyloid (Aβ) excess amounts as senile plaques in extraneuronal spaces in the brain. This event, which resulted from disrupted expression of amyloid precursor protein (APP) and/or Aβ clearance, impairs the synaptic function and gradually induces AD symptoms (Estelami *et al.*, 2016; Fotuhi *et al.*, 2020; Lin *et al.*, 2020; Rashid *et al.*, 2020; Westmark *et al.*, 2007).

CGG trinucleotide repeat expansion to more than 200 repeats in the 5′-untranslated region (UTR) of fragile X mental retardation (*FMR1*) gene causes fragile X syndrome (FXS) (Real *et al.*, 2011; Renoux *et al.*, 2014). FXS, which is 2 fold more prevalent in men than women (Westmark and Malter, 2007), is the main monogenic cause of autism and mental retardation (Renoux *et al.*, 2014). Hypermethylation of this expanded DNA followed by transcriptional silencing of the FMR1 gene prevents the expression and subsequent function of a regulatory RNA binding protein, fragile X mental retardation protein (FMRP) (Real *et al.*, 2011; Renoux *et al.*, 2014). This protein exerts a translational inhibitory effect on its target mRNAs, such as APP (Renoux *et al.*, 2014; Westmark and Malter, 2007). FMRP binding to the coding region G-quartet–like cis-element on the APP mRNA, represses the APP translation which may play a fundamental inhibitory role in Alzheimer's disease progression (Lee *et al.*, 2010; Westmark and Malter, 2007). The anti-inflammatory and therapeutic effect of Frankincense or Olibanum, the oleo gum resin product of genus Boswellia, has been exploited for many years in various chronic inflammatory diseases treatment and memory improvement (Beheshti and Karimi, 2016; Ebrahimpour *et al.*, 2017; Hosseini-Sharifabad *et al.*, 2016; Jebelli *et al.*, 2019; Mahboubi *et al.*, 2016). According to several studies, its main ingredient, β-Boswellic acids, has a positive effect on brain development, neurite outgrowth, and new nerve network formation, especially in the hippocampus (Asadi *et al.*, 2019; Hosseini-Sharifabad *et al.*, 2016; Sedighi *et al.*, 2014). On the other hand, Rivastigmine is one of the known drugs that is prescribed to AD patients to retard AD-related memory declining progress (Bejar *et al.*, 1999). Here, we examined the protective and therapeutic effects of Frankincense on the $AlCl_3$-induced AD model rats by behavioral tests. Rivastigmine, an approved drug for AD, was also used as a control. Furthermore, the expression profile of the *FMR1* gene in the hippocampus of the treated rats was quantified by qRT-PCR and compared with the results achieved from Rivastigmine and the control group.

Materials and Methods

Preparation of frankincense

Pulverized resin (200 gr) (*Boswellia serrata* from *Goldarou* Co, Isfahan, Iran) was soaked in 2 liters of distilled water for 24h. Then, it was warm heated on a 60 °C water bath for 4 hours, and the resulting mixture was filtered. The solution was lyophilized by freeze-drying (Christ, Germany) and the white powder was stored at 4°C until use. Upon use, it was dissolved in distilled water 1 mg/mL.

Animals and treatments

42 eight-month-old male Wistar Albino rats (200-250 g) were purchased from the *Pasteur* Institute of Iran, Tehran, and kept six per a polycarbonate cage under a constant condition (temperature: 23±3◦c and mild humidity) with a 12/12h light/dark cycle (lights on at 6:00 a.m.). Animals had free access to food and water in their cages.

Rats were randomly categorized into six groups: control, $AlCl_3$ model of AD, two groups treated with aqueous extract of Frankincense or Rivastigmine before $AlCl_3$ treatment, and two Alzheimer models treated with Frankincense or Rivastigmine. In this investigation, each group includes seven members. The experimental protocol of treatment used in each group is presented below (Table 1). This study was approved by the Ethics Committee of Tabriz University of Medical Sciences and was under the ethical declaration of Helsinki.

Table 1. Daily treatment protocol of each separate group of rats.

Groups	Treatment protocol (daily)
1. Control	Distilled water
2. $AlCl_3$-treated (AD model)	$AlCl_3$ (20 mg/Kg) for 8 weeks
3. Rivastigmine+ $AlCl_3$ (Rivastigmine-Protected group)	Rivastigmine (0.3 mg/Kg) for 2 weeks, continued together with $AlCl_3$ (20 mg/Kg) for 8 weeks
4. Frankincense+$AlCl_3$(Frankincense-Protected group)	Frankincense (200 mg/Kg) for 2 weeks, continued together with $AlCl_3$ (20 mg/Kg) for 8 weeks
5. $AlCl_3$+Rivastigmine (Rivastigmine-Therapeutic group)	$AlCl_3$ (20 mg/Kg) for 8 weeks, followed by Rivastigmine (0.3 mg/Kg) for 8 weeks
6. $AlCl_3$+Frankincense (Frankincense-Therapeutic group)	$AlCl_3$ (20 mg/Kg) for 8 weeks, followed by Frankincense (200 mg/Kg) for 8 weeks

Morris water maze

To measure the spatial memory performance of the rats, we performed the Morris water maze (MWM) or behavioral training, as previously described (Sadeghi *et al.*, 2014). Briefly, the apparatus was a circular pool of 136 cm in diameter and 60 cm deep. The maze filled up with water to 25 cm high. The water temperature was kept close to 28°C throughout the experiment. The escape platform (10×24 cm) was placed 1 cm below the surface of the water in the north-east center. Each animal was located on the platform for 10-second free exploration (before the test), and they were allowed to terminate any trial in 40 seconds. The test was completed in 6 consecutive days. 3 parameters including escape latency, the total distance moved, and swimming speed was used to evaluate the performance of each rat in the memory test.

RNA extraction and qRT-PCR

At the end of the behavioral test, all animals (control and test groups) were anesthetized deeply with an intraperitoneal administration of the ketamine and xylazine mixture and killed by decapitation. Their hippocampi were dissected from the brain and frozen in liquid nitrogen to RNA extraction.

The total RNA was extracted using the RNX-plus solution (*Cinnagen*, Tehran, Iran) according to the manufacturer's protocol and reversely transcribed into complementary DNA using a TAKARA cDNA synthesis kit (Japan). Quantitative PCR reactions were carried out using the RealQ Plus 2x Master Mix Green (Amplicon) on the Illumina Eco Real-Time PCR System (Illumina, USA). The primer sequences were as follow: *GAPDH* (as an endogenous control): forward, 5′-AACGACCCCTTCATTGACC-3′ reverse, 5′-TCCACGACATACTCAGCACC-3′. *FMR1*: forward, 5′-ACTGAGAAATGAAGAAGCCAG-3′ reverse, 5′-AAATGTGCAGGTATCCTCATC-3′. The relative expression level of *FMR1* was calculated by the $2^{-\Delta\Delta CT}$ method. The amplification efficiency of the reactions was calculated and applied to the relative expression analyses. Each reaction was done in a duplicate format.

Statistical analysis

All analyses were conducted with SPSS 19 statistical package (IBM Inc., Chicago, IL, USA) and GraphPad Prism 6 (GraphPad Software, San Diego, California). Independent and intragroup paired t-test was used to compare the means and a *P*-value less than 0.05 was considered statistically significant. All figures were drawn by the mean of GraphPad Prism 6. The results reported as means ± standard deviation (SD).

Results

Evaluation of swimming speed parameter

$AlCl_3$, Rivastigmine, and frankincense treatment showed no significant differences ($p>0.05$) in the swimming speed of the treated rats compared with the control group. Since no motor disturbance was revealed between the control and the test groups, the escape latency and distance travel scores were computable.

Evaluation of escape latency parameter

Decreasing in escape latency becomes very slow after the second day in the $AlCl_3$ treated group while it continues strongly for the others (Fig. 1). Intragroup Paired t-test analysis also indicated a significant difference between second and sixth-

day results in all groups except the $AlCl_3$ model group ($p<0.00$). This may imply the learning impairment in the AD model rats than the treated and control groups. Although the downward slope in the time latency shows no significant difference between the $AlCl_3$ and other groups ($p>0.05$) as a whole, this reduction is clear, especially in the last three days of the MWM experiment ($p<0.05$). This difference is not significant in the group treated with Frankincense, though it is very close to the critical p-value score ($p=0.07$). According to these results, both Frankincense and Rivastigmine indicated protective and therapeutic impacts on the $AlCl_3$-induced memory impairments, though the impact of Frankincense was insignificantly lower than that of Rivastigmine (Fig. 1).

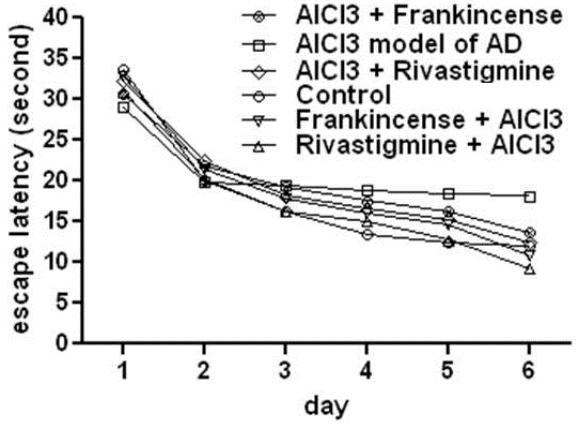

Fig. 1. Escape latency parameter: The graph presents the six-day score recorded for six tested groups in Morris Water Maze. The results reported as means ± SD.

Evaluation of travel distance parameter

The recorded scores indicated a significant improvement in the learning ability of Rivastigmine- and Frankincense-treated rats in comparison with the $AlCl_3$-induced AD model ($p<0.05$). Reduction in the traveled distance was more evident in the last three days of all groups, except the $AlCl_3$-induced AD model. Memory disturbance that occurred in the AD rats caused a little change between the second and sixth-day records, while these records showed a significant difference in the others ($p<0.05$) (Fig. 2). It should also mention that, according to the results, the protective effect of Rivastigmine and Frankincense is more severe than their therapeutic effect in memory improvement. Moreover, there were no significant differences between the effects of Rivastigmine and Frankincense ($p>0.05$).

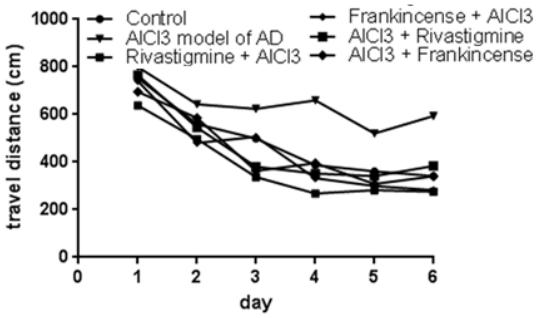

Fig. 2. Travel distance parameter: The graph represents a clear difference in the recorded scores of AD model rats and the other groups. The results reported as means ± SD.

Effect of $AlCl_3$ on the expression of the *FMR1*

The expression of the *FMR1* gene was analyzed in the rat's hippocampi from all groups by quantitative reverse transcription PCR (qRT-PCR). Treatment of rats by $AlCl_3$ significantly diminished the expression of the *FMR1* gene compared with the control group ($p<0.05$) (Fig. 3). This finding suggested a probable relationship between $AlCl_3$-exerted neurotoxic effects and the reduction of *FMR1* gene expression in the hippocampus.

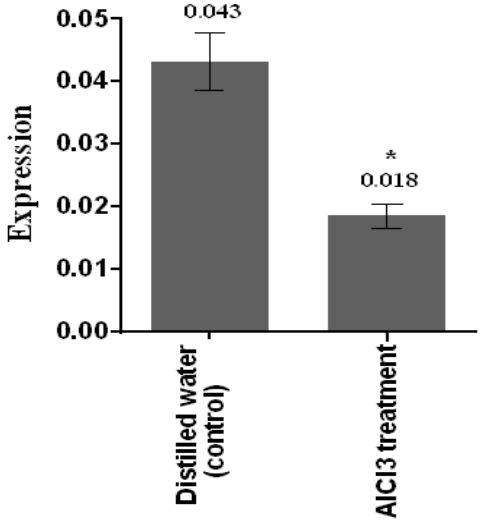

Fig. 3. Comparison of the *FMR1* gene expression levels in hippocampi of the rats treated with $AlCl_3$ and control group: $AlCl_3$ treatment significantly diminished the *FMR1* gene expression level. *: denotes a significant difference $p \leq 0.05$.

Effect of the protective protocol treatments on the *FMR1* gene expression

Our results showed that a two-week-long consumption of Rivastigmine, before $AlCl_3$ treatment, significantly prevented the $AlCl_3$-induced *FMR1* expression decline (p=0.000), and increased it to a level that was significantly higher than that of the control group (p<0.05) (Fig. 4). However, consumption of Frankincense has no remarkable effect on the $AlCl_3$-induced decline of *FMR1* gene expression (p>0.05). Rats that received Frankincense rather than Rivastigmine showed a little increase in *FMR1* expression level in comparison with the $AlCl_3$-treated (AD model) group (Fig. 4).

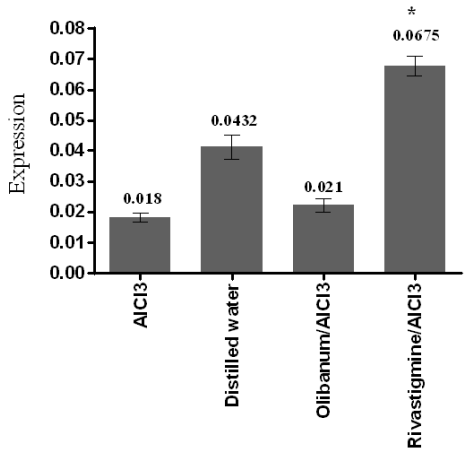

Fig. 4. Effect of the protective protocol treatments of Rivastigmine and Frankincense on the *FMR1* gene expression: Olibanum/$AlCl_3$; rats received Frankincense for 2 weeks which were then continued together with $AlCl_3$ treatment for another 8 weeks. Rivastigmine/$AlCl_3$; rats received Rivastigmine for 2 weeks which were then continued together with $AlCl_3$treatment for another 8 weeks. Results were reported as mean ± SD. *; p<0.05.

Effect of the therapeutic protocol treatments on the FMR1 gene expression

To model AD, rats were treated with $AlCl_3$ for 8 weeks. Afterward, AlCl3 treatment was stopped and the modeled rats obtained Rivastigmine or Frankincense for further 8 weeks. Finally, the effect of Rivastigmine and Frankincense administration on the *FMR1* gene expression was compared between the groups. According to the results illustrated, there were no significant changes of *FMR1* gene expression, between Rivastigmine- or Frankincense-treated groups and the control group (p>0.05), however, its expression levels in the Rivastigmine- and Frankincense-treated groups were higher than that of the $AlCl_3$-treated AD model group (Fig. 5). Expression differences between the Rivastigmine-treated group, but not the Frankincense-treat group (p=0.07), and the AD model group were statistically significant (p<0.05). Although the expression level in the Rivastigmine-treated group was higher than in the Frankincense-treated group, the difference was not statistically significant (p>0.05) (Fig. 5). These findings indicated that both Rivastigmine and Frankincense could hamper the $AlCl_3$-induced decline of the *FMR1* gene expression.

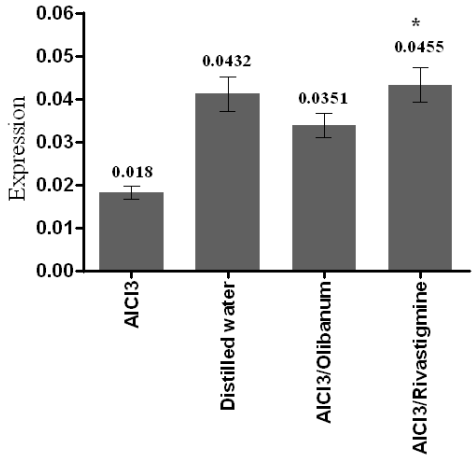

Fig. 5. Effect of the therapeutic protocol treatments of Rivastigmine and Frankincense on the *FMR1*gene expression: $AlCl_3$/Olibanum; rats received $AlCl_3$ for 8 weeks which were then followed by Frankincense administration for another 8 weeks. $AlCl_3$/Rivastigmine; rats received $AlCl_3$ for 8 weeks which were then followed by Rivastigmine administration for another 8 weeks. Results were reported as mean ± SD. *; p<0.05.

Discussion

Here we report the protective and therapeutic effects of Frankincense and Rivastigmine on the $AlCl_3$-induced memory impairment in rats. Behavioral tests showed that $AlCl_3$ can significantly decline special memory performance in $AlCl_3$-treated rats compared with the control group (Figs. 1 and 2). These findings were in line with other researches that applied $AlCl_3$ as an AD-inducing neurotoxic factor (Al-Amin *et al.*, 2019; Estelami *et al.*, 2016; Khalaj-

kondori *et al.*, 2016; Kumar *et al.*, 2019; Wu *et al.*, 2012). According to the MWM results, both Rivastigmine and Frankincense had protective as well as therapeutic effects on the $AlCl_3$-induced special memory impairment. Consumption of Frankincense or Rivastigmine for two weeks before treating rats with $AlCl_3$ efficiently protected the rats from $AlCl_3$-induced special memory impairment (Figs. 1 and 2). Both escape latency and travel distance parameters were significantly decreased in Rivastigmine- and Frankincense-protected groups (Rivastigmine+ $AlCl_3$ and Frankincense+ $AlCl_3$ groups) in comparison with the $AlCl_3$-treated (AD model) group. Though, the differences between Rivastigmine-protected and Frankincense-protected groups were insignificant. These observations were repeated when we assayed the therapeutic effect of Frankincense or Rivastigmine. In all experiments, the effect of Rivastigmine was a bit higher than Frankincense but the differences were insignificant. Al-Amin et al. reported that the $AlCl_3$-induced oxidative stress and neurotoxicity could also be impeded by levocarnitine in Swiss albino mice (Al-Amin *et al.*, 2019). Furthermore, it can be ameliorated by selenium (Lakshmi *et al.*, 2015), the combination of Rivastigmine and Memantine with Artesunate (Kumar *et al.*, 2019), Quercetin, and etodolac in combination or alone (Singh *et al.*, 2014) in rats. The positive effects of Frankincense on memory performance have been documented by many researchers (Asadi *et al.*, 2019; Hosseini-Sharifabad *et al.*, 2016; Mahboubi *et al.*, 2016). Beheshti *et al.* (2016) reported that LPS-treated rats show memory improvement following hippocampal TNF-α reduction because of Frankincense treatment (Beheshti and Karimi, 2016). The combined administration of this herbal resin and Melissa officinalis antioxidant improves the memory function in scopolamine-treated rats (Mahboubi *et al.*, 2016). The main ingredient of this resin, Boswellic acid, induced more dendritic spines and brain development (Hosseini-Sharifabad *et al.*, 2016). Interestingly, in 2019, Asadi *et al.* reported that administration of Frankincense for four weeks could improve explicit motor memory acquisition and retention in elderly men (Asadi *et al.*, 2019).

Several studies have addressed the molecular mechanism by which Frankincense or its main ingredients such as α-Boswellic acids, β-Boswellic acids, and Incensole acetate impact memory performance. For example, α-Boswellic acid upregulated Reelin expression and prevented the formation of tau phosphorylation and neurofibrillary tangles in primary fetal human astrocytes (Fathi *et al.*, 2017). Incensole acetate exerted an anti-inflammatory and neuroprotective effect on the human olfactory bulb neural stem cells via preventing the Aβ25-35-induced oxidative cell death (El-Magd *et al.*, 2018). Furthermore, β-Boswellic acid or Frankincense modulated expression of acetylcholinesterase (AchE) (Ebrahimpour et al., 2017), CREB-1 and CREB-2 transcription factors (Jebelli *et al.*, 2019), inflammation and apoptotic related genes (Gomaa *et al.*, 2019). Here, we also considered the *FMR1* gene expression as a potential target. Since, FMRP, the product of the *FMR1* gene, acts as an RNA binding protein and regulates the expression of amyloid precursor protein (APP), the main culprit in AD progression (Westmark and Malter, 2007). Furthermore, the instability of CGG repeat expansion, at the 5′-UTR of the *FMR1* gene, producing Fragile X-associated symptoms, is the prevalent cause of inherited mental retardation (Kraan *et al.*, 2014).

Our results showed that the expression of the *FMR1* gene was significantly declined by $AlCl_3$ treatment (Fig. 3). However, interestingly, the administration of Frankincense or Rivastigmine conflicted with the $AlCl_3$-induced decline of the *FMR1* gene expression leading to its upregulation (Fig. 5). These observations highlighted that $AlCl_3$ probably impairs the memory at least partly by downregulation of the *FMR1* gene, while administration of Rivastigmine and Frankincense could alleviate the memory disfunction by upregulation of the *FMR1* gene expression. Nonetheless, the effect of Rivastigmine in upregulation of the *FMR1* gene was higher than that of Frankincense.

Conclusion

In conclusion, our results indicated that $AlCl_3$ could decline *FMR1* gene expression and impair rats' memory performance. Administration of Frankincense or Rivastigmine could conflict

with the $AlCl_3$-induced neurotoxicity and alleviate memory impairment. Behavioral experiments highlighted that the effects of Frankincense might be comparable to some extent with those of Rivastigmine on fighting the neurotoxic effects of Aluminum exposure, and finally, these effects might at least partly be mediated by modulation of *FMR1* gene expression.

Acknowledgments

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Conflicts of interest

There is no conflict of interests.

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