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Prophylactic effects of *Ixora coccinea* leaf on the haematological, biochemical, and atherogenic profile in male Wistar rats administered anticancer drug Cisplatin

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ABSTRACT

Background & Aim: This study was aimed at investigating the prophylactic effects of hydroethanolic extract of *Ixora coccinea* leaf (HEICL) on Cisplatin (cis diamminedichloroplatinum-II, CDDP)-induced alteration in atherogenic, haematological, and biochemical profiles in male Wistar rats.

Experimental: Thirty male rats were assigned into 6 groups (n=5) in which groups A, B, C, and D received normal saline (0.2 mL), CDDP (10 mg/kg), HEICL at 200 mg/kg, and HEICL at 400mg/kg. Groups E and F received CDDP 10 mg/kg with HEICL at 200 mg/kg, and 400 mg/kg, respectively.

Results: The phytochemical analysis of the AEAC revealed the presence of some phytochemical constituents such as alkaloids, flavonoids, saponins, tannins, reducing sugar, phenol, resin, and volatile oil. However, glycosides, steroids, and anthraquinone were absent. The Acute toxicity result indicated that HEICL has an LD_{50} above 5000mg/kg. CDDP caused a significant ($P<0.05$) decrease in the haematological parameters relative to the control but administration of CDDP with HEICL improved the parameters. CDDP caused a significant ($P<0.05$) increase in the levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL), but a significantly ($P<0.05$) lower level of HDL. Treatment with CDDP and HEICL significantly ($P<0.05$) abrogated these CDDP-induced alterations. Similar ameliorative effects of HEICL were found in CDDP-induced alterations in atherogenic indices, such as Castelli's Risk Index I (CRI-1), Castelli's Risk Index II (CRI-II), Atherogenic Coefficient (AC), and Atherogenic Index of Plasma (AIP) indices relative to the control.

Recommended applications/industries: The above study suggests that HEICLmay be useful in treating heart conditions because it protects against CDDP-induced alterations in the haematological, lipid, and atherogenic parameters.

1. Introduction

Many pharmaceuticals in today's pharmacopeia cause liver damage with varying clinical expositions. Chemotherapy-induced liver damage is frequently unanticipated or idiosyncratic. In the most severe cases, drug-induced liver impairment necessitates liver transplantation or results in death (Lee, 2003). Despite

the tremendous advancement made in understanding the mechanisms of action and the relationship between the liver and chemotherapy, the core etiology of hepatic toxicity remained unclear (Grigorian and O'Brien, 2014). In many instances, chemotherapy or radiation therapy alone cannot achieve total tumor remission, the intended clinical response, and causes considerable adverse effects even at therapeutically effective doses (Park *et al.*, 2009).

CDDP is an organic platinum analogue that is extensively used as first-line adjuvant therapy in the treatment of testicular, gut, stomach, head and neck, ovarian, cervical, germ cell cancers, and non-small cell lung carcinoma (Ekinci *et al.*, 2017; Hu *et al.*, 2014). Because the cytotoxic and apoptotic effects of CDDP are not only directed at cancer cells but also normal dividing cells, CDDP treatment is affected by a variety of issues, including drug resistance and negative side effects such as nephrotoxicity, bone marrow suppression, gastrointestinal toxicity, neurotoxicity, ototoxicity, and hepatotoxicity are usually noticed following treatment with this agent (Atessahin *et al.*, 2006; Gomez-Sierra *et al.*, 2018).

In addition, hepatotoxicity induced by chemotherapeutic drugs may lead to lipid metabolism disorders and even hyperlipidemia (Han and Huang, 2015; Leung *et al.*, 2018). Research has shown that LDL, HDL, and TC levels are inversely related to the severity of hepatotoxicity (Ghadir *et al.*, 2010). It is generally known that abnormal lipid profiles play a role in the development of cardiovascular diseases (CVD), with abnormal low-density lipoprotein cholesterol (LDL) levels being the main target of CVD therapy.Lipid assessments are crucial for risk assessment in the primary prevention of cardiovascular disease (Bhardwas *et al.*, 2013). Different ratios or combinations of these lipid profile characteristics have proven to be more significantly predictive of the risk of developing CVDs than independently using just the lipid profile indicators (Bhardwas *et al.*, 2013). The atherogenic index of plasma (AIP), atherogenic coefficient (AC), and Castelli's risk indices (CRIs) are the ratios of such lipid profile parameters that have been studied as markers of lipid atherogenic risk (Igwe *et al.*, 2016).In addition to the commonly used lipid profile variables, estimated lipid fraction ratios are suggestively gaining interest in the clinical setting for determining the risk of CVD (Koleva *et al.*, 2015). Significant increases in plasma levels of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol are known risk factors for cardiovascular disease. They are also linked to obesity, hypertension, and these two conditions (Rakib *et al.*, 2014).

There is an imminent need to add supportive medications and/or nutrients to chemotherapy regimens to mitigate the side effects of chemotherapeutics, including CDDP (Zhao *et al.*, 2018). It is possible to employ a variety of herbal medicines to treat CDDP-related side effects. Due to medicinal herbs' generally minimal side effects, they have historically been the preferred option for treating pathological side effects (Bhardwaj *et al.*, 2021). *Ixora coccinea* has been traditionally used in folkloric medicine to treat diverse ailments. Different parts of the plants are of therapeutic value. The flowers are employed to cure sprains, bronchitis fever, sores, chronic ulcers, scabies, haemoptysis, dysmenorrhea, dysentery, dysmenorrhoea, haemoptysis, hypertension, menstrual abnormalities, and dermatitis (Saha *et al.*, 2008). The decoction made from the cleaned root is reported to be effective in treating anorexia, nausea, hiccups, wounds, and chronic ulcers (Torey *et al.*, 2010).

However, despite its alleged medical value, there is a paucity of information on the impact of these drugs on hematology, biochemical, and especially atherogenic profiles. Based on the varied reports on *Ixora coccinea's* (IC) pharmacologic properties, our study attempted to investigate the prophylactic effects of HEICL against CDDP-induced toxicity in male Wistar rats.

2. Materials and Methods

2.1. Chemicals and reagents

Cisplatin (CP) (Unistin 50 ml/50 mg Vial Eimc United Pharmaceutical Badr City, Cairo, Egypt). Assay kits for lipid profile (total cholesterol (TC), triacylglycerol (TAG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), and total lipids (TL) concentrations) were purchased from Sun long Biotech co. (Shangyi, Hangzhou, Zhejiang, China). Other reagents were of analytical grade.

2.2. Collection and identification of plant material

Fresh leaves of IC were collected from the premises of the Federal University of Agriculture, Makurdi, Benue State, Nigeria. The plant was identified by a taxonomist; a voucher specimen number UAM/FH/237/20 already exists in the College of Forestry herbarium, Federal University of Agriculture, Makurdi, Benue State.

2.3. Preparation of plant materials

The leaves of IC were rinsed by placing them in running water to remove dirt and contaminants, air-dried under room temperature for two weeks, pulverized using an electric blender, and stored in an air-tight container for further use and extraction was carried out using a hydroethanolic solvent. About 100g of powdered leaves of *IC* leaf powder was soaked in a conical flask and dissolved in 400 mL of 80% ethanol and 100 mL of distilled water (4:1 v/v). This mixture was kept at room temperature for 48 hours with frequent agitation every 2 hours. Filtration was done with a clean Muslin cloth and Whatman filter paper no. 1 into a cylinder at the end of the 48 hours. The filtrate was concentrated in a water bath at 45°C. The concentrated HEICL was weighed to determine the yield and stored in a refrigerator at a temperature of 4^0C until it was needed.

The weight of the extract was determined, and the percentage yield was calculated by the expression:

Percentage yield = [Weight of extract (g)/ Weight of dry sample (g)]× 100

2.4. Phytochemical screening

The extract was subjected to quantitative analysis of its phytochemical constituents such as saponins, tannins, reducing sugar, phlobatannins, glycosides, anthraquinones, alkaloids, flavonoids, etc) using standard procedures as described by Odebiyi *et al.* (1978).

2.5. Determination of acute oral toxicity

The OECD, 2001 described the methodology used to determine acute oral toxicity. For the study, five adult female albino rats were used. Before the dose, each animal fasted the previous night. A dose of 5000 mg kg-1 body weight was given to one rat and monitored for 48 hours for any signs of toxicity, including death.

Following the 1st rat's survival, the 2nd, 3rd, 4th, and 5th rats were administered intermittent doses at 48-hour intervals and monitored for toxic effects, including death. The five rats were sacrificed and disposed of in accordance with ethical guidelines after being given their final dose 48 hours later. All five rats were then monitored for two weeks for any delayed symptoms of toxicity, including death.

2.6. Experimental design

Thirty male Wistar rats were purchased from Animal House, College of Medicine Benue State University, Makurdi, and kept under standard environmental conditions (24–25 °C, 12h/12h light/dark cycle) and fed on a pellet diet. Water was given *ad libitum*. They were acclimatized for two weeks before the experiment. The experimental protocol was by the guidelines on the care and well-being of research animals (N.H.I, 1985) and was approved by the Ethics Committee of the Department of Veterinary Physiology and Biochemistry, Federal University of Agriculture, Makurdi Benue State, Nigeria. The rats were handled according to the standard protocols for the use of laboratory animals for experiments.

2.7. Drugs and dosage

A single dose (10 mg/kg) of CDDP was injected intraperitoneally (IP). This dose is widely accepted to induce testicular toxicity in rats. A single dose of the drug was suspended in 0.2 mL of normal saline (0.9 g/dL NaCl) solution.

2.8. Animals and treatment

Two weeks after acclimatization, the animals were randomly divided into 5 groups of 10 animals each as follows:

Control group (A) received an intraperitoneal (IP) injection of 0.2 mlsaline for 26 days.

Group B received normal saline IP for 26 days and a single IP injection of CDDP (10 mg/kg) on day 21.

Group C received 200 mg/kg body weight of HEICL orally for 20 days. Group D received 400 mg/kg body weight of HEICL orally for 20 days. Group E received 200 mg/kg of HEICL orally for 20 days and CDDP (IP) on the 21st day and group F received 400 mg/kg of HEICL orally for 20 days and CDDP (IP) on the 21st day.

All the experimental animals were maintained at ambient temperature throughout the experimental period. Body weight and food intake were monitored every week throughout the experiment. At the end of the experimental period, animals were sacrificed and blood and tissue samples were collected for further investigation

2.9. Collection and preparation of blood

On day 28 (7 days after CDDP injection), the rats were anesthetized by thiopental injection (100 mg/kg, i.p.) and sacrificed by cervical dislocation. Blood samples were obtained via retro-orbital puncture and distributed into sample sterile tubes. The blood was left on the bench for at least 2 hours before being spun with a centrifuge at 3000 rpm for 10 minutes. The serum was taken with a clean Pasteur pipette, collected into a sterile sample vial, and refrigerated until needed for biochemical analysis.

2.10. Haematological studies

Hemoglobin concentration was determined according to the method described by Benjamin, (1978) by using Sahli's hemocytometer, and packed cell volume percent was determined by the microhaematocrite technique (Dacie and Lewis, 1995). Erythrocytic and total leukocytic counts were performed by using a Double improved Neubauer hemocytometer (Dacie and Lewis, 1995).

2.11. Determination of lipid profiles

Serum triacylglyceride (TAG) total cholesterol (TC) and high-density lipoprotein cholesterol (HDL) concentration were determined using the enzymatic colorimetric method (Bucolo and David, 1973). Calculation of the concentration of low-density lipoprotein cholesterol (LDL) in the serum was previously described by Friedewald *et al.* (1972).

2.12. Calculations of the atherogenic indices

Serum total non-HDL cholesterol (TnHDL) concentration was calculated as TC– HDL by method of Castelli *et al.* (1983), while Cardiac risk ratio (CRR) and Castelli's Risk Index II (CRI-II) were determined as TC/ HDL and LDL/ HDL, respectively (Igwe *et al.*, 2016; Brehm *et al.*, 2004).

Atherogenic index of plasma (AIP) and atherogenic coefficient (AC) levels were calculated as log (TG / HDL) and (TC - HDL) / HDL, respectively (Dobiásová, 2004; Haneman and Zidenberg-Cherr, 2008).

2.13. Statistical analysis

Data obtained from this study are expressed as arithmetic mean ± standard error of mean (Mean ± SEM). One-way analysis of variance (ANOVA) was used to access the difference between means followed by Tukey's multiple comparison test. GraphPad Prism 8.01 was the statistical package used for the analysis and p-values <0.05 were considered statistically significant for differences in means.

3. Results and discussion

3.1. Phytochemical screening

The result of the quantitative phytochemical composition of HEICL is presented in Table 1. Results obtained showed the presence of phytochemicals such as alkaloids, flavonoids, saponins, tannins, reducing sugar, phenol, resin, and volatile oil. However, glycosides, steroids, and anthraquinone were absent.

Table 1. Phytochemical test result of HEICL.

Test	Results
Flavonoids	+++
Phenol	+++
Tannins	++
Steroids	-
Alkaloids	+++
Glycosides	---
Terpenoids	+++
Anthraquinone	--
Resins	++

= Positive; - = Negative

3.2. Oral acute toxicity study

The oral acute toxicity test showed no mortality following the oral administration of HEICL at a dose above 5000 mg kg^{-1} body weight as prescribed by OECD (2001). No signs of toxicity were observed for the initial period of 48 hours and thereafter for 12 days. The lethal dose of the extract was considered greater than 5000 mg kg^{-1} body weight according to OECD (2001).

3.3. Administration of HEICL inhibited the deleterious effects of CDDP-induced haematological alteration in male rats

Table 2 summarizes the major haematological parameters studied. The levels of RBC, PCV, Hb, MCH, MCV, MCHC, WBC, Neutrophils, and lymphocytes were significantly lower (P<0.05) in the CDDP group relative to the control. The groups that were administered HEICL alone produced results comparable to the control group. However, when CDDP and HEICL were administered concurrently, these haematological parameters increased significantly (P<0.05) in a dose-dependent manner as compared to the CDDP group.

Table 2. The prophylactic effects of HEICL on the mean of the haematological parameters in male Wistar rats treated with CDDP.

Parameters	Dst H_2O	CDDP	200 mg/kg HEIC	400 mg/kg HEICL	200 mg/kg HEICL+ CDDP	400mg/kg HEICL+ CDDP
RBC (× 10^{12}/L)	5.17± 0.22	3.50± 0.12[a]	5.07± 0.03	5.73± 0.15	4.17± 0.09[b]	4.17± 0.12[b]
PCV (%)	54.33± 1.76	25.67± 1.76[a]	56.67± 0.33	55.67±0.67	34.67± 0.88[b]	37.00±0.58[b]
Hb (g/dL)	13.13± 1.95	9.43± 0.41[a]	13.03± 0.67	12.43± 1.233	11.17± 0.68[b]	13.00±0.40[b]
MCV (fL)	75.57± 1.39	60.37± 1.14[a]	69.20± 3.415	72.30± 4.158	53.10± 0.76[b]	53.00± 1.16[b]
MCH (pg)	25.20± 0.44	20.33±0.6692[a]	23.07± 1.16	24.10± 1.40	23.10± 0.15	24.43± 0.26[b]
MCHC (g/L)	34.03± 0.98	30.63± 0.34[a]	33.40± 0.00[b]	33.27± 0.03	29.13± 0.22	31.27± 0.43
WBC (×10^9/L)	2.50± 0.100	1.73± 0.15[a]	3.20± 0.12	3.33± 0.09	2.20± 0.12[b]	2.63± 0.09[b]
MNT(×10^9/dL)	2.50± 0.45	2.10± 0.25	2.80± 0.58	2.60± 0.48	2.40± 0.51	2.11± 0.25
BSP(×10^9/L)	0.00± 0.00	3.00± 0.58[a]	1.33± 0.67	1.00± 1.00	2.00± 1.16	1.33± 0.88[b]
NTL (×10^9/L)	34.00± 3.06	32.67± 0.89[a]	35.86± 1.421	37.67± 0.67[b]	36.67± 1.86	35.57± 1.41
LYT (×10^9/L)	68.67± 1.20	52.00± 0.58[a]	67.00± 2.517	65.00± 4.041	55.33± 0.88[b]	56.33±1.45[b]
ESL (×10^9/L)	2.37± 0.33	2.33± 0.88	2.000± 1.16	2.13±1.20	2.00±1.16	2.30±0.33

a= significantly different from the group in which distilled water was administered (P<0.05). b= significantly different from the group in which CDDP alone was administered (P<0.05).
A= Distilled water, B= CDDP, C= 200 mg/kg of HEICL, D= 400 mg/kg of HEICL, E= CDDP + 200 mg/kg HEICL, F= CDDP+ 400 mg/kg HEICL, RBC= Red Blood Cell; Hb= Haemoglobin; PCV= Packed Cell Volume; MCV= Mean Corpuscular Volume; MCH= Mean Corpuscular Haemoglobin; MCHC= Mean Corpuscular Haemoglobin Concentration; WBC= White Blood Cell; LYT= Lymphocyte; BSP= Basophil; MNT= Monocyte; NTL= Neutrophil; ESL=Eosinophil.

3.4. Prophylactic effect of HEICL leaf on CDDP-induced alteration in lipid and atherogenic profile in male rats

Table 3 summarizes the prophylactic effects of HEICL on lipid profiles such as total cholesterol, HDL, LDL, and triglycerides in male Wistar rats administered CDDP. While CDDP treatment significantly (P<0.05) elevated total cholesterol, LDL and triglyceride levels in the treated rats, it significantly (P<0.05) lowered HDL levels in the CDDP group compared to the control group. The administration of HEICL with CDDP significantly (P<0.05) corrected blood lipid profile indicators, with the most significant (P<0.05) protection observed in the HEICL pre-treatment group compared to the CDDP-treated group. HEICL pre-treatment had effects parallel to the control group.

Table 3. Effects of HEICL and CDDP on the lipid and atherogenic profile in the experimental rats.

Parameters	TC (mg/dL)	TG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	TnHDL (mg/dl)	CRR	CRI	AC	AIP
Group A	71.90±1.33	61.73±1.01	37.57±2.6	23.58±0.44	34.33±1.03	1.91±0.02	0.63±0.01	0.91±0.12	0.25±0.03
Group B	93.80±1.7[a]	89.20±1.10[a]	26.2±1.59[a]	39.00±6.30[a]	67.6±0.02[a]	3.58±0.13[a]	1.49±0.02[a]	2.58±0.26[a]	0.53±0.01[a]
Group C	77.1±0.76	65.73±0.7	41.80±0.6	28.09±0.75	35.30±0.14	1.`84±0.13	0.67±0.50	0.84±0.14	0.19±0.01
Group D	75.5±0.68	66.57±0.1	38.90±1.6	26.36±0.86	36.60±0.03	1.94±0.04	0.68±0.13	0.94±0.06	0.23±0.02
Group E	86.8±0.44[b]	77.37±1.1[b]	29.67±51.2[b]	34.2±1.90[b]	57.13±0.12[b]	2.93±0.07[b]	1.16±0.02[b]	1.92±0.02[b]	0.42±0.01[b]
Group F	84.0±1.5[b]	72.87±3.2[b]	32.5±1.6[b]	32.8±0.70[b]	51.504±0.01[b]	2.53±0.12[b]	1.00±0.06[b]	1.60±0.03[b]	0.35±0.10[b]

a= statistically significant when compared with negative control (distilled water only) at P<0.05. b= statistically significant when compared with the positive control (CDDP) at P<0.05.
A= Distilled water, B= CDDP, C= 200 mg/kg of HEICL, D= 400 mg/kg of HEICL, E= CDDP + 200 mg/kg HEICL, F= CDDP + 400 mg/kg HEICL, TC: Total Cholesterol; TG: Triglyceride; HDL: High Density Lipoprotein Cholesterol; LDL: Low Density Lipoprotein Cholesterol; TnHDL: Total Non-HDL; CRI-I: Castelli's Risk Index I; CRI-II: Castelli's Risk Index II; AC: Atherogenic Coefficient.

Clinically, a good number of chemotherapy patients develop haematological indices and lipid metabolism disturbances. Similarly, chemotherapy may increase the risk of liver impairment in individuals with lipid metabolic disorders. Because the liver is critical in maintaining plasma cholesterol levels, if there are drug-induced liver defects, there will be elevated levels of serum total cholesterol (TC) and LDL cholesterol (Atawodi *et al.*, 2014). There were significant increases in serum levels of total cholesterol (TC), triglycerides (TG), and LDL cholesterol after CDDP exposure relative to the control group and the groups administered HEICL only. The current study may be credited to the drug's adverse effect, contributing to hepatocellular dysfunction and impaired lipid metabolism, which is consistent with Akindele *et al*. (2014). Elevated levels of TC, LDL, and low levels of HDL have been linked to an increased risk of cardiovascular disease (Parinita, 2012). Triglycerides are synthesized by the liver and incorporated into very-low-density lipoprotein (VLDL) cholesterol for transport into peripheral tissues; thus, when the liver function is impaired, its ability to synthesize VLDL is compromised, resulting in elevated levels of TG (Manninen *et al.*, 2002). Atherogenic dyslipidemia, defined by a high LDLC/HDL ratio and higher TG, is implicated in the development of coronary heart disease (Niroumand *et al.*, 2015). Multiple clinical data attempted to identify a better marker of atherogenic dyslipidemia that can predict the risk of cardiovascular disease (CVD) and be used to assess therapy response rather than the conventional ratio (Niroumand *et al.*, 2015; Mudhaffar, 2013). The atherogenic index of plasma (AIP), as a metric of lipoprotein particle size, was revealed to be more indicative of CVD risk than specific lipids and/or the TC/HDL ratio (Niroumand *et al.*, 2015; Dobiasova and Frohlich, 2001). Thus, current scientific data suggests that AIP is a strong determinant of the risk of atherosclerosis and CVD (Niroumand *et al.*, 2015). CDDP-exposed rats had a significant rise in the values of the cardiac risk ratio (CRR), atherogenic coefficient (AC), and classical ratio (CR), but only a little increase in AIP when compared with the control group, indicating a modest risk of atherosclerosis and CVD. These findings support prior research that has shown that dyslipidemia and atherogenic indices rise with increased CVD risk and vice versa (Nwagha *et al.*, 2010; Niroumand *et al.*, 2015).

The hematopoietic system is considered delicate in studying the adverse effects or toxicities induced by antineoplastic agents in animals and humans. In the current work, administration of CDDP exhibits significant toxic effects in hematological parameters in rats 7 days post-treatment, and the pretreatment with HEICL showed significant protection against hematotoxicity. The toxic effects of CDDP on hematological parameters were confirmed by significant depletion in the count of erythrocytes, Hb, MCV, MCH, MCHC, and PCV. In addition, rats administered CDDP also had low levels of WBCs and lymphocytes. The data indicate that CDDP and anemia disease share a common etiological cause. It could be demonstrated by different mechanisms showing bone marrow suppression or elevated osmotic fragility of erythrocytes. As a result, CDDP administration may result in anemic disorders because it inhibits hematopoietic tissues, disrupts erythropoiesis, and causes higher erythrocyte reduction due to decreased erythrocyte membrane permeability and poor iron metabolism (Ashraf, 2014; Yuan *et al.*, 2014).

However, the preponderance of the hematological indices that were altered in the rats treated with CDDP showed a substantial modulation in the rats pretreated with HEICL. The most of hematological parameters and RBC indices were demonstrated to be protected against CDDP-induced suppression by HEICL, which increased RBC counts and Hb concentration to values that were near normal. Similarly, HEICL improved significantly the lowering of MCV, PCV, MCH, and MCHC levels in treated rats with CDDP. The erythrocyte count increase caused by HEICL may be related to either an increase in erythropoiesis or HEICL's capacity to reduce the membrane rigidity connected with its cholesterol-lowering impact. The result obtained is congruent with a similar work by Hamlaoui-Gasm *et al*. (2012).

4. Conclusion

In conclusion, *Ixora coccinea* is an ornamental plant with pharmacological and therapeutic effects that have not been investigated properly. *Ixora coccinea* leaves'

hydroethanolic extract has been revealed to have powerful therapeutic benefits, making it a promising candidate plant for the treatment of cardiovascular and cerebrovascular conditions. This gives the plant's historic usage in treating cardiac ailments a scientific justification.

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