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Evaluation of the haemostatic potentials of aqueous extract of *Hyptis suaveolens* leaves in wistar rats

[§]Mokwenye Ifeoma, Ikewuchi, Catherine Chidinma and Okoye Ngozi Franca

Department of Biochemistry, Faculty of Science, University of Port Harcourt, Choba, Rivers State, Nigeria.

[§]**Corresponding author**: Mokwenye Ifeoma, Email: fycious@gmail.com

Abstract

Hyptis suaveolens is widely used in ethnomedicine for the treatment of bleeding and wounds amongst a number of other ailments. This study investigated the haemostatic activities as well as the effects of *Hyptis suaveolens* on some haematological parameters in Wistar rats. Preliminary phytochemical, mineral and trace metal analyses, as well as toxicity studies were carried out on the plant extract. Twenty (20) adult female Wistar rats having an average weight of 152.4 g were divided into four (4) groups comprising five (5) animals per group. Group 1 served as the control and received no treatment. Group 2 received 100 mg/kg bodyweight of extract; Group 3 received 200 mg/kg bodyweight of extract while Group 4 received 400 mg/kg bodyweight of extract. All treatments were administered orally for 21 days. The clotting time (sec), bleeding time (sec), prothrombin time (sec), partial thromboplastin time (sec) and haematological indices of the animals were all investigated and the results were analysed using one-way ANOVA. The extract significantly increased ($p \leq 0.05$) the clotting and bleeding times at 200 mg/kg and 400 mg/kg doses of administration compared with control. The extract also significantly increased the red blood cell (RBC) and haemoglobin (Hb) levels at all doses of administration compared with the control. The prothrombin and partial thromboplastin times along with other haematological parameters investigated, showed no significant variations. The significant lowering ($p \leq 0.05$) of the bleeding and clotting times of the animals that received 200 mg/kg and 400 mg/kg dose respectively of the extract compared with control, suggests that the aqueous extract of *Hyptis suaveolens* possesses haemostatic potentials.

Keywords: *Hyptis suaveolens,* clotting time, bleeding time, prothrombin time, partial thromboplastin time, haemostatis.

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INTRODUCTION

Medicinal plants remain a vital part of traditional or ethnomedicine in many parts of the world. In Africa and most developing nations, there is still a heavy reliance on herbal or traditional medicine for the treatment of diseases largely due to the availability, accessibility and potency of medicinal plants (Okoye *et al*., 2014).

Hytis Suaveolens (L.) Poit belongs to the genus 'Hyptis' which is a vast genus in the family Lamiaceae, having over 300 different species of herbs, shrubs, and even a few little trees (Mishra *et al.*,.2021). *Hyptis suaveolens* typically does well in warm, wet, tropical or subtropical climates, but can also withstand semi-arid climates (David *et al.,* 2021). *Hyptis suaveolens* is native to more than 50 countries on six of the seven continents including: Brazil, Polynesia, Ecuador, Belize, El Salvador, the Caribbean, Honduras, Puerto Rico, Jamaica, Mexico, Ghana, South Africa, Mauritius, Senegal and Nigeria (Li *et al.,* 2020). Names for this plant vary from country to country. Locally, it is known as bushmint, bush tea or pignut; in Brazil, it is called alfazema-brava, bamburral, or tapera velha; in El Salvador, chichinguaste; in Nicaragua, Chanor Picnut; in Mexico, Chia or Chan; and in China, Shan Xiang or maolaohu (Umedum *et al.,* 2014; Li *et al.,* 2020). In Nigeria, it is commonly called curry leaf. It is also called Daddoyata-daji in Hausa and Efiri in Yoruba (Okonta *et al*., 2021). Among Illah people of Delta, South South Nigeria, it is known as 'ogu anwuta', where it is widely used in homes to repel mosquitoes and also to arrest post-partum bleeding by traditional mid-wives (personal communication- Jidenmah Mokwenye 04/04/2019). The leaves of the plant are characterised by a strong minty odour if crushed. The plant is packed with medicinal essential oils and phytochemicals including; tannins, saponins, phenols, flavonoids, terpenoids, alkaloids, and sterols (Sharma *et al*., 2019; Li *et al*., 2020; Mishra *et al*., 2021; Aliyu et al., 2022) *H. suaveolens* possesses potent antioxidant and antibacterial properties maybe useful in treating common bacterial infections and disorders associated with oxidative stress (Bashir et al., 2019; Iqbal *et al*., 2021; Prabhakaran & Prathyusha 2022). The plant also possesses significant anti-inflammatory and wound-healing properties (Machado et al., 2021; Gayathri *et al*., 2021); as well as potent insect repellent/ insecticidal properties (Adjou *et al.,* 2019; Adelaja *et al*., 2021; Aremu *et al*., 2022; Ali *et al.,* 2022; Aliyu *et al.,* 2022). In Nigeria, *Hyptis suaveolens* plant has high health and economic value where it is widely used as seasoning, insect repellent, and in ethnomedicine as treatment for eczema/skin disorders, headaches, flatulence, diarrhoea, rheumatism, malaria and diabetes (Okoye et al., 2014; Abdulrahman *et al*., 2019; Olukowade *et al.,* 2021; Adelaja *et al.,* 2021; Okonta *et al.,* 2021).

Haemostasis is a physiological process that prevents blood loss as a result of injury through the production of a blood clot while maintaining blood fluidity (Zaidi & Green, 2019). It consists of three basic processes. The first is vasoconstriction, or the narrowing of blood vessels, at the location of the injury or damage; which is followed by the formation of a platelet plug as a transient blockage (primary haemostasis) and then finally, the formation of a fibrin clot (secondary haemostasis) (O'Donnell *et al.*, 2019). The haemostatic process is made possible by complex interactions between blood vessels and endothelial cells, platelets, coagulation factors, coagulation inhibitors, clot dissolution or fibrinolysis (Zaidi & Green' 2019). These complex interactions are tightly regulated and maintained in a delicate balance; and a deviation from this balance may predispose one to a higher risk of thrombosis or haemorrhage (O'Donnell *et al*., 2019; Zaidi & Green, 2019). As humans, the risk of injuries that may lead to haemorrhage is ever present. Pregnant women also bear the risk of post-partum haemorrhage with remains a leading cause of maternal mortality globally (Hawker & Weeks 2020). Serious metabolic and cellular damage and eventual death may result from uncontrolled, severe and prolonged haemorrhage (Huang *et al*., 2020). Haemostasis is vital to preserving lives and as such substances that will assist or even speed up the process should be studied (Tanko *et al*., 2012). Haemostatic agents can affect the process of haemostasis by influencing either of three basic steps or processes of haemostasis (Huang *et al*., 2020). In traditional medicine, Plants and herbs with haemostatic properties are used to control bleeding from injuries (Tanko *et al.,* 2012). *Hyptis suaveolens* plant has already been demonstrated by several researches to possess medicinal as well as wound healing properties. However, there are limited studies on its haemostatic activities. Thus, this study was designed to investigate the haemostatic

potentials of the aqueous extract of *Hyptis suaveolens* in Wistar rats.

MATERIALS AND METHODS

Plant materials

Fresh *Hyptis suaveolens* plants with healthy foliage were harvested from Ogbada, Illah in Oshimili North local Government Area of Delta State. Identification and documentation of the samples was done by Ekeke Chimezie (Ph.D) of the Department of Plant Science and Biotechnology, University of Port Harcourt and deposited in the herbarium with the voucher number UPH/V/1403.

Preparation of plant material

The leaves were rinsed in distilled water; air dried and ground using a manual blender. The ground samples were suspended in 3500 ml of distilled water and stirred thoroughly using a spatula for about 10 minutes. The mixture was sieved through clean muslin and the filtrate was first concentrated at 40 ^{0}C in a rotary evaporator to a fraction of the initial volume. The concentrate was then placed inside a water bath at 37 ^{0}C for total dryness. The extract was reconstituted to the desired concentration with distilled water before being used for treatment (Okoroiwu *et al.*, 2016).

Proximate, phytochemical and metal analyses

The proximate composition of the extract was analysed. The extract was also screened for the presence of some phytochemicals (alkaloid, flavonoid, saponin, tannin, oxalate, phytate and cyanogenic glycosides), metals (potassium, sodium, calcium and magnesium) and trace metals (chromium, nickel, copper, zinc, cadmium, lead, iron and manganese). All analyses were carried out following standard procedures (AOAC, 1995).

Animals

Adult female Wistar rats were used in this study. The animals were maintained at the animal house of the Department of Pharmacy, University of Port Harcourt. They were housed in well ventilated plastic cages under ideal laboratory conditions and fed with normal rat chow and water *ad libitum*. They were allowed a one-week acclimatization period before treatment commenced. All experiments conducted were in line with the standards of the Institutional Research Ethics Committee at the University of Port Harcourt and also the National Institute of Health Guidelines for Animal Care and Use of Laboratory Animals (National Institute of Health Publication Number, 85-23).

Acute toxicity studies

The extract's Oral acute toxicity (LD_{50}) was determined following the up-and-down method of acute toxicity testing: Twelve adult female Wistar rats weighing an average of 154 g were coded and assigned 3 groups, each group having 4 rats each. In Phase 1 treatment, each group received an oral dose of 200 mg, 400 mg, and 800 mg per kg (body weight) of extract respectively. After administration, the test animals were monitored closely for 48 hours for indications of toxicity or mortality. In Phase 2 treatment, the animals were then administered 600, 3200 and 5000 mg/kg (body weight) of the extract respectively. The animals were again monitored closely for 48 hours for indications of toxicity or mortality and the LD_{50} was determined (Bruce, 1985).

Experimental design and sample collection

Twenty adult female Wistar rats weighing an average of 152.4 g were allotted into four groups; each group having five animals. The extract was orally administered on a daily basis for twenty-one days. The dosage of administration was adapted, with modification, from Ikewuchi & Ikewuchi (2010). The assigned experimental groups are;

Group 1: (control animals) received daily normal feed and water.

Group 2: received daily normal feed and water + oral dose of *Hyptis suaveolens* extract (100 mg/kg bodyweight).

Group 3: received daily normal feed and water + oral dose of *Hyptis suaveolens* extract (200 mg/kg bodyweight).

Group 4: received daily normal feed and water + oral dose of *Hyptis suaveolens* extract (400 mg/kg bodyweight).

All investigations were conducted 24 hours after the administration of the final dose of treatment. The Bleeding and Clotting time experiments were conducted first, after which the animals were anaesthetized by exposure to diethyl ether and sacrificed. Blood was obtained through cardiac puncture from each rat into sodium citrate and EDTA (ethylenediaminetetra-acetic acid) sample

bottles. The samples in the sodium citrate sample bottles were immediately spun in a centrifuge for 15 minutes at 3000 rpm to obtain platelet poor plasma. The supernatant plasma was transferred carefully to fresh plastic test tubes to be used for prothrombin and partial thromboplastin analyses. The samples collected in the EDTA sample bottles were analysed for haematological indices.

Investigation of haemostastic parameters

Bleeding time

The bleeding time analysis was carried out utilizing Duke's method with some modifications (Okoroiwu *et al*., 2016). A surgical blade was used to make a small incision at the tip of the tail of each rat, just enough for it to bleed. A stop watch was started simultaneously as the first drop from the cut was seen. As bleeding continued, blood was cleaned off gently using a dry cotton wool swab every 15 seconds interval. The stop watch was stopped immediately there was no further visible bleeding from the cut.

Clotting time

To determine the clotting times of the animals, Ivy's method was employed with some modifications (Okoroiwu *et al.,* 2016). A dissection blade was used to cut the tip of the tail of each rat to cause bleeding. From the incision made, a single drop of blood was collected onto a clean dry microscope slide with a stop watch started simultaneously as the blood hit the slide. The tip of a clean dry pin was gently passed through the blood droplet on the slide at intervals of 15 seconds and the stop watch was stopped immediately a fibrin thread was observed.

Prothrombin time (PT)

Prothrombin time (PT) was analysed from the separated platelet poor plasma samples using a PT test kit from Giesse Diagnostics, Via Cervinara, 45-00132 ROME ITALY; following the manufacturer's protocol.

Activated partial thromboplastin time (APPT)

Activated partial thromboplastin time (APPT) was analysed from the separated platelet poor plasma samples using an APPT test kit from Giesse Diagnostics, Via Cervinara, 45-00132 ROME ITALY; following the manufacturer's protocol.

Analyses of haematological indices

Haematological analysis was carried out automatically using the Medonic M-32B 3-part hematology analyzer produced by Boule Medical, Sweden.

Statistical analysis

All the data evaluated were presented in form of mean ± standard error of mean (SEM). Evaluations of statistical significance were carried out using one-way ANOVA of the Statistical Package for Social Sciences (SPSS, version 20). Values of $p < 0.05$ were regarded as significant.

RESULTS

Analyses of the proximate, phytochemical and metal composition of *Hyptis suaveolens* extract

Analysis of the proximate composition of the extract showed that it contained: protein (6.56%), carbohydrate (8.71%), lipid (3.20%), fibre (0.81%), moisture (77.92%) and ash (2.80%). Phytochemical analysis revealed the presence of: alkaloid (2.48%), flavonoid (3.08%), saponin (1.60%), tannin (0.54%), oxalate (11.12%) phytate (4.83%) and cyanogenic glycosides (0.01 mg/kg). Metal analysis showed the presence of the following minerals: potassium (3213.00 mg/kg), sodium (67.98 mg/kg), calcium (2690.00 mg/kg) and magnesium (550.00 mg/kg); and trace metals: chromium (10.20 mg/kg), nickel (6.55 mg/kg) copper (18.45 mg/kg), zinc (117.00 mg/kg), cadmium (8.10 mg/kg), lead (24.25 mg/kg), iron (510.00 mg/kg) and manganese (60.05 mg/kg).

Acute toxicity studies

There were no indications of toxicity with respect to the parameters that were observed (salivation, erect fur, fur shedding, reduced movement, weakness, coma, convulsion, paw licking and stretching/ writhing) and no mortalities were recorded. It was determined therefore, that *Hyptis suaveolens* leaf extract is non-toxic and its LD_{50} was estimated to be greater than 5000 mg per kg body weight.

Effects of *Hyptis suaveolens* extract on bleeding and clotting times

The bleeding times of the animals treated with 200 mg/kg and 400 mg/kg of the extract were significantly lowered ($p \leq 0.05$) compared with control. Similarly, the clotting times of the animals

treated with 200 mg/kg and 400 mg/kg of the extract were significantly lowered ($p \leq 0.05$) compared with control (Table I).

Effects of *Hyptis suaveolens* extract on prothrombin and partial thromboplastin times

There were no significant alterations ($p \leq 0.05$) in the prothrombin and partial thromboplastin times at all the doses administered compared with control (Table II).

Effects of *Hyptis suaveolens* extract on haematological parameters

The extract, at all doses of administration significantly elevated ($p \leq 0.05$) the RBC count and the Hb levels compared with control. There were no significant changes in the other haematological indices (WBC, PCV, PLT, LYM, MCV, MCH, and MCHC) evaluated (Table IIIa and IIIb).

Table I. Bleeding and clotting times of aqueous *Hyptis suaveolens* extract treated Wistar rats

Parameter	Clotting time (sec)	Bleeding time (sec)
Group 1 (Control)	145.20 ± 10.28^a	148.40 ± 5.84^a
Group 2 (100 mg Extract/kg bw)	127.40 ± 7.28^a	134.60 ± 3.67^a
Group 3 (200 mg Extract/kg bw)	118.40 ± 3.50^b	114.60 ± 7.02^b
Group 4 (400 mg Extract/kg bw)	104.80 ± 4.68^b	77.60 ± 11.05^b

Values are mean ± Standard Error Mean (S.E.M). Values with superscript (^{b}) are significantly different at ($p \leq 0.05$) in comparison with the control (^{a})

Table II. Prothrombin (PT) and partial thromboplastin (APPT) times of aqueous *Hyptis suaveolens* extract treated Wistar rats

Parameter	PT (sec)	APPT (sec)
Group 1 (Control)	173.56 ± 10.35^a	214.60 ± 8.10^a
Group 2 (100 mg Extract/kg bw)	145.52 ± 20.55^a	179.60 ± 16.52^a
Group 3 (200 mg Extract/kg bw)	156.24 ± 19.28^a	200.00 ± 15.40^a
Group 4 (400 mg Extract/kg bw)	160.20 ± 15.66^a	205.00 ± 10.78^a

Values are mean ± Standard Error Mean (S.E.M). Values with superscript (^{b}) are significantly different at ($p \leq 0.05$) in comparison with the control (^{a})

Table IIIa Haematological indices of aqueous *Hyptis suaveolens* extract treated Wistar rats

Parameter	Hb (g/µL)	RBC (10^{12}/l)	WBC (10^{9}/l)	PCV (%)	PLT (10^{9}/l)
Group 1 (Control)	11.92 ± 1.07[a]	6.16 ± 0.53[a]	10.74 ± 1.88[a]	34.00 ± 1.82[a]	574.80 ± 82.72[a]
Group 2 (100 mg Extract/kg bw)	14.36 ± 0.19[b]	7.66 ± 0.20[b]	15.38 ± 1.34[a]	38.80 ± 0.80[a]	679.80 ± 54.25[a]
Group 3 (200 mg Extract/kg bw)	14.66 ± 0.45[b]	7.64 ± 0.28[b]	12.50 ± 1.69[a]	37.60 ± 1.12[a]	708.00 ± 47.59[a]
Group 4 (400 mg Extract/kg bw)	14.58 ± 0.38[b]	7.52 ± 0.25[b]	16.06 ± 1.49[a]	37.20 ± 1.07[a]	796.00 ± 63.45[a]

Values are mean ± Standard Error Mean (S.E.M). Values with superscript ([b]) are significantly different at ($p \leq 0.05$) compared to the control ([a])

Table IIIb Haematological indices of aqueous *Hyptis suaveolens* extract treated Wistar rats (cont'd)

Parameter	LYM (%)	MCV (fL)	MCH (pg)	MCHC (g/µL)
Group 1 (Control)	84.30 ± 3.65[a]	55.26 ± 1.34[a]	19.64 ± 0.29[a]	35.58 ± 0.58[a]
Group 2 (100 mg Extract/kg bw)	76.34 ± 3.07[a]	53.74 ± 1.36[a]	18.76 ± 0.29[a]	35.02 ± 0.49[a]
Group 3 (200 mg Extract/kg bw)	75.96 ± 3.34[a]	55.50 ± 1.22[a]	19.22 ± 0.17[a]	34.66 ± 0.71[a]
Group 4 (400 mg Extract/kg bw)	78.82 ± 2.50[a]	55.02 ± 1.33[a]	19.42 ± 0.29[a]	35.36 ± 0.35[a]

Values are mean ± Standard Error Mean (S.E.M). Values with superscript ([b]) are significantly different at ($p \leq 0.05$) compared to the control ([a])

DISCUSSION

In this study, the leaves of *Hyptis suaveolens* were found to contain in addition to basic food nutrients and minerals, phytochemicals such as; alkaloid, cyanogenic glycosides, flavonoid, oxalate, phytate, saponin and tannin in different concentrations; with oxalate, phytate, flavonoid and alkaloid having the highest concentrations. Similar phytochemical and mineral content of *Hyptis suaveolens* leaves have been reported in some other studies (Shenoy *et al.,* 2009; Ijeh *et al*., 2007). According to Edeoga *et al*. (2006), *H. suaveolens* is also rich in alkaloids, flavonoids, tannins, phenolics, saponins as well as essential oils. Flavonoids have been shown to have anti-cancer effects by stimulating apoptosis, inducing cell cycle arrest, inhibiting the proteasome, and interfering with the activity of cancer-causing enzymes (Mishra *et al*., 2021). Flavonoids also function as natural anti-inflammatory compounds (Choy *et al.*, 2019). Alkaloids are secondary metabolites that possess analgesic, antiplasmodial, and antibacterial properties (Okonta *et al*., 2021). The flavonoid and alkaloid content of *H. suaveolens* may contribute to its antioxidant, anti-inflammatory and antibacterial properties as a medicinal plant. The flavonoid and triterpenoid present in *Hyptis suaveolens* leaves may also play a role in its wound healing properties as demonstrated in a study by Shenoy *et al.* (2009).

The oral LD_{50} of *Hyptis suaveolens* extract which was determined in this study to be over 5000 mg per kg body weight indicates its non-toxicity and unlikelihood to cause adverse effects when administered orally. The LD50 for *Hyptis suaveolens* leaf extract was also found to be higher than 5000 mg/kg in other studies (Shenoy *et al.* 2009; Olukowade *et al.,* 2021)

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Haemostasis is a multistep process that keeps blood flowing normally under physiological settings and stops excessive bleeding after vascular injury (Zaidi & Green, 2019). It starts with vasoconstriction and the activation of thrombin, then moves on to the adhesion and activation of platelets, the formation of fibrin from circulating fibrinogen, and finally the inactivation mechanism of coagulation. (Tanko *et al*., 2012;). Platelet count and coagulation parameters mediated by both intrinsic and extrinsic pathways are crucial to the haemostasis process (Chinko & Amah-Tariah, 2020). The purpose of this study was to investigate the potential haemostatic activity of the aqueous leaf extract of Hyptis *suaveolens* by looking at how it affected the animals' bleeding time, clotting time, prothrombin time, and partial thromboplastin time. Clotting time is used to evaluate the intrinsic clotting factors (I, II, V, VIII, IX, X, and XII), whereas bleeding time is used to measure the activity of blood vessels and platelets during haemostatis (Sarkar *et al.*, 2019). Prothrombin time and activated partial thromboplastin time both evaluate the three pathways of coagulation-extrinsic, intrinsic and common (Sarkar *et al.,* 2019). The decrease in the bleeding time by the extracts could mean that it stimulated vasoconstriction and platelet plug synthesis while the reduction in the clotting times may be due to an influence of the extract on any of the clotting factors of the intrinsic pathway (Alkizim *et al.,* 2020). This shows that the extract has haemostatic abilities. The extract caused no changes in the prothrombin and activated partial thromboplastin times. This could mean that it had no involvement in the activities of these parameters. The haemostatic capabilities of *Hyptis suaveolens* aqueous leaf extract may be connected to its saponin and tannin contents as seen in its phytochemical analysis. Studies have found that tannins can arrest bleeding from an injured vessel by precipitating proteins to form vascular plugs (John-Africa & Aboh, 2015). Free calcium ions also play a crucial role in the haemostatic mechanism where they convert prothrombin to thrombin (Chinko & Amah-Tariah 2020). The high calcium content of *H. suaveolens* as seen in this study, may have contributed to its reduction effect on the clotting times of the animals. The process of wound healing involves the following connected steps; haemostasis, inflammation, proliferation and remodeling; with haemostasis being a critical first step (Hoffman, 2008). If haemostasis is compromised, wound healing is hindered. *Hyptis suaveolens* leaves showed significant haemostatic activities in this study and this could indicate its potential wound healing abilities. This validates an earlier study which revealed that *Hyptis suaveolens* petroleum ether leaf extract demonstrated wound healing abilities (Shenoy *et al*., 2009).

Investigation of haematological indices can provide useful insight about the occurence of disease/inflammation, stress factors and necrosis (Jurcik *et al*., 2007). It has also helped in determining the effects of a plant extract or product on an animal's blood (Yakubu *et al*., 2007). The elevation the red blood cell (RBC)

count and the haemoglobin (Hb) levels by the extract could mean that it stimulates erythropoiesis. The extract did not significantly affect the other haematological indices investigated and this could indicate its non-involvement in the activities of these parameters and further validates its non-toxcity.
The results obtained from this study have shown that *Hyptis suaveolens* extract possesses haemostatic abilities and shows no signs of toxicity.

CONCLUSION

It can be deduced therefore, that *Hyptis suaveolens* aqueous leaf extract has haemostatic properties as it significantly improved the bleeding and clotting times of the test animals. It can also be inferred that *Hyptis suaveolens* leaves are non-toxic, and consequently can be safely used as herbal medicine. Further studies to determine the biological active component/s responsible for its haemostatic activity as well as its haemostatic mechanism may be carried out in the future.

Conflict of interest

The authors have no conflict of interest to declare.

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Author contribution

IM, CCI and NFO conceived and designed the experiment. CCI created the experimental protocol, contributed reagents used for the analysis and supervised the laboratory experiments. IM procured the plant samples, carried out the laboratory experiments, performed the statistical analysis and compiled the manuscript. NFO supervised the laboratory experiment and revised the manuscript. All authors approved the final draft of the manuscript.

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