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Mulungu – Rainforest Anxiolytic

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1. Introduction

There are over one hundred species of plants of the genus *Erythrina* in the tropics and many of them are native to the American continent (Neill 1988). *Erythrina* species are known to produce alkaloids, flavonoids and terpenes (Garcia-Mateos et al., 1998). As with other species of *Erythrina*, alkaloids appear to be one of the main constituents mulungu (Parsons and Palframan, 2010). Mulungu (*Erythrina mulungu*) is a branched tree native to Brazil, growing in rain-forestry of Amazonia. Since its flowers are the same red color as coral, the plant is sometimes also called "flor de coral" and in English literature "coral tree". The designation *Erythrina* also includes the species *Erythrina velutina*, endemic to the semi-arid regions of Northeastern Brazil, and *Erythrina mulungu*, a plant native to Southern Brazil.

In native herbal medicine, a leaf or bark decoction or tincture from mulungu has long been used in folk medicine due to their tranquilizing effects and as natural sedative. It is also anxiolytic and antibacterial (Garín-Aguilar et al., 2000). In both Brazil and Peru mulungu is used for epilepsy (Vasconcelos et al., 2007). Practitioners in the United States use mulungu to quiet hysteria from trauma or shock, as a mild sedative to calm the nervous system, to treat insomnia and promote healthy sleeping patterns. Anxiety disorders are among the most prevalent psychiatric diseases and mulungu offers novel therapy chance (Balbani et al., 2009; Patocka, 2009). Latest the present results suggest that *Erythrina* has anxiolytic-like effects on a specific subset of defensive behaviors, particularly one that has been related in clinical terms to generalized anxiety. These observations support the popular use of extracts of the plant as tranquilizing agents.

2. Ethnobotany

Erythrina is a genus of flowering plants in the pea family, *Fabaceae*. It contains about 130 species, which are distributed in tropical and subtropical regions worldwide. They are trees, growing up to 30 m in height. The generic name is derived from the Greek word ερυθρός (*erythros*), meaning "red", referring to the flower color of certain species. These trees are religious for some ethnic minority and are used as floral emblems in many countries. For example Cockspur Coral Tree (*E. crista-galli*) is the national flower of Argentina and Uruguay. The Coastal Coral Tree (*E. caffra*) is the official city tree of Los Angeles, California. The state trees of Mérida and Trujillo in Venezuela are "bucaré ceibo" (*E. poeppigiana*) and Purple Coral Tree ("bucaré anauco", *E. fusca*), respectively. *E. variegata* is used as floral

emblem in Yonabaru, Okinawa. Some coral trees are used widely as street and park trees, especially in tropical countries. These trees are very suitable as "frame tree" for vanilla vines to grow up on or are used as "shade trees" in coffee or cocoa plantations (Westley and Powell, 1993). The plants of the genus *Erythrina* were used in Pre-Columbian America in traditional medicine (Towle, 2007) to calm agitation and for insomnia and other disorders of the nervous system.

3. Ethnopharmacology

Pharmacological assays performed with the alkaloids of *Erythrina americana* have shown anticonvulsant, hypnotic and analgesic effects (Garín-Aguilar et al., 2000; Koné et al., 2004). The species *Erythrina glauca* and *Erythrina lysistemon* have been reported to possess antiviral, antibacterial, and estrogenic activity (Ito, 1999; Tanee et al., 2007). Furthermore, analgesic and anti-inflammatory effects were observed for an aqueous extract of the stem bark of *Erythrina senegalensis* (Saidu et al., 2000).

Erythrina mulungu, tree high up to 10 m, is at home in South America. In Brasilia it is known as *colorines*, *chilicote* or *tzompanquahuitl* (Agra et al. 2007). In herbal medicine, a leaf or bark decoction or tincture from mulungu is considered to calm agitation and other disorders of the nervous system, including insomnia (Rodrigues and Carlini, 2003; Vasconcelos et al., 2007). Mulungu also decreased blood pressure and normalize heart arrhythmia (Begossi et al., 2004). There have also been some reports on the therapeutic use of the plant's inflorescence by herbal practitioners (Onusic et al. 2003). In Pre-Columbian civilizations decoction from the bark of this tree was used for suppression of fight fear and wartime hardship (Duke, 2008). At present, mulungu is used in the area of South America, mainly in Brasilia and Peru, as sedative and also in epilepsy (Teixeira-Silva et al., 2008).

People's healers and some practitioners in The United States use mulungu to quiet hysteria from trauma or shock, as a mild, hypnotic sedative to calm the nervous system, to treat insomnia and promote healthy sleeping patterns, to regulate heart palpitations, and to treat hepatitis and liver disorders. Nevertheless, despite its wide popular utilization, the supposed therapeutic properties of *Erythrina mulungu* only recently began to be evaluated in preclinical studies.

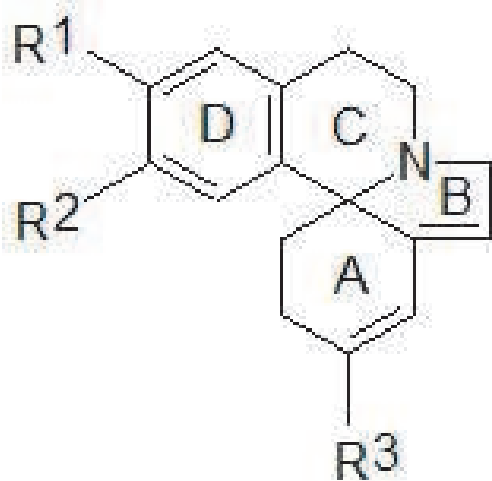
4. Chemistry of *Erythrina* constituents

The chemicals constituents of mulungu have been studied extensively after modern medical science find health potential of this biomedicine. In this biological material have been found large amounts of novel flavonoids, triterpenes, and alkaloids (Da-Cunha et al., 1996; Majinda et al., 2005; Cui et al., 2009). The genus *Erythrina* is very rich in secondary metabolites particularly of the flavonoids class. A literature survey showed the presence of flavanones, flavonols, chalcones, cinnamoylphenols, stilbenoids, isoflavones, isoflavans, isoflavanones, pterocarpanes, isoflav-3-enes, 3-phenoxychromones, coumestans, 3-phenylcoumarins, lignans, cinnamate esters, simple phenolics, triterpenes, sesquiterpenes, long-chain carboxylic acids, and long-chain alcohols (Majinda et al., 2005). Flavonoids represent a group of very active chemicals with various properties and are almost always present in *Erythrina* species.

The most considerable group of biologically active compounds of mulungu are alkaloids (Ozawa et al. 2009). The alkaloids have been found in 78 of 107 species in the genus

Erythrina; mulungu is documented with 20 isoquinoline alkaloids (Tanaka et al., 2008; Parsons and Palframan, 2010). The alkaloids accumulated not only at the end of maturation in the seeds but also in young tissues. On a dried basis, a high content of alkaloids was observed in flowers and dry seeds in comparison to low levels in dry pods. The highest concentrations were found in the mature seeds (García-Mateos et al., 1996). Many of these have demonstrated anti-inflammatory, cardioactive, narcotic, and sedative activities (Parsons and Palframan, 2010).

The pivotal structure of erythrinan alkaloids is tetraheterocyclic nitrogen compound with tetrahydroisoquinoline moiety called erythrinane (**I**) (Amer et al., 1991). Compounds of these structure were known for a long time (Koniuszy et al., 1949), but until medical science research of mulungu ignited concern over these alkaloids. Heft of erythrinan alkaloids are derivatives of **I** substituted at nucleus A and D by hydroxyl or alkoxy groups. The most considerable erythrinan alkaloids are erysotrine (**II**), erythravine (**III**), erysodine (**IV**), and erysopine (**V**) (Fig. 1) (Flausino et al., 2007a,b). For ever new erythrinan alkaloids are recovered (Tanaka et al., 2008; Cui et al., 2009, Parsons and Palframan, 2010).



Alkaloid	R ¹	R ²	R ³
I	H	H	H
II	OCH ₃	OCH ₃	OCH ₃
III	OCH ₃	OCH ₃	OH
IV	OH	OCH ₃	OCH ₃
V	OH	OH	OCH ₃

Fig. 1. Chemical structures of erythrinan alkaloids. Erythrinan alkaloids are derived from tetraheterocyclic nitrogen compound with tetrahydroisoquinoline moiety called erythrinane (**I**). Heft of erythrinan alkaloids are derivatives of **I** substituted at nucleus A and D by hydroxyl or alkoxy groups. The most considerable erythrinan alkaloids are erysotrine (**II**), erythravine (**III**), erysodine (**IV**), and erysopine (**V**).

5. Toxicology

Mulungu is relatively safe remedy. Acute oral toxicity (LD₅₀) of aqueous extract of stem bark of *E. variegata* was 425 mg/kg in mice (Pitchaiah et al., 2010). Lollato et al. (2010) estimated for extracts of *E. speciosa* LD₅₀ value for mice as being higher than 2000 mg/kg.

The toxicity of chloroform stem bark extract of *Erythrina senegalensis* DC, a medicinal plant with anti-inflammatory activity, was studied in vivo and in vitro by Udem and co-workers (2010). The LD₅₀ intraperitoneal of the extract was 526 mg/kg after an acute toxicity test (24 h). A brine shrimp lethality test with the extract gave LC₅₀ of 60.86 ppm. The chronic studies revealed alterations in the levels of biochemical markers of hepatic and cardiac damage. The alterations were, however, not significant except in the group fed the highest inclusion of the extract (1.0 g extract/kg feed) where significant ($p < 0.05$) increases in the activities of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase were observed. Hematological assessments of mice in this group showed significant ($p < 0.05$) decreases in the red blood cell count and the packed cell volume. Increases in the relative weights of the liver and heart were also significant ($p < 0.05$). Lipid peroxidation product levels assayed as malondialdehyde was significantly ($p < 0.05$) elevated in the groups fed 0.5 and 1.0 g/kg of feed at day 84. Significant histopathological changes like myocardial hemorrhages and degeneration of hepatocytes were observed in the heart and liver respectively.

Mulungu is less toxic than most of synthetic tranquilizers, e.g. LD₅₀ value for diazepam in mice at peroral administration is 49 mg/kg (Hogskilde et al., 1987). To evaluate the acute toxicity of the aqueous extract of *Erythrina velutina* leaves, which is frequently used in folk medicine as a tranquilizer, adult Wistar rats were treated *per os* with the limit dose of 5 g/kg of the extract and then observed for 14 consecutive days. No animals died and no signs of toxicity were detected either during the behavioral observations or at the autopsies, what indicates a reasonable lack of toxicity for the extract (Craveiro et al., 2010).

6. Biological activity

The traditional use of mulungu for anxiety and stress has been validated by researchers in a few studies, where it was shown to alter anxiety-related responses (Flausino et al. 2007a,b). An animal model (correlating to human generalized anxiety disorder, as well as panic disorder) was undertaken on a water-alcohol extract of mulungu (Vasconcelos et al. 2004; Ribeiro et al. 2006; Flausino et al. 2007a). Vasconcelos and co-workers (2004) studied the effects of hydroalcoholic extracts of both *Erythrina velutina* and *Erythrina mulungu* on the behavior of female mice submitted to the open-field test and to the elevated plus-maze after oral or intraperitoneal administration. The highest doses (800 mg/kg, oral, and 400 mg/kg, intraperitoneal) of the hydroalcoholic extracts decreased locomotor activity both in the open-field and in the elevated plus-maze test. The authors concluded that these results supported, at least in part, the popular use of the two species of *Erythrina* as tranquilizers in Brazilian folk medicine. Another study (Dantas et al., 2004) performed with intraperitoneal administration of an aqueous *Erythrina velutina* extract showed that the extract prolonged the duration of sleep induced by sodium pentobarbital at higher doses and blocked the acquisition of foot shock memory at lower doses. These results led the authors to propose that *Erythrina velutina* might interfere with the mnemonic process and might have a sedative action (Dantas et al., 2004).

The researchers reported that the mulungu extract had an effect similar to the commonly-prescribed anti-anxiety drug diazepam (Onusic et al. 2003; Ribeiro et al. 2006; Teixeira-Silva et al. 2008). Raupp and co-workers (2008) administered orally the hydroalcoholic extract of the stem bark of *Erythrina velutina* in mice submitted to the following tests: elevated plus-maze, forced swim, spontaneous locomotor activity, and habituation to active chamber. Chlordiazepoxide and imipramine were used as standard drugs. In the elevated plus-maze test, chronic, but not acute, *Erythrina velutina* (100 mg/kg) administration increased the percentage of open arm entries, an effect also seen in both acute and chronic treatments with chlordiazepoxide (7.5 mg/kg). In the forced swim test, only imipramine (25 mg/kg) decreased immobility time. Impairment of habituation was seen only with acute imipramine administration and with the lowest doses of *Erythrina velutina* extract tested in acute (10 mg/kg) and chronic (50 mg/kg) administrations. These results suggest that chronic administration of the hydroalcoholic extract of the stem bark of *Erythrina velutina* exerts an anxiolytic-like effect on mice, and it could serve as a new approach for the treatment anxiety, although it may have an amnesic effect at low doses.

It was suggested in many studies that the alkaloids in *Erythrina* may alter GABAergic neurotransmission (Ribeiro et al. 2006; Teixeira-Silva et al. 2008; Khanum and Razack, 2010). GABA acts as a neurotransmitter in the brain and abnormalities with its function is implicated in diseases including epilepsy, anxiety, and depression. Nevertheless, mechanism of anxiolytic effect of erythrina alkaloids is evidently different from diazepam. These alkaloids induced contractions seem to involve GABA_A receptor activation, acetylcholine release, muscarinic receptor activation, augmentation of Ca²⁺ entry through L-type calcium channels, and calcium release from the intracellular stores. These findings provide further support for *Erythrina velutina* traditional uses (Carvalho et al. 2009).

Hydroalcoholic extracts from the stem bark of *erythrina velutina* and *Eerythrina mulungu* have anticonvulsant effects only in the strychnine-induced seizure model, suggesting their possible action in glycine system and a potentiation of pentobarbital sleeping time, suggesting depressant action in the CNS (Vasconcelos et al. 2007). Data of Dantas and co-workers (2004) showed that the crude extract of *E. velutina* at lower doses interferes with mnemonic process for different tasks, while at higher doses, the sedative and neuromuscular blocking actions are the main effects. Anticonvulsant profile of erythrina alkaloids was recently studied by Faggion et al. (2011). They isolated the alkaloids (+)-erythravine and (+)-11- α -hydroxy-erythravine from the flowers of *Erythrina mulungu* and evaluated the action of these compounds against chemically induced seizures in rats (Faggion et al. 2011). These results showed that the administration of different doses of (+)-erythravine inhibited seizures evoked by bicuculline, pentylenetetrazole, and kainic acid at maximum of 80, 100, and 100%, respectively, whereas different doses of (+)-11- α -hydroxy-erythravine inhibited seizures at a maximum of 100% when induced by bicuculline, NMDA, and kainic acid, and, to a lesser extent, pentylenetetrazole (60%). All animals were protected against death when treated with different doses of (+)-11- α -hydroxy-erythravine in the tests using the four chemical convulsants. Identical results were obtained when using (+)-erythravine in the tests of bicuculline, NMDA, and pentylenetetrazole, and, to a lesser extent, kainic acid.

Further research has validated the traditional use of mulungu as an antimicrobial agent for throat and urinary infections. Mulungu has demonstrated antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, and antimycobacterial activity against *Mycobacterium fortuitum* and *M. smegmatis* (Virtuoso et al., 2005; Ferreira de Lima et al., 2006). Some

isoflavonoids, mainly erycristagallin (3,9-dihydroxy-2,10-di(gamma,gamma-dimethylallyl)-6a,11a-dehydropterocarpan), isolated from *Erythrina variegata* have antibacterial activity against cariogenic oral bacteria (Sato et al., 2003). The findings indicate that erycristagallin has a potential as potent phytochemical agent for prevention of dental caries by inhibiting the growth of cariogenic bacteria and by interfering with incorporation of glucose responsible for production of organic acids.

Two new compounds with antibacterial effect, erybacin A and erybacin B, were isolated from the roots of *Erythrina herbacea*. Their structures were established on the basis of spectroscopic analyses. Erybacin A is a rare, naturally occurring 1-hydroxy-1,3-diphenylpropan-2-one derivative. The isolated compounds were evaluated for their antibacterial activity against 13 strains of methicillin-resistant *Staphylococcus aureus* (MRSA). The new compound erybacin B showed a potent bactericidal activity against MRSA (Tanaka et al., 2010b).

Hydroalcoholic extracts from the stem bark and leaves of *Erythrina velutina* and *Erythrina mulungu* have also antinociceptive effects which was not reversed by naloxone, i.e. these are independent of the opioid system (Vasconcelos et al., 2003; Marchioro et al., 2005).

Alkaloid erysodine is a competitive antagonist at neuronal nicotinic acetylcholine receptors (Mansbach et al., 2000). The potent and competitive nature of erysodine's antagonism together with its ability to enter the brain after systemic administration suggest that erysodine may be a useful tool in characterizing neuronal nicotinic acetylcholine receptors (Decker et al., 1995). Recent findings show that erysodine and also dihydro-beta-erythroidine are potent and selective competitive inhibitors of alpha4beta2 nicotinic acetylcholine receptors (Iturriaga-Vásquez et al., 2010).

Erythrinan alkaloids cristanine A and cristanine B were isolated from the bark of *Erythrina crista-galli*. In Brazil, the bark of the title tree is used for the treatment of rheumatism and hepatitis as well as for sedation and hypnogenesis. However, the title alkaloids cristanine A and B are inactive concerning the inhibitory activity on lipopolysaccharide-induced nitric oxide production (Ozawa et al., 2010). Probably erythrinan alkaloids are also responsible for the antiinflammatory and analgesic effects of the ethanolic extract of *Erythrina indica* (Rajeev et al., 2010). *Erythrina indica* leaves are traditionally used in Kerala to treat inflammation, ulcers, earache etc.

7. Current practical use of *Erythrina*

Mulungu, drug from the tree *Erythrina mulungu*, is not very widely known or used in advanced countries. Mostly appearing as an ingredient in only a few herbal formulas for anxiety or depression. *Erythrina* plants produce alkaloids, flavonoids and terpenes and are commonly used in folk medicine due to their tranquilizing effects. Currently, the most widely prescribed medications for anxiety disorders are benzodiazepines. However, the clinical uses of benzodiazepines are limited by their side effects such as psychomotor impairment, potentiation of other central depressant drugs and dependence liability. Therefore, the development of new medications processing anxiolytic effect without the complications of benzodiazepines would be of great importance in the treatment of anxiety related disorders.

The use of herbal medicines by physicians in Europe, Asia, and America, exploring their traditional remedies to find a suitable cure of these 'mind affecting diseases' and herbal medicines are often considered to be gentle and safe alternative to synthetic drugs. Nevertheless, till this time no relevant clinical study exist.

Recently many studies of other *Erythrina* species from different parts of world appeared. These studies show that bioactive products of these trees may be useful in modern medicine also in other statements. From the bark of *Erythrina addisoniae* new flavonoids of stilbenoid type were isolated. These compounds are strong inhibitors of viral neuraminidases. Quite new compound, which is a formylated stilbenoid derivative, exhibited strong inhibition of both influenza H1N1 and H9N2 neuraminidases with IC₅₀ values of $8.80 \pm 0.34 \mu\text{g/mL}$ and $7.19 \pm 0.40 \mu\text{g/mL}$, respectively (Nguyen et al., 2010).

From the bark of *Erythrina abyssinica* has been isolated new coumestans and benzofurans with stimulatory effects on AMP-activated protein kinase (AMPK) (Nguyen et al., 2010) which has been proposed as a therapeutic target for the treatment of metabolic syndrome including obesity and type-2 diabetes. These results suggest that benzofurans and coumestans may be new lead compounds for regulating the AMPK enzyme. Prenylated flavanones from the same of source inhibited protein tyrosine phosphatase PTP1B activity in an *in vitro* assay with IC₅₀ values ranging from 15.2 ± 1.2 to $19.6 \pm 2.3 \mu\text{M}$, whereas very known potent inhibitor of PTP1B known as RK-682 (Hamaguchi et al., 1995) used as a positive control displayed an IC₅₀ value of $4.7 \pm 0.5 \mu\text{M}$ (Long et al., 2010).

Two new dimethylpyrano-isoflavones, named erymildbaedin A and B, were isolated from the stem bark of *Erythrina mildbraedi* - Cameroonian medicinal plant. Some of them strongly inhibited the growth of human breast, prostate, and endometrial adenocarcinoma cell lines (Tchokouaha et al. 2010).

Another flavonoids with the antibacterial activity were isolated from *Erythrina caffra*, deciduous subtropical tree indigenous to South Africa. All the compounds were active against both Gram-negative and Gram-positive bacteria. The minimum inhibitory concentration values obtained (MIC) ranged from $3.9 \mu\text{g/mL}$ to $125 \mu\text{g/mL}$ (Chukwujekwu et al., 2010). A new bis-isoflavonoid, biseryvarin A, was isolated from the roots of *Erythrina variegata*. Biseryvarin A is the first dimeric isoflavonoid possessing isoprenoid groups from the genus *Erythrina*. Biseryvarin A showed low activity MRSA. The methanol extract of the bark of *Erythrina variegata* showed significant anti-malarial activity toward *Plasmodium falciparum* *in vitro* using the lactate dehydrogenase assay. The ethyl acetate fraction showed the most activity, exhibiting equipotency against both strains of parasite with IC₅₀ of $23.8 \mu\text{g/mL}$ against 3D7 and $9.3 \mu\text{g/mL}$ against K1. Furthermore, by using the anti-malarial activity to follow separation, the ethyl acetate fraction was separated by combination of column chromatography to yield an active compound. The chemical structure of active compound was determined on the basis of spectroscopic evidences and comparison with those previously reported and identified as an isoflavonoid, warangalone. The warangalone showed anti-malarial activity against both strains of parasite used with IC₅₀ of $4.8 \mu\text{g/mL}$ against 3D7 and $3.7 \mu\text{g/mL}$ against K1 (Herlina et al., 2009). Next flavonoids were isolated from *Erythrina vogelii*, a Cameroonian medicinal plant (Ali et al. 2010), in *Erythrina senegalensis* were found hepatoprotective flavonoids (Njayou et al., 2010) with low toxicity (Atsamo et al., 2010). Flavonoids of pterocarpane-type with antibacterial, antiplasmodial and cytotoxic activities, were isolated from the stems of *Erythrina fusca* (Innok et al., 2010).

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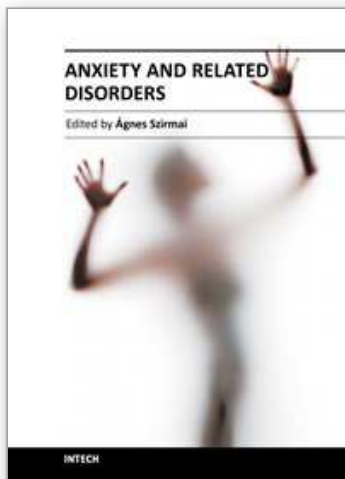
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Anxiety and Related Disorders

Edited by Dr. Ágnes Szirmai

ISBN 978-953-307-254-8

Hard cover, 292 pages

Publisher InTech

Published online 29, August, 2011

Published in print edition August, 2011

Anxiety disorders are one of the most common psychiatric disorders worldwide and many aspects of anxiety can be observed. Anxious patients often consult primary care physicians for their treatment, but in most cases they do not accept the diagnosis of anxiety disorder. Anxiety is a symptom that could be seen in many organic disorders and can accompany almost any psychiatric disorder. Anxiety disorders are frequent and are associated with significant distress and dysfunction. Stigmatization is an important factor in insufficient diagnosis. The problems of anxiety cover all fields of life. This book intends to describe the epidemiological aspects and the main co-morbidities and consecutive diseases of the anxiety disorders.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Patocka Jiri (2011). Mulungu – Rainforest Anxiolytic, *Anxiety and Related Disorders*, Dr. Ágnes Szirmai (Ed.), ISBN: 978-953-307-254-8, InTech, Available from: <http://www.intechopen.com/books/anxiety-and-related-disorders/mulungu-rainforest-anxiolytic>

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