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PHARMACOGNOSTICAL, PHYTOCHEMICAL AND ANTICANCER STUDIES OF *DENDROPHTHOE FALCATA* (L.F.) ETTINGSH. (LORANTHACEAE) GROWING ON THE HOST PLANT *AZADIRACHTA INDICA* (MELIACEAE)

SARITHA KODITHALA[1]*, G. PRAKASH YOGANANDAM[2] AND M. KIRANMAI[3].

[1]*Department of Pharmacognosy, Nizam institute of pharmacy, Deshmukhi, Nalgonda, Andhrapradesh, India.*
[2]*Department of Pharmacognosy, Mother Theresa Post graduate & Research Institute of Health Sciences (MTPG&RIHS), (A Govt. of Puducherry Institution) Indira Nagar, Gorimedu, Puducherry-605006, India.*
[3]*Department of Pharmaceutical Chemistry, Nizam institute of pharmacy, Deshmukhi, Nalgonda, Andhrapradesh, India.*

ABSTRACT

Objective: The present study is designed to study the pharmacognostical, preliminary phytochemical and anti cancer studies of *Dendrophthoe falcata* (L.f) Ettingsh (*Loranthaceae*) on the host plant *Azadirachta indica*(Meliaceae) . Materials and methods: Pharmacognostical studies involve the anatomical sections and powder analysis of leaf, physicochemical studies such as extractive values, ash values and fluorescent analysis were performed. For methanolic extract preliminary phytochemical studies revealed the presence of carbohydrates, glycosides, proteins, gums, mucilages, tannins and saponins. These findings will be useful towards establishing standards on identification, purity, quality and classification of the plant, which is gaining relevance in the plant drug research. Methanolic extract of the leaf prepared by soxhlet method of extraction was subjected to in vitro and in vivo (Ehrlich ascitic carcinoma cells) anti cancer activities. Results: The methanolic extract of *Dendrophthoe falcata w*as evaluated and compared against standard drug 5-flourouracil. 100mg/kg of methanolic extract (MEDF) shows significant anticancer activity which was in correlation with the presence of phenolic and flavonoid constituents of the extract**.** Conclusion: It was concluded that the anti cancer activity due to the presence of alkaloids, phenolics and flavonoids which are rich in *D.falcata* which grows on host plant *Azadirachta indica*, it may be because of the host plant which is rich in flavonoids and phenolics.

KEYWORDS: ***Dendrophthoe falcata, Azadirachta indica,*** **Methanolic extract of *D,falcata* (MEDF), 5-flourouracil and Ehrlich ascitic carcinoma cells,**

SARITHA KODITHALA
Department of Pharmacognosy, Nizam institute of pharmacy, Deshmukhi, Nalgonda, Andhrapradesh, India.

Corresponding author

INTRODUCTION

The genus *Dendrophthoe* is evergreen, shrubby partial parasitic plant distributed in the tropical and subtropical regions of the world. The whole parasitic plant is used in indigenous system of medicine as cooling, bitter tonic, astringent, aphrodisiac, narcotic, diuretic, pulmonary tuberculosis, asthma, menstrual disorders, swelling wounds, ulcers, renal and vesicle calculi and vilated conditions of kapha and pitta (1). *Dendrophthoe falcata* belonging to the family *Loranthaceae* is an angiospermic hemiparasitic plant was most frequently observed on many host plants, comprises of 20 species and about 7 species are found in India. The medicinal properties of *D.falcata* are generally influenced by the host plant for example, when grown on *Calotropus gigantia* (L) (*Asclepiadaceae)* the parasitic plant is considered useful for improving cognitive function, on *Tamarindus indicus* L (*Fabaceae*) it is used to treat impotence and on *Shorea robusta* (*Dipterocarpaceae*) it is used to treat paralysis, the fruit tastes sweet and consumed as the food (2). The leaf paste is reported to be used for skin diseases and is taken in abortions while its paste along with *Urtica doica* L (*Urticaceae*) is used to treat bone fracture (3). *D. falcata* bark juice/decoction used in menstrual troubles and asthma while its paste is applied on boils, setting dislocated bones and extracting pus. The decoction of whole plant is used to treat joint pains (4) and leaf juice is used for relief from chest pain (5), Quercetin, Kaempherol, Quercetrin are the different flavonoids isolated and reported from whole plant of *D. falcata*. (6,7). The reported biological activities of *D. falcata* are antioxidant, anti inflammatory (8), anti tumor (9,10), anthelmentic potential (11) anti nociceptive and general toxic studies (12), tablet binder (13), anticonvulsant and muscle relaxant (14), Immuno modulatory (15), wound healing and anti microbial (16), anti fertility (17) and anti hyperlipidaemic (18).

Cancer is one of the most dreaded disease of 20th century and spreading further continuously with increasing incidence in 21st century. Cancer is a group of more than 100 different diseases, characterized by uncontrolled cellular growth, local tissue invasion and distant metastases (19). Multidisciplinary scientific investigations are making best efforts to combat with this disease; perfect cure is yet to be brought into the world medicine. Cancer is caused by internal factors (tobacco, chemicals, radiation, hormones and immune conditions (20, 21) and can be treated with surgery, radiation, chemotherapy, hormone therapy and biological therapy. Over 60% of currently used anti cancer agents are derived in one way or other from natural sources including plants, marine organisms and micro organisms (22). It is estimated that more than 50% of all the patients diagnosed with cancer explore complementary and alternative medicine especially herbal medicine (23, 24). The anti cancer agents from plant sources are vinca alkaloids, cytotoxic podophyllotoxins from *Podophyllum hexandrum* (22,25), taxanes, camphothecins and combrestatins which are being used in cancer treatment with varied degrees of success (26,27). Different classes of antigenotoxicants have various mechanisms of action. Antigenotoxic activities of various phytochemicals have great potential in the fight against human cancer (28). The main objective of present study is to investigate the pharmacognostical, phytochemical and anti cancer potential of *D .falcata*, parasitic plant grown on host plant *Azadirachta indica.*

MATERIALS AND METHODS

Collection of leaf material and authentication

Plant material were collected by good collection practice from Piler, Chittoor Dt. Andhra Pradesh and it was identified by the botanist Dr. P. Jayaraman, Director, Plant Anatomy Research Center, Medicinal plant research unit, Tambaram, Chennai, with the voucher specimen number PARC/2008/207 and was kept in department of museum for future reference.

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PHARMACOGNOSTICAL STANDARDIZATION

Microscopical study of the leaves (22, 23)

Plant specimens for the proposed study were taken to select healthy plants and normal organs. The required samples of leaves were cut and removed from the plant and fixed in FAA (formalin-5ml+acetic acid-5ml+70% ethyl alcohol-90ml). After 24hrs of fixing, the specimens were dehydrated with a graded series of tertiary butyl alcohol. The specimens were cast into paraffin blocks. The paraffin embedded specimens were sectioned with the help of rotary microtome. The thickness of the section was 10-12 micro meter. The sections were stained with toluidine blue. For studying the stomatal morphology, venation pattern and trichome distribution, paradermal sections as well as clearing of leaf with 5%NaoH (or) epidermal pealing by partial maceration. Powered materials of different parts were cleared with NaOH and mounted in glycerin medium after staining. Different cell components were studied and measured. Results were showed in fig 1.

Physiochemical evaluations (24)

Dried leaf powder material was used for the determination of ash values, extractive values, Moisture content, stomatal number, stomatal index, palisade ratio, vein termination number and vein islet number (table no.1), phytochemical constituents such as Carbohydrates, proteins and amino acids, flavonoid, phenols, glycosides, alkaloids, tannins, gums and mucilage. All the reagents used were of analytical grade.

Extraction procedure

The leaves of the plant were shade dried and ground and ground to get a coarse powder of 60-80 mesh sieves. 120 gm of the powdered plant material was extracted successively using solvents of increasing polarity by soxhlet apparatus. The extracts were concentrated by distillation to yield a solid residue.

ANTICANCER STUDY

In vitro anti-tumor activity (9, 10)

Though animal models provide more predictable results, in-vitro testing is still preferred prior to in vivo testing of a potential chemotherapeutic agent. The tumor cell lines (U937 monocytoid leukemia) were obtained from National Facility for Animals Tissue and Cell culture, Pune, India. The growth of cell lines were maintained in RPMI -1640 medium supplemented with 10% heat inactivated fetal bovine serum and other essential antibiotics, cells were grown at 37^oC in a humidified atmosphere of 5% CO_2 and 90% air in a CO_2 incubator. 100µl of cell suspension and different concentration (5, 10, 20µg/ml) of test extracts were taken in a sterile 96 well micro titer plate. The viable count was done for the test extracts as well as standard drug (Ara-C 20µg/ml) by tryphan blue exclusion method.

In vivo antitumor activity

Collection of blood samples and determination of hematological parameters

Invivo anti cancer method was approved by the institutional ethical committee IAEC 52/2008 and blood sample were collected by retro-orbital plexus method and hematological parameter will be evaluated during the course.

Induction of cancer in experimental mice (30-31)

Adult Swiss albino mice of male sex weighing about (20-25g) over night fasted (IAEC 52/2008), were subjected to a single intra peritoneal injection of Ehrlich ascitic cells (1 x 10^6 cells). After injection, the animal had free access to food and water. Cancer was completely induced in 6 days. Animals divided into 5 groups. G- I serve as normal control which receives normal saline solution for 9 days. G- II Positive (Control) normal saline + 2x10^6 EAC cells suspended in BSS by IP route. G- III 50mg MEDF orally/Kg for 9 days +2x10^6 EAC cells suspended in BSS by IP route. G- IV 100mg MEDF orally/Kg for 9 days +2x10^6 EAC cells suspended in BSS by IP route. G- V 20 mg/Kg 5-Fluoro Uracil (standard) received by orally for 9 days + 2x10^6 EAC cells by IP route. After administration of last dose, followed by 18hrs fasting 3 mice from each were sacrificed

for the study of antitumor activity. Tumor volume, hematological parameters (Hb-content, RBC, and WBC differential count) was studied. From the remaining animals the median survival time (MST) and increased life span % (ILS %), were calculated after 6 weeks. Results were subjected to statistical analysis (ANOVA) to compare the efficacy along with standard.

RESULTS

Microscopic characters

Leaf: The leaf has smooth and even abaxial and adaxial sides and the midrib is more prominent on the abaxial side. The ground tissue inner to the adaxial epidermis consists of small, angular, densely tannin bearing cells (fig 1-3). The lower part of the midrib has large, circular ground parenchyma cells with less tannin content (Fig 4). The vascular system consists of three or four thick vertical segments of xylem with narrow thick walled angular cells. Phloem occurs along the lower end of each xylem segment (Fig. 5). The mesophyll tissue consists of an adaxial zone of two or three layers of palisade cells and adaxial band of similar palisade cells as the adaxial zone. The palisade is densely filled with tannin. In between the adaxial and abaxial tanniniferous palisade zones, occur 5 horizontal rows of spongy parenchyma. These rows have alternate circular, tanniniferous cells and vertically oblong hyaline cells, these two types of cells are in alternate horizontal rows (fig 5&6)

Venation: Lateral veins and vein-lets are thick and straight. The vein islets are fairly distinct wide and variable in size and shape (fig.7). The extreme ends of the terminations have clusters of short, rectangular tracheids are lignified and reticulatly pitted.

Stomata and epidermal cells: Oblong and rectangular width slit like stomatal pore (fig.8). The guard cells are 15x30µm, the stomata are parasitic type and have 2 or 4 rectangular subsidiary cells parallel to the guard cells.

Petiole (fig.9): Elliptical sectional view with short, thick and blunt wings the petiole was1.2mm thick and 1.8mm wide it have thin epidermal layer of small thick walled cells with prominent cuticular layers. The ground tissue was parenchymatous and homogenous. Brachyscleroids are abundant in the ground tissue. They are lobed with pointed arms and thick lignified wall. The lumen was wide and walls have simple canal like pits.

Powder microscopy of the leaf

Fragments of the lamina show unique venation. The major veins formed circular, seen a distinct vein-islets these are variable in shape and size. Within each islet separated by forked, dendroid vein terminations are seen. The terminations were short and thick. Epidermal peelings with stomata were also seen in the powder. The epidermal cells are polyhedral with straight walls. Stomata are elliptical to rectangular in shape and parasitic type (fig.10).

Scleroids

Brachy scleroids with amoeboid outline are abundant in the lamina. They were located whithin the mesophyll the isolated scleroids have a central body and pointed arms. This type of scleroids was called astroscleroids or star shaped scleroids (fig 11, 12).

Figure I
D.falcata exomorphic features, anatomical section of the leaf, petiole and powder characters of the leaf.

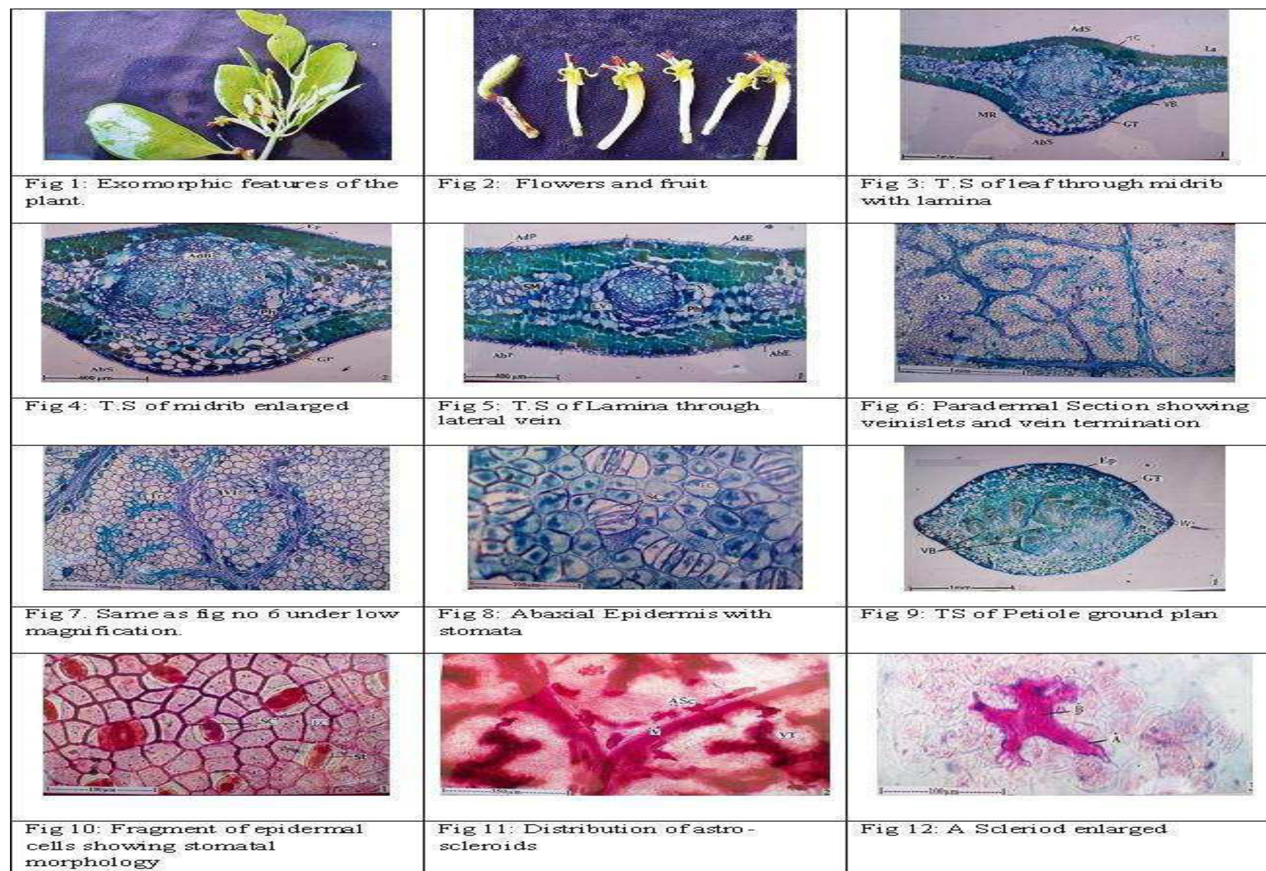

Fig 1: Exomorphic features of the plant.
Fig 2: Flowers and fruit
Fig 3: T.S of leaf through midrib with lamina
Fig 4: T.S of midrib enlarged
Fig 5: T.S of Lamina through lateral vein
Fig 6: Paradermal Section showing veinislets and vein termination
Fig 7. Same as fig no 6 under low magnification.
Fig 8: Abaxial Epidermis with stomata
Fig 9: TS of Petiole ground plan
Fig 10: Fragment of epidermal cells showing stomatal morphology
Fig 11: Distribution of astro-scleroids
Fig 12: A Scleriod enlarged

(ABE-Abaxial Epidermis, ABP-Abaxial Palisider Mesophyll, ADE-Adaxial Epidermis, ADP-Adaxial Paliside Tissue, Lb-Lateral Vein, Ph-Phloem,X- xylem, Sm-Spongy Mesophyll Tissue, TTR-Terminat Tracheids, Vi-Vein islets, Vt- Vein Termination, Ec-Epidermal cells, Sg-Subsidory cells, A-Arm, ASC-Astro Scleriods, B-Body of the scleroid, Ec-Epidermal Cells, Sc-Subsidory Cells, St-Stomata, V-Vein, Vt-Verin Termination).

Table 1
Physicochemical analysis of leaf powder of D.falcata

Parameters	Values	Parameters	Values
Stomatal number- Upper &Lower epidermis	128 &160	Aqueous extract	25.16(%w/w)
Stomatal index- Upper & lower epidermis	19 & 22	Methanol extract	4.25(%w/w)
Vein islet number	3-5	Ethanol extract	4.18(%w/w)
Vein termination number	4-6	Ethyl acetate extract	3.81(%w/w)
Total ash	10.11(%)	benzene	2.40(%w/w)
Water soluble ash	7.20(%)	Petroleum ether	1.76(%w/w)
Acid soluble ash, Sulphated ash	4.37 & 8.86(%)	Loss on drying	3.87(%)

Table 2
Short term In vitro Cytotoxicity (Tryphan blue exclusion Method) of MEDF

Concentration (µg/ml)	Number of Viable cells	Number of Death cells
control	120	2
10	100	10
20	80	22
30	65	33
40	50	40
50	48	55
100	22	82

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Table 3
long term in vitro cytotoxicity (MTT assay) of MEDF

Concentration(µg/ml)	OD-1	OD-2	OD-3	Average	% cytotoxicity
control	0.254	0.243	0.244	0.247	-
5	0.224	0.234	0.228	0.229	7.4
10	0.163	0.171	0.173	0.169	31.6
25	0.032	0.037	0.041	0.037	85.6
50	0.003	0.005	0.008	0.005	97.8

Table 4
Effect of MEDFon survival time, life span, tumor volume, EAC bearing mice.

Treated group	Survival time(days)	Increased life span (%)	Tumor volume(ml)
G-1	-	-	-
G-2	19.66±0.88	-	4.10±0.38
G-3	30.16±0.60	53.41	2.73±0.36
G-4	34.20±0.87	73.95	2.24±0.26
G-5	36.76±0.72	86.97	1.71±0.07

Statistical significance (p) calculated by one-way ANOVA followed by Dunnett's test.
****p < 0.01 calculated by comparing treated groups with EAC control group.***

Table 5
MEDFon heamoglobin, RBC, WBC (differential count) and Protein analysis.

Treatment Group	Hb(g%)	RBC (million/mm)	WBC (103cells/mm^3)	Lymphocytes	Neutrophils	Monocytes	Protein analysis (g/dl)
G-1	18.27±0.42	12.02±0.15	6.68±0.15	70.45±0.41	20.73±0.4	2.25±0.09	8.52±0.32
G-2	8.23±0.54	4.80±0.11	19.35±0.18	30.31±0.42	68.47±0.52	3.90±0.07	14.33±0.44
G-3	13.57±0.35	9.98±0.16	12.50±0.24	55.33±0.72	55.47±0.82	2.88±0.12	11.16±0.32
G-4	16.82±0.29	11.84±0.15	9.48±0.35	62.44±2.5	42.20±0.39	2.81±0.17	9.2±0.4
G-5	17.98±0.32	12.01±0.22	6.75±0.14	67.22±0.35	30.06±0.07	2.77±0.19	7.9±0.28

Statistical significance (p) calculated by one-way ANOVA followed by Dunnett's test.
****p < 0.01 calculated by comparing normal groups and treated groups with EAC control group.***

DISCUSSION

The plant *Dendrophthoe falcata* (L.f) Ettingsh family loranthaceae is a hemiparasitic plant which grows on different host plants. In the present study the *Azadirachta indica* (Neem) is the host plant. Folkloric uses of *D.falcata* are cooling, bitter tonic, astringent, aphrodisiac, narcotic, diuretic, pulmonary tuberculosis, asthma, menstrual disorders, swelling wounds, ulcers, renal and vesicle calculi and vilated conditions of kapha and pitta(1) and the plant was selected based on the literature survey. Morphological studies determine the evergreen leaves, coriaceous, highly variable in size and shape, most often ovate-oblong, 7.5 to 20 cm long and 2 to 10 cm wide, apex and base usually obtuse, margins often minutely white; petioles 0 to 13 mm long. Microscopical evaluation performed the transverse section of the leaf, midrib, lamina, petiole and the powder microscopy. Leaf has smooth even abaxial and adaxial sides. Midrib is more prominent on abaxial side. Adaxial side is broadly semicircular or slightly convex. Midrib has thin epidermal layers of small rectangular cells with thick cuticle. Ground tissue inner to the adaxial epidermis consists of small, angular, densely tannin cells. Since toluidine blue is a polychromatic stain and the staining results were remarkably good. The dye rendered pink color to the cellulose walls, blue to the lignified cells, dark green to suberin, violet to the mucilage, blue to the protein bodies etc.

Physicochemical studies determines the stomatal number (128 and 160), stomatal index (19 and 22), vein islet number (3-5), vein termination number **(**4-6). The determination of

ash values was carried out which gives an idea of the earthy matter or the inorganic composition and other impurities present along with the drug. Total ash (10.11%), water soluble ash (7.20%), acid soluble ash (4.37%) and sulphated ash (8.86%) respectively. The aqueous extractive values were determined highest and was recorded to be 25.1(%w/w) and methanol extract 4.25 (%w/w), ethanol extract 4.18 (%w/w), ethyl acetate extract 3.81 (%w/w), benzene 2.40 (%w/w), petroleum ether extract 7.60 (%w/w) in table 1, preliminary phytochemical screening revealed the presence of carbohydrates, proteins and amino acids, tannins, glycosides, alkaloids, saponins, flavonoids and phenolics.

Cancer is often associated with increased risk of death and the toxic side effects caused by the modern medicine, many cancer patients seek alternative and complementary methods of treatment such as usage of phyto medicine. Now a day's researchers are focusing their research towords the development of an eco friendly anti cancer drugs from plant source. The Ehrlich Ascitic carcinoma was initially described as a spontaneous murine mammary adenocarcinoma. It is a rapidly growing carcinoma with very aggressive behavior and is able to grow in almost all strains of mice (29). In ascetic form it has been used as a transplantable tumor model to investigate the anti tumor effects of several substances. Plant extracts were screened for their cytotoxic potentials against EAC cells (30, 31). In short term tryphan blue exclusion method 100 µg/ml shown the reduction in viable cell count and increase in death cells were observed results were shown in table 2. In long term in vitro cytotoxicity (MTT assay) 50 µg/ml shows the 97% may be due to the loss of mitochondria in table 3. In vitro and in vivo studies are performed. 100mg/kg of methanolic extract of *D.falcata* shows the significant results when compared with the standard drug. The observations are compared against standard drug and the results are found to be survival time (34.20±0.87), life span (86.97), tumor volume (1.71±0.07) in table 4 and heamoglobin (16.82±0.29), RBC (11.84±0.15), WBC (9.48±0.35), lymphocytes (62.44±2.5), neutrophils (42.20±0.39), monocytes (2.81±0.17) and protein analysis (9.2±0.4) in table 5, respectively

CONCLUSION

In the previous study on host plant *Shorea robusta, the D. falcata* showed the anti tumor activity. In our present study *D. falcata* on host plant *Azadirachta indica* was selected for the anti cancer activity and significant results were found when compared with all other host plants. Hence it was concluded that the anti cancer activity due to the presence of alkaloids, phenolics and flavonoids which are rich in *D.falcata* which grows on host plant *Azadirachta indica*, it may be because of the host plant which is rich in flavonoids, phenolics.

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