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**PHYTO-CONSTITUENTS BIOEFFICACY AND PHYTO-
PHARMACOLOGICAL ACTIVITIES OF TERMINALIA CHEBULA
- A REVIEW****Ranjeet Sawant¹, Sandeep V. Binorkar², Manish Bhoyar³ Gangasagre N.S.⁴**

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PHYTO-CONSTITUENTS BIOEFFICACY AND PHYTO-PHARMACOLOGICAL ACTIVITIES OF TERMINALIA CHEBULA - A REVIEW**ABSTRACT**

Background: *Terminalia chebula* Ritz. (T. chebula), which is a member of the Combretaceae family, is frequently used medicinal herb in *Ayurved*, *Unani*, *Siddha* & Homeopathy system of medicine. Traditionally & in folklore practices it is being used to treat most of the systemic disorders. This systematic review was conducted with an objective to search, explore & compile the phyto- chemical constituents & their efficacies to understand its potential as therapeutic agent.

Design, Material & method: Published scientific literature on T. chebula by various research scholars, organizations & Pharmacopeias were reviewed. The review criterion was restricted to bio-efficacy and phyto-pharmacological activities of *Terminalia chebula*.

Results and Conclusions: This review shows various experimental studies conducted on Bio-active compounds isolated from T. chebula has prospective use in alleviating ageing, cancer, various GIT disorders etc.

KEY-WORDS- Terminalia chebula, Haritaki, phytoconstituents, antioxidant, antineoplastic

INTRODUCTION:

Use of medicinal plant to cure specific ailments has been invoked from ancient times. This Medico lore is passed over from generation to generation traditionally all over the world. Nature has bestowed mankind with several plants which contains natural substances which cure diseases & promote health. Such medicinal plants are also rich sources to develop secondary metabolites which are also potential in curing different ailments. In the past decades there is increased attention and interest in use of herbal medicines globally. [1] The World Health Organization reported that 80% of the world population relies chiefly on traditional medicines involving the use of plant extracts or their active constituents. [2] Most of these traditional, ethno-medicinal herbs are utilized without any scientific validations. Therefore such treatments require thorough scientific investigations. *Terminalia chebula* (Haritaki) has been extensively used in *Ayurveda*, *Unani* & Homeopathy medicine & has become cynosure of modern medicine. The fruits of tree possess diverse health benefits and have been used as traditional medicines as house hold remedy. [3], [4], [5]

Recently, the herb is of great interest to researchers across the globe because of its reported medicinal properties like anti-oxidant, antibacterial, antifungal, anti-neoplastic, antiviral, anti-diabetic, cardio protective, Immuno-modulatory etc.[6] As *T. chebula* is a well known Rasayana which prevents aging and imparts longevity, immunity and body resistance against diseases and also used extensively in several Ayurvedic formulations prescribed for infectious diseases such as chronic ulcers, leucorrhoea, pyorrhoea and fungal infections of the skin. The purpose of this review was to gather the recent as well as previous published information on pharmacological, phyto-chemical and toxicological effects of the wonder drug *T. chebula* and present it before scientific community to facilitate for further researches and to understand the subject of its potential image as multi-dimensional therapeutic agent.

METHODOLOGY

Published literature on recent development in research related to *T. chebula* considering various research articles published by scholars in Central Database of Pubmed, various national & international indexed journals were reviewed. Also Monographs published by various research organizations & Pharmacopeia were studied to sought out the information about medicinal uses of *T. chebula*. Information extracted from 116 published articles and cross references thereof were collected. The search criterion was restricted to bio-efficacy and phyto-pharmacological activities of *Terminalia chebula*.

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BOTANICAL CLASSIFICATION

Kingdom : Plantae
Division : Magnoliophyta
Class : Magnoliopsida
Order : Myrtales
Family : Combretaceae
Genus : Terminalia
Species : chebula
Binomial name : *Terminalia chebula* Retz.

Plant Description

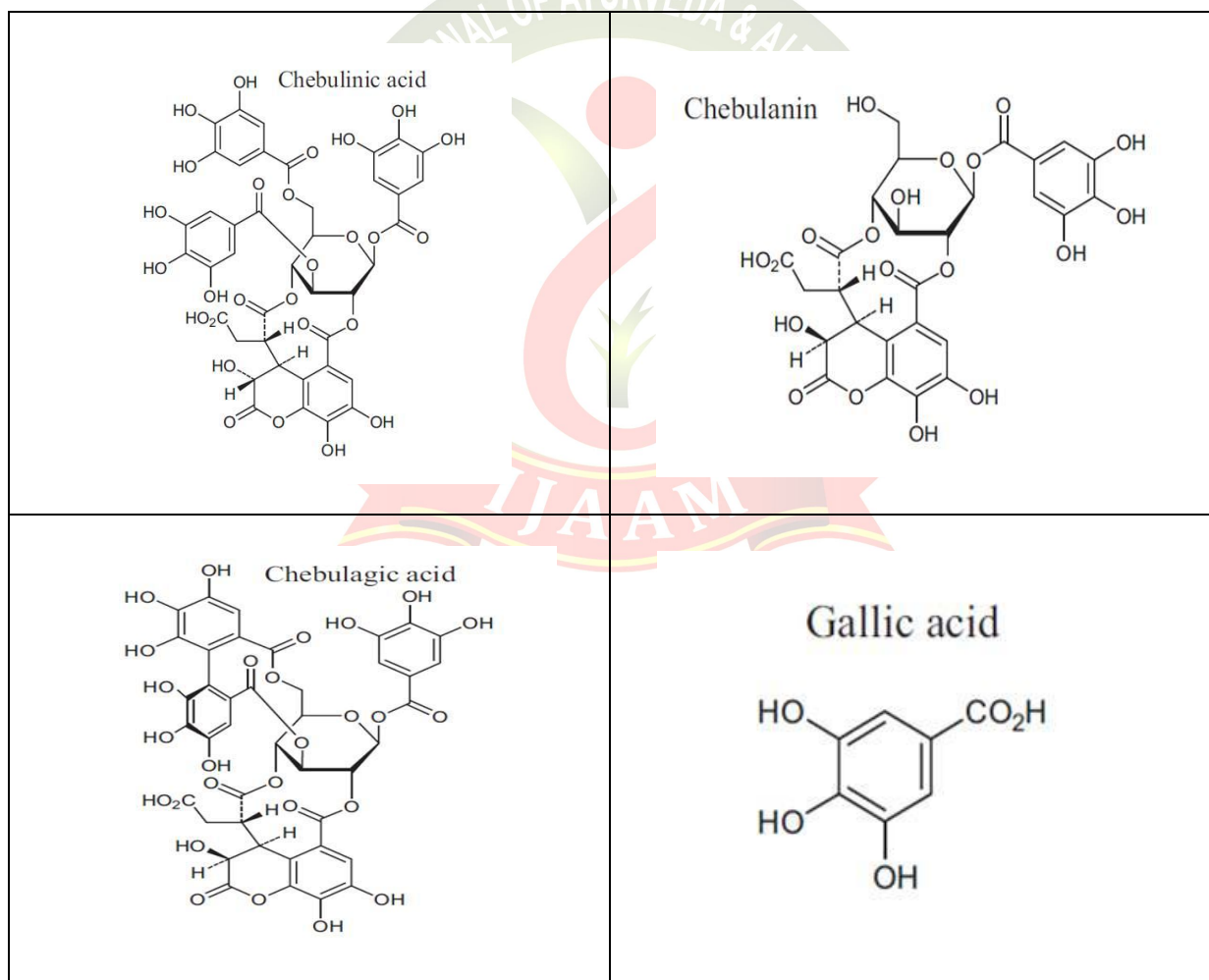
Terminalia chebula is a tree native to north east India & Indio-Burma region. It is a medium-sized deciduous tree with a height of up to 30 m. The leaves are elliptic rhombus, with an acute tip, cordate at the base, glabrous above a yellowish pubescence below. The flowers are monoecious, mono- tonous white to yellow, with a strong odor. The fruit are glabrous, ellipsoids ovoid drupes,

yellow to orange brown in colour. ^[7] [Figure 1, 2, 3, 4]

Phyto constituents

T. chebula, though contains several phytoconstituents like tannins, flavonoids, sterols, amino acids, fructose, resin, fixed oils etc., however, it is fairly rich in different tannins (approximately 32% tannin content). Further, tannin content of *T. chebula* largely depends on its geographic location. The chief components of tannin are chebulic acid, chebulinic acid, chebulagic acid, gallic acid, corilagin and ellagic acid. ^[8] [Figure 5, 6, 7, 8]

Phytochemicals like anthraquinones, ethaedioic acid, sennoside, 4,2,4 chebulyl-d glucopyranose, terpinenes and terpinenols have also been reported to be present. ^{[9], [10]} Recent studies shows that *T. chebula* contains more phenolics than any other plant. ^[11]

**Pharmacological Activities**

Various tannins and alkaloids found in *T. chebula* have many potential uses in medicine. It has been found to be hepatoprotective, anti-neoplastic,

immunosuppressive & a potent alpha-glucosidase inhibitor, useful in diabetic studies etc. It has been shown to be active

against *Staphylococcus aureus* and *Candida albicans*.

Antibacterial activity

T. chebula exhibited antibacterial activity against various Gram positive, Gram negative bacteria such as *Salmonella typhi*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Bacillus subtilis* and *Pseudomonas aeruginosa* suggesting its broad spectrum antimicrobial activity. [12], [13], [14], [15], [16] [17] [18] Another study revealed that gram positive organisms inhibited on larger extent as compare to gram negative organisms. [19] The gallic acid and ethyl ester showed effects methicillin-resistant *Staphylococcus*. [20] *T. chebula* is well effective against *Helicobacter pylori*, a bacterium responsible for gastritis, ulcer and stomach cancers. [21]

T. chebula fruit extract had strong antibacterial activity against intestinal bacteria, *Clostridium perfringens* and *Escherichia coli* [22]

Anti-amoebic & anti-protozoal activity

T. chebula showed anti-amoebic activity against *Entamoeba histolytica* in experimental caecal amoebiasis in vivo. [23] The acetone extract of *T. chebula* seeds showed anti plasmodial activity against *Plasmodium falciparum*. [24]

Antifungal activity

An aqueous extract of *T. chebula* exhibited antifungal activity against a number of dermatophytes and yeasts. It is effective against the pathogenic yeast *Candida albicans* and dermatophytes *Epidermophyton*, *Floccosum*, *Microsporum gypseum* and *Trichophyton rubrum*. [25], [26], [27], [28]

Antiviral activity

The extract of fruits of *T. chebula* showed inhibitory effects on human immunodeficiency virus-1 reverse transcriptase. [29], [30] A study proved that *T. chebula* fruits contain four human HIV-type 1 integrase inhibitors such as gallic acid and three galloyl glucoses, and suggested that galloyl moiety had a major role for inhibition of the 3'-processing of HIV-1 integrase by these compounds. [31], [32] The aqueous extract of *T. chebula* executed the most prominent Anti-HBV activity by decreasing the level of extracellular HBV virion DNA at concentration ranging from 64 to 128 µg. [33] Two hydrolyzable tannins, chebulagic acid and punicalagin, isolated from the dried fruits of *T. chebula* inhibited HSV-1 entry at non-cytotoxic doses in human lung cells by preventing binding, penetration, and cell-to-cell spread, as well as secondary infection. [34], [35]

Immuno-modulatory activity

Aqueous extract of *T. chebula* produced an increase in humoral antibody titer and delayed type hypersensitivity in mice. [36] Crude extract of *T. chebula* stimulated cell mediated immune response in experimental amoebic liver abscess in golden hamsters. [37] *T. chebula* found effective against the progression of advanced glycation end products induced endothelial cell dysfunction [38]

Anti-neoplastic activity

Ethanol extract of fruit inhibited cell proliferation, induced cell death in several malignant cell lines of human (MCF-7, HOS-1, PC-3, PNT1A) and mouse (S115). [39] In another study, Acetone extract of bark and fruit powder of *T. chebula* exhibit anti-carcinogenic activity. [40] In all cell lines studies, the extract decreased cell viability, inhibited cell proliferation, and induced cell death in a dose dependent manner. [41]

Anti oxidant activity

T. chebula exhibited anti-lipid peroxidation, anti-superoxide radical formation and free radical scavenging activities. [42], [43], [44], [45] In vitro evaluation of *T. chebula* shows that tri-ethyl chebulate is a strong antioxidant and free-radical scavenger, which might contribute to the anti-oxidative ability. [46] The aqueous extract of *T. chebula* seems to be able to protect cell organelles from radiotherapy induced damages. [47]

Antidiabetic activity

Methanolic extract & chloroform extract of *T. chebula* reduced the blood sugar level in normal and alloxan diabetic rats significantly. [48], [49] *T. chebula* fruit and seeds also exhibited dose dependent reduction in blood glucose of streptozotocin induced diabetic rats both in short term and long term study. [50], [51]

Hypolipidemic and hypocholesterolemic activity

T. chebula extract showed Hypolipidemic activity against experimentally induced atherosclerosis & cholesterol-induced hypercholesterolemia in rabbits. [52], [53], [54], [55], [56] *Triphala* (*T. Chebula*, *T. Belerica*, *E. Officinalis*) formulation was found to have hypolipidaemic effects on the experimentally induced hypercholesteremic rats. [57] The *Vara Asanadi Kwath* (Poly herbal decoction) showed significant reduction in hyper-lipidemia in high fat diet induced hyperlipidemic rats. [58]

Cardioprotective activity

Cardioprotective effect of ethanolic extract of *T. chebula* fruits was demonstrated in isoproterenol induced myocardial damage in rats. It was

documented that pre treatment with *T. chebula* extract had cardioprotective effect. [59], [60], [61] Pericarp of *T. chebula* has also been shown cardio-protective activity in isolated frog heart model. [62]

Hepatoprotective activity

Ethanollic extract of *T. chebula* fruit showed strong hepatoprotective activity. [63] It also showed similar property against anti-tuberculosis drug Rifampicin, Isoniazid and Pyrazinamide (combination) induced toxicity due to its prominent anti-oxidative and membrane stabilizing activities. [64] Protective effects of an aqueous extract of *T. chebula* fruit on the tert-butyl hydroperoxide-induced oxidative injury was observed in cultured rat primary hepatocytes and rat liver has also been documented. [65], [66]

Antinociceptive activity

The ethanolic extract of *T. chebula* fruits showed a potential drug for bioactivity-guided isolation of natural analgesic agents in the management of chronic pain. [67]

Anti-anaphylactic activity

animal study show that when extract of *T. chebula* was administered following induction of anaphylactic shock, the serum histamine levels were reduced, indicating its strong anti-anaphylactic action. [68], [69] Aqueous extract of *T. chebula* showed significant increasing effect on tumor necrosis factor-alpha production from rat peritoneal mast cells representing its strong anti-anaphylactic action. [69]

Wound healing activity

Topical administration of alcoholic extract of the leaves of *T. chebula* caused much faster healing of rat dermal wounds in vivo. [70], [71], [72] Extract-treated incision wounds showed increased tensile strength of tissues by about 40%. [61] In alloxan induced diabetic rats, the extract of *T. chebula* fruit exhibited 82% reduction in the wound area due to faster epithelialization compared to controls. [73] Tender fruit extract of *T. chebula* promoted cutaneous wound healing in rats due to a powerful anti-bacterial and angiogenic activity. [74] A paste prepared from *T. chebula* & *T. belerica* offers a distinctive on wound healing activity. [75]

Radio protective & Chemo modulatory activity

T. chebula extract in dose of 80 mg/kg body weight prior to whole body irradiation of mice resulted in reduction of peroxidation of membrane lipids in the liver and decrease in radiation-induced damage to DNA. [76] *T. chebula* extract also protected the human lymphocytes from undergoing the gamma radiation induced damage

to DNA exposed in vitro to gamma-radiation. [76], [77] *T. chebula* extract could be used as therapeutic agent for cancer prevention as it blocked or suppressed the events associated with chemical carcinogenesis. [78] The study showed radio-protective effect of aqueous extract of Triphala in mice exposed to gamma radiations with highest number of survivals. [79]

Cytoprotective activity

Gallic acid and chebulagic acid, isolated from fruit extract of *T. chebula*, blocked cytotoxic T lymphocyte (CTL)-mediated cyto-toxicity. [80], [81] The life-span of HEK-N/F cells was elongated by 40% in UVB-induced oxidative damage exhibiting cytoprotective effect. [82] It exhibited the development of duodenal ulcers and appeared to exert a cytoprotective effect on the gastric mucosa in vivo [83]

Anti-arthritis activity

The hydroalcoholic extract of *T. chebula* produced a significant inhibition of joint swelling as compared to control in both formaldehyde-induced and CFA-induced arthritis. *T. chebula* could be used as a disease-modifying agent in treatment of rheumatoid arthritis. [84] Study shows that acetone extract of *T. chebula* fruits have better effect on controlling CFA induced arthritis showing the definite effect in reducing the inflammatory components. [85] Aqueous extract of dried fruit of *T. chebula* showed anti-inflammatory by inhibiting inducible nitric oxide synthesis. [86] Chebulagic acid extracted from tender fruit of *T. chebula* significantly suppressed the onset and progression of collagen induced arthritis in mice. *T. chebula* in a polyherbal formulation (Aller-7) exhibited anti-inflammatory effect against arthritis in rats. [87]

Gastro enteric activity

T. chebula displaced potential antiulcerogenic activity in ethanol & cold restraint stress induced ulcer method in rat. [88] Intragastric administration of the crude drug to rats, at a dose of 1.5 g/l for 15 days, reduced the number of gastric ulcerations induced by pentagastrin and carbachol. [89] The methanolic extract of *T. chebula* showed significant reduction in gastric volume, free acidity & ulcer index in pylorus ligation and ethanol induced ulcer model wistar rats. [90] In a study on Charles foster rats, it was found that *T. chebula* increases the percent gastric emptying suggesting its usefulness as alternative to prokinetic drugs available today. [91] A study showed Purgative action of an oil obtained from *T. chebula*. [92]

Anti-allergic activity

T. chebula, ingredient of a poly herbal formulation (Aller-7), showed potent in vitro anti-allergic activity. [87] Hydro-ethanol extract of *T. chebula* exhibit antihistamine and antispasmodic in guinea-pig ileum. [93] Oral administration of an aqueous extract of fruit significantly suppressed histamine release from rat peritoneal mast cells [94] and also significantly increased production of tumour necrosis factor (TNF) by anti-dinitrophenyl IgE. [95]

Antiplasmodial activity

The water extract of *T. chebula* showed antiplasmodial activity in vitro in multidrug-resistant strain of *Plasmodium falciparum* [96] and in vivo study of *T. chebula* seed Acetone extract showed anti-plasmodial activity in a study. [24]

Anti-helminthic activity

The extracts of dried leaves and seeds of *T. chebula* showed complete inhibition by ovicidal and larvicidal activities in ethyl acetone and ethanol extracts tested in vitro. [97]

Anticaries activity

The aqueous extract of *T. chebula* strongly inhibited the growth, sucrose induced adherence and glucan induced aggregation of *Streptococcus* mutants. Mouth rinsing with a 10 % solution of the extract inhibited the salivary bacterial count and glycolysis of salivary bacteria for up to 90 min post rinsing. [98], [99], [100]

Nephroprotective effect

The fruit extract of *T. chebula* is helpful to alleviate the cadmium induced nephrotoxicity in rats. [101] The Vara Asanadi Kwath (decoction) showed significant reduction in hyper-lipidemia in high fat diet induced hyperlipidemic rats. [58]

Anti-spermatogenic activity

The oral administration of ethanolic extract of bark of *T. chebula* showed histological alterations in seminiferous tubules in testes of mice at dose of 300 mg/kg bw for 28 days. The level of sialic acid in the epididymis and that of fructose in the seminal vesicle were significantly reduced in aqueous extract-treated mice compared to controls. [102] male rats treated with *T. chebula* fruit extract at 100mg/kg dose showed significant decrease in motility, count and increase in morphological abnormalities in spermatozoa. [103]

Toxicology & Drug interaction

Dietary administration of the fruit to rats, as 25% of the diet, produced hepatic lesions which included centri-lobular vein abnormalities and centri-lobular sinusoidal congestion. Marked renal

lesions were also observed, and included marked tubular degeneration, tubular casts and inter-tubular congestion. A brown pigmentation of the tail and limbs was also observed after 10 days. [104] The median lethal dose of a 50% ethanol extract of the fruit was 175.0 mg/kg bw after intra-peritoneal administration. [105] Acute toxicity study conducted in rats with water extracts of dried fruits of *T. chebula* at single dose of 5000mg/kg bw did not show any toxicity signs. [106] whereas studies conducted in mice shows the dose of > 3gm/kg bw found lethal. [107] In chronic toxicity study for 270 days female rats revealed no significant difference in weight gain. However male rats significantly showed slight decrease in body weight & body weight gain. In the entire period of study, no sign of morbidity & disease seen. [106] Hematological values suggest that the extract did not cause any defects in rat. [108] On chemical examination of blood reveals minor changes but within normal range. [109], [110] In another oral toxicity study, the single oral dose of the extract at 2000 mg/kg did not produce mortality or abnormal lesions in the internal organs of rats. [111] A report describes two relapse of depression in patient well controlled with Citalopram after starting an ayurvedic herbal mixture containing *T. chebula*. [112] Also just like combination of acetaminophen and alcohol can potentiate hepatotoxicity so too *T. chebula* fruits can create hepatotoxic combination when undergo metabolism with tetracycline, erythromycin or chlorpromazine. [113]

RECENT STUDIES ON T. CHEBULA

Topical application of *Terminalia chebula* extract found to reduce inflammation caused by croton oil-induced dermatitis in mice. [114] Aqueous extracted carbohydrate polymer from *T. chebula* showed anti-tussive Activity on Citric Acid-Induced Cough. [115] The optimum extract obtained from fruit of *T. chebula* suggests its use as a biological alternative for eradication of biofilm formation in medical devices in place of commonly used hospital chemical biocides. [116] A study on *Terminalia chebula* 10% mouth rinse demonstrated reduction in microbial plaque, gingival inflammation and neutralizing salivary pH in comparison with chlorhexidine 0.12% mouth rinse. [117] Apart from this there are several therapeutic potentials of the wonder drug *T. chebula*. [118] It is being continuously screened for further pharmacological, phytochemical & medicinal activities. Continuous review is required for the benefit of all ayurvedic and traditional practitioners, researchers so that the horizon of prescribing *T. chebula* in proper form, precise dose with proper indication will be extended.

DISCUSSION

Traditional medicinal herbs have been exhibiting a crucial role in treating various disorders since centuries. Several existing medicines are directly or indirectly derived from higher plants. Hence plant derived drugs have an important place in both traditional and modern medicine. The plants of Genus *Terminalia* comprise 250 species widely distributed all over the world. [119] Among those *T. chebula* species possesses extreme medicinal values in Ayurveda, Unani, Siddha & Homeopathy. Various reviewed literature has reported antimicrobial, antifungal, anti oxidant, cytoprotective, antiviral, antidiabetic, wound healing, cardio protective, anti-neoplastic, immune-modulator etc. Varieties of *T. chebula* & their detailed indications have been mentioned in several ayurvedic classics. [120] Most of the studies are mainly concentrated on antioxidant, antimicrobial & antineoplastic properties. Various hydrolysable tannins such as gallic acid, chebulic acid, punicalagin, chebunanin, neo-chebulinic acid, ellagic acid, chebulagic acid, chebulinic acid have been isolated from the fruits of *T. chebula*. Most of these phytoconstituents are present in different molecular form such as dimers, tetramers & polymers. The molecular form depends on method of extraction. In aqueous and ethanolic extracts lower molecules are prevalent which is advantageous in medical point of view. [120] Ayurveda comprises the holistic approach where as reviewed experimental studies focused on efficacy of isolated individual phyto-constituents. Though *T. chebula* has a number of pharmacologically active components, very little work has been done clinically evaluating its efficacy on isolated compounds.

CONCLUSION

In spite of the intense control and our dependence on contemporary medicines and remarkable advances in synthetic drugs, a huge fragment of the world population is still using herbal drugs. *T. chebula* is one of the most important medicinal herbs used in medication of complementary & alternative medicines because of having a number of pharmacological properties. Theoretical studies are still challenge in microbiological studies as there could be variations in experimental conditions & reality. The data obtained should be further investigated for the validation in support with further researches.

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