Botany, phytochemistry, pharmacology and Unani traditional uses of Jadwar (Delphinium denudatum Wall.): A Review

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ABSTRACT

Delphinium denudatum Wall (DD), commonly known as Jadwar in India, is an essential plant of the Unani system of medicine. In Unani medicine, Jadwar is considered an antidote to poisons, refrigerant, nerve tonic, cardiotonic, demulcent, lithotriptic, diuretic, and antipyretic. It is beneficial in the treatment of fungal infections, paralysis, facial palsy, epilepsy, infantile convulsions, migraine, mania, hysteria, numbness, tremors, cholera, jaundice, cardiac diseases, arthritis, rheumatism, toothache, aconite poisoning, snake bite, scorpion sting and all kinds of pain. Many bioactive constituents are isolated from DD, including flavonoids, triterpenoids, alkaloids, including delphocurarine, staphisagrine, delphine, condelphine, denudatin, delnudine, delnuline, vilmorri anonymouse, vilmorrianone, a diterpenoid alkaloid. The scientific analysis of Jadwar demonstrates many of the activities mentioned in Unani literature. Nevertheless, further research is needed to identify the mechanism, active constituent, and usefulness of Jadwar in clinical practice. Given the encouraging results against neurological disorders in the prefaces, this aspect should be thoroughly investigated to make it a standard medicine.

Keywords: Delphinium denudatum, Jadwar, Nirbasi, Unani medicine, Neuroprotective; Antidote.

INTRODUCTION

Herbal medicine is one of the most excellent branches of complementary and alternative medicines used for various ailments since ancient times [1]. Delphinium denudatum Wall. ex Hook.f. & Thomson (Ranunculaceae), commonly known as Jadwar in India, is a medicinal herb consist of dried tuberous roots of DD. It is found in Western Himalayas at altitudes of 8000 to 12000 ft, mainly on grassy slopes. Its length varies from 40 to 80 cm [2-5]. The name Delphinium is derived from a Greek word, which means dolphin, as the nectar resembles a dolphin [6]. The term jadwar is Persian “jadwar” in Arabic, meaning the great purifier or antidote [5]. The Persian name Malh-Parvin (moon and Pleiades) is possibly given to this plant as it blossoms at the beginning of summer when the Pleiades rise [7]. Due to its antidotal properties, Jadwar in India was named Narbasi / Nirbisi [8]. Nir means opposing or eliminating, and Bisi means poison (Bis or Vish). Bis of Nirbisi is also used for aconite poison, as Jadwar is the antidote of aconite poisoning. [7]. It is protected externally by suberized metaderm, which is made up of brown tubular cells. It is characterized by its relatively small blue and purple flower [2].

Hindus suppose the only plant that can grow in the vicinity of aconite is the Jadwar, which is an antidote to it, and they also say that there is a kind of rat called Bish mush bisha that lives on Jadwar [8]. It has been introduced as an aphrodisiac. Potent anticonvulsant compounds from this plant have also been reported [1,4,10,11]. The root is used to reduce people’s withdrawal symptoms on de-addiction treatment in Unani and Ayurveda’s various medical formulations. [12]. Roots contain flavonoids, alkaloids, including delphocurarine, staphisagrine, delphine, condelphine, talatizidine, isotalatizidine, panicutine, hetisinone-8-acetylheterophyllisine, vilmorrianone, panicutine, denudatine, and triterpenoids [8,11,13].

MATERIALS And METHODS
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The information on DD was obtained from online databases, including PubMed, Google Scholar, Web of Science, Science Direct, and a library search was conducted from classical Unani textbooks. The keywords used for the search were as follows Delphinium denudatum, Jadwar, Jadwaar Khataai, Maah Parveen, Nirbasi. Scientific names and synonyms were validated through the Plant List (www.theplantlist.org). This review mainly focuses on data collected from traditional uses in the Unani system, pharmacological activities, phytochemical constituents, toxicology, and beneficial information for future research perspectives.

Vernaculars

Arabic: Antila saudavi, Baloot-el-ardh, Zhadvar; Ayurvedic: Nirvishaa, Nirvishi; English: Larkspur, Blood veined sage; Greek: Sáturyús; Nepali: Nilobikh; Hindi: Bas’ha, Nirbasi, Tarbasi; Marathi: Jadwr, Niribshi; Gujarati: Nirvishi; Persian: Maah Parveen, Zadwr; Sanskrit: Jadwár, Nirvishi, Vishalakarani; Urdu: Jadwár; Unani: Satriyoos, Jadwaar Khataai, Maatiryaaq.

Botany

The Ranunculaceae consists of 59 genera and 2,500 species of annual to perennial herbs, shrubs, or woody climbers, commonly known as the buttercup or crowfoot family. It is cosmopolitan, present throughout the world, but mainly present in cold and temperate regions of the North and South hemisphere. Very few representative members are also found in tropical and subtropical regions except in the Montane area [17,18].

The Delphinium genus is a rich source of more complex biologically active compounds, mainly diterpenoid and norditerpenoid alkaloids. [4]. The genus comprises 370 species distributed worldwide in northern temperate regions. Munz (1967 & 1968) reported 244 species from Asia, with a diversity centre in South-West China and the Eastern Himalayas, where 150 species exist. The genus is characterised in India by 27 species and two infraspecific taxa, primarily confined to the temperate and alpine Himalayan areas, and one species, Delphinium malabaricum, is endemic to the Western Ghats of South India. The Himalayas is considered the genus’ primary speciation site, which suggests that these taxa may have undergone a particular evolution process. [18].

The leaves of DD are 5-15 cm in diameter, rounded outline, divided into 3-5 broadly obviated segments, segments into oblong lobes or 2-3 mm wide teeth. Flowers are regular, bisexual, and about 2.5 cm long, with 1.2 cm of upper outer petals and a 1.4-1.5 cm spur. The upper inner petals are white, while the rest are blue. The perianth is either simple or splits into a corolla and a calyx. There are numerous and free stamens. In regular flowers, the carpels are typically numerous or lacking; the seeds are light blue, small, and endospermic. A suberized berry is covered by a suberised metaderm, and bears numerous small circular scars which are the remains of lateral roots. The outer region consisting of a single layer of the irregularly shaped brown tabular cell with suberised walls. Cortex is composed of a small zone of around 5 to 10 layers of thin-walled, polygonal to rectangular parenchymatous cells. Root parenchymatic cells contain starch grains, the majority of which occur in groups. There are no fibers, calcium oxalate, or cork cells. The drug powder seems to be light yellow. When treated with NaOH, prepared in methanol, and observed under ultraviolet light, it was yellowish-green [2, 7].

The rhizome is blackish-brown in colour, 3 cm to 6.5 cm long and 1 cm to 2 cm wide at the crown in length, conical shape, very hard, externally covered by a suberised metaderm, and bears numerous small circular scars which are the remains of lateral roots. The outer region consisting of a single layer of the irregularly shaped brown tabular cell with suberised walls. Cortex is composed of a small zone of around 5 to 10 layers of thin-walled, polygonal to rectangular parenchymatous cells. Root parenchymatic cells contain starch grains, the majority of which occur in groups. There are no fibers, calcium oxalate, or cork cells. The drug powder seems to be light yellow. When treated with NaOH, prepared in methanol, and observed under ultraviolet light, it was yellowish-green [2, 7].

Flower of delphinium denudatum

Source: [1]

Dried roots of Delphinium denudatum

Source: [2]

Chemical constituent

DD have many bioactive constituents, some of which are flavonoids, triterpenoids, alkaloids, including delphocurarine, staphisagrine, delphine, condelphine, talatizidine, isotalatizidine, panicutine, hetisinone, 3-hydroxy-2-methyle-4H-pyran-4-one, denudatin, delnudine, delnuline, vilmorinin anonymous, vilmorrianone, diterpinoiudt alkaloid: 8-acetylhetero-phyllisine, and a diterpenoid alkaloid C25H39NO6 identical to condelphine. Diterpenoids alkaloids are generally of the veatchine or atisine type. Several pharmacologically active diterpenoid alkaloids of C19 and C20 were reported from different Delphinium species. [5-7,11-13].

Ahmad et al. isolated three new DD norditerpenoids alkaloids, 1β-hydroxy, 14β-acetyl condelphine, jadwarine-A, jadwarine-B, together with two known isotalatizidine hydrate and dihydropentajugine alkaloids [11]. Denudatine (C21H33N02) contains two hydroxyis, an N-methyl, a C-methyl, and an exocyclic methylene group. Selenium dehydrogenation of denudatine gave 1-methyl-6-ethylphenanthrene.
and 1-methyl-6-ethyl-3-azaphenanthrene characteristic products of the dehydrogenation of atisine [3,20].

Sterol and fatty acids were detected at the roots of Jadwar. Campesterol, stigmasterol, and sitosterol were almost exclusively produced from sterols. Cholesterol and delta 5-avenasterol have also been identified in trace quantities. [5,21]. The gas-liquid chromatography analysis showed that there was a 1:3 ratio of saturated and unsaturated fatty acids. Characteristic higher plant fatty acids were also present [5-7]. Fatty acids of DD are Capric, Lauric, Myristic, Palmitic, Palmitoleic, Stearic, Oleic, Linoleic, Linolenic, [10]. Jadwar root also contains sugar, protein, phenol, carbohydrate, iron, zinc, calcium, magnesium, and potassium [6,7].

Description of jadwar in Unani literature

Jadwar is a piece of a root resembling Indian birthwort but is thinner and less potent than it. The best Jadwar is that which grows near aconite and hampers the growth of aconite. Ibn Masarjawai states that Jadwar is similar to doronicum actions but is less potent [22]. Ibn-e-Sena wrote a book on cardiac drugs called Advia-e-Qalbia. In this book, he mentioned also mentioned Jadwar. These drugs possess different cardioprotective properties [9]. According to Ibn Sina and Ibn Baitar, it is an antidote to any poison, including aconite and viper poison. Ibn Sina briefly explains Jadwár in the following words: “It has the shape of Aristolochia’s root, but smaller” [16,23]. Haji Zein-ell-attár, the well-known Persian physician and apothecary, described Jadwar as a root that resembles the size and form of the root of Indian Cypress, more rigid and more robust, and is the same as the Indian drug Nirbisi, the best of a pulpash shade internally [8,15,16]. He stated four drugs sold as Jadwar, namely, a white type, a purplish, a black, and a yellow. Cathay’s people (the historical name for China in English) call the yellow type as Kurti and the purplish Burbi; the other two types come from India [7,23]. He also stated that between India and Cathay, there is a mountain called Farajal, where the plant grows with aconite, and the latter loses its poisonous properties and is eaten freely by people. [7, 8, 15, 16, 23].

Some authors described five types of Jadwar: first, ‘Jadwár khatai’ is the greatest and is mostly used therapeutically; the exterior is black, and the interior is purple-brown, ovoid shape, tastes sweet initially and very bitter afterward. The second one, both inside and outside, is brown or yellowish-brown, tastes bitter, and is the second-best. The third type is bitter, black inside out, and turns blue on grinding. The fourth kind is blackish and bitter, probably a tuber of Curcuma species comes from Deccan Hills. Nepal and Tibet have also introduced both the third and fourth types to India. The fifth form, blackish, delicate, and very nasty, is called ‘Jadwarz Andulusi’. Ibn al-Baitar described it as one of the best tonics and refrigerants and an antidote to snakebite and aconite. In India, Curcuma zedoaria is called Jadwár khatta. [8,15,16,23].

PROPERTIES OF JADWAR IN UNANI LITERATURE

Temperament: Hot and Dry in second degree [3, 16, 24]

Dose: 225mg to 2g [3, 16, 24]

Pharmacological action

In Unani medicine, Jadwár is considered a Tiryaqe-sumoom (Antidote to poison), Muqawwi-e-Asab (Nerve tonic), Muqawwi-e-Qalb (Cardiotoxic), Mufarrheh (Exhilarant), Musakkin (Sedative), Dafe Humma (Antipyretic), Mufatteh (Deobstruent), Mohalil (anti-inflammatory), Mulattif, Mundij, Muqawwi hararate ghareziya wa muharrar katawab, Muqawwi Basar (Vision Improving), muqawwi Dandan (Tonic for tooth), Mushtahi (Appetizer) [3,16,22-24].

Therapeutic uses

Naza Muzmin (Chronic Catarh), Iltehab Tajawee-e-Anaf (Sinusitis), Sara (Epilepsy), Istirkha (Paralysis), Haiza (Cholorrea), Yarqan (Jaundice), Zof-e-Meda (Weakness of the Stomach), Qulanj (Colic). It is applied to the bite site for scorpion bites, and each hour is licked the powdered root with honey. With Usbq (Dorema amoniacum) and Meda laki (Litsea sebifera) it is applied in lymphadenitis. The rootlet decoction is used as a tonic. It is used to aid the treatment of syphilis it rheumatism and is chewed to prevent toothache [3,8,16,22-24].

Adverse effect: it produces intestinal abrasion (Mushij ama) [3,16,22-24]

Correctives: To prevent intestinal abrasion it is given with Kateera (Tragacanth gum), Fresh milk, Aas jau (decoction of Hordeum vulgare), Shikanbeen, kishneez khush (Cumium cyminum) [3,16,22-24]

Substitute: Zaranbaad (Long zedoary) in the triple quantity of jadwar acts as its substitute [3,10,22-24]

Important Unani Formulation

Habbe-Jadwar (prescribed in neurasthenia, sexual debility, attenuated semen, premature ejaculation, depression, chronic fatigue, chronic catarh), Khamira Gaozaban Ambhari Jawahirwala Ood-e-Saleeb Wala (indicated in low blood pressure), Jawhar Mohra, Marham-e-Jadwar (for ulcers, wounds, scrofula, lymphadenitis), Habb-e-Jawahir, Zimad-e-Warm-e Lozatain are some of the formulations of Unani System of Medicine [3,7,12,15,21].

PHARMACOLOGICAL ACTIVITY

CNS activity

In the 6-hydroxydopamine (6-OHDA) rat model of parkinsonism, Ahmad et al. investigated the impact of jadwar extract on the neuronal injury. Rats were treated for three weeks with jadwar extract (200, 400, and 600 mg/kg BW). On day 22, 2 μL of 6-OHDA or a vehicle is injected into the animals’ right striatum. The result showed that the dose-dependent Delphinium extract attenuated SOD and CAT activities in the striatum, which was substantially decreased by the lesion. After 6-OHDA injection, a substantial decrease in the dopamine level and its metabolites and an increase in dopaminergic D2 receptors in the striatum were observed. Both parameters were significantly recovered with extract treatment [39]. Another research indicates that isolatolatadizine hydrate isolated from the jadwar aerial portion has a potent dual cholinesterase inhibitor and can be used in Alzheimer’s disease as a targeted drug [4].

Anticonvulsant activities

Haidary et al. examined the impact of the jadwar-isolated aqueous fraction on Sustained Repetitive Firing (SRF) in neonatal cultured rat hippocampal pyramidal neurons. SRF blockade is one of the main cellular-level mechanisms of antiepileptic drugs. The aqueous fraction (0.2-0.6 mg/ml) results were compared to phenytoin, the standard antiepileptic drug. The findings indicate that Repeated Repetitive Firing in hippocampal neurons is inhibited by the aqueous fraction like phenytoin, in a use-dependent and voltage-dependent. The result concludes that aqueous fraction contains potent anticonvulsant
compounds [25]. Another research describes the FS-1 subfraction’s anticonvulsant activities, which were obtained by purifying an aqueous fraction extracted from the jadwar roots. In CF 1 mice, FS-1 showed very potent anticonvulsant activity, which was analogous to the effects of the well-known antiepileptic drug phenytoin in the Maximum Electroshock Test. Like the antiepileptic drug valproic acid (350 mg/kg), FS-1 also suppressed PTZ-induced trigger seizure and weakening of the righting reflex with tonic fore and hind limb extension by 100 per cent. In 80 per cent of animals, BIC-induced seizures were suppressed. Nevertheless, FS-1 exhibited a weak anticonvulsant effect on PIC-induced seizures, significantly decreasing mortality and delaying seizures. FS-1 did not affect the extensor seizures caused by strychnine (STN). The results show the compounds’ strong and potent anticonvulsant activity in jadwar FS-1 [26].

In another study, Raza et al. performed anticonvulsant activity of jadwar’s ethanolic extract (EE) and aqueous fraction (AF) using maximum electroshock test (MEST) and pentylentetrazol (PTZ), bicuculline (BIC), picrotoxin (PTX), and strychnine (STN) induced subcutaneous for anticonvulsant activity. In PTZ and BIC induced seizures, EE showed weak dose-dependent anticonvulsant properties. AF comparatively more potent anticonvulsant activity against seizures induced by PTZ and BIC and exhibited dose-dependent activity against MEST’s hind limb tonic extension phase [27].

Anti-anxiety properties

Abid et al. investigated the anti-anxiety properties of DD root and Amaranthus spinosus leaves. The hydroalcoholic extract of both drugs was given to Wistar albino rats, and Elevated Plus Maze, Staircase, Actophotometer, and Light and Dark tests were used to evaluate anti-anxiety properties. Both the hydroalcoholic extracts have produced good anxiolytic activity in a dose-dependent manner. The best result was obtained by an combination of them in a higher dose [12].

Anti-depressant activity

Zafar et al. evaluated the central depressant activity of the aqueous extract of jadwar in mice, using pentobarbitone sodium-induced hypnosis (PSH), spontaneous motor activity (SMA), and open-field behaviour (OFB) tests. The results show that jadwar induced a significant increase in pentobarbitone sodium-induced hypnosis in sleeping time. A significant decrease in activity counts on photo actometer readings was observed in the SMA test. In all the tests, the jadwar extract showed consistent and significant depressant activity [28].

Antinociceptive activity

Zaheer et al. evaluated the analgesic activity of DD ethanolic extract and methanol fraction on Wistar albino rats using Eddy’s Hot Plate method and Tail Flick response method. The result reveals the significant dose-dependent analgesic activity of the DD extracts in both tests. Nevertheless, the analgesia degree was markedly higher in groups that received higher doses of extracts [29].

In another study, the DD aqueous root extract was assessed for antinociceptive effects in mice. At the four levels of dose, jadwar extract showed a dose-dependent antinociceptive effect in the thermal and chemical analgesic models. Pre-treatment with naloxone did not alter the extract’s analgesic effect, suggesting that their action involves some mechanism other than opioids [30].

Morphine de-addiction

A study assesses the role of ethanolic and methanolic extracts of the roots of DD in morphine dependence. Both extracts were administered p.o. in a different regimen. The result showed that the administration of EE and MF orally in both morphine-dependent groups caused a significant reduction in scores of ‘counted’ and ‘checked’ signs of morphine abstinence syndrome compared to the morphine control group. The EE and MF significantly reduced the mean scores of different ‘counted signs’ and ‘checked signs’ of morphine withdrawal syndrome and could prove to be an alternative remedy for morphine de-addiction [10].

The de-addiction properties of DD in morphine-dependent rats are explored in another study. Rats have been made morphine-dependent by intra-peritoneal morphine sulphate injection. The alcoholic extract of Dd was administered per oral in different regimens. The result showed that the Dd extract caused a significant reduction in the frequency of “counted signs,” as well as “checked signs,” and can be an alternative remedy for morphine de-addiction [31]. In another study, the aqueous extract showed a substantial effect against morphine-induced tolerance and addiction in mice. Oral extract administration showed a significant dose-dependent withdrawal inhibition of naloxone [32]. Chronic treatment with DD suppressed dose-dependent morphine withdrawal. Repeated administration of Dd attenuated the development of tolerance to the morphine analgesic effect, also produces a significant dose-dependent change in tail-flick latency from the pre-treated saline group [33].

Antioxidant activity

Siddique et al. evaluated the In-vitro and In-vivo antioxidant activity of aqueous root extract of DD. DPPH-HPLC method was used to carry out the free radical-scavenging activity of aqueous root extract. The in-vivo antioxidant potential of aqueous extract was screened in the animal model, and oxidative stress was induced by cisplatin. The result showed that aqueous root extract showed 83.38 per cent inhibition, where ascorbic acid (standard drug) was produced as a 92.67 per cent inhibition. It is concluded that the DD aqueous root extract has antioxidant activity and could offer a promising role in the treatment of nephrotoxin-induced renal injury such as cisplatin [34].

Antimicrobial activity

Kumari et al. investigate the antimicrobial potential of different plant parts (stem, root, leaf) of DD extracts against bacteria, actinobacteria, and fungi. Plant extracts were prepared in different solvents (methanol, ethanol, ethyl acetate, acetone, hexane, chloroform and water) according to their polarity. The qualitative and quantitative estimations of antimicrobial activity were performed following plate assays through the disk diffusion and minimum inhibitory concentrations. All parts of the plant exhibited antibacterial activity, with the maximum in the case of the stem. Ethanolic stem extract exhibited the highest antibacterial activity (15.33±0.11 mm) against S. marcescens among several solvents, and aqueous leaf extract exhibited the highest anti-actinobacterial activity (21.0 ± 0.07 mm) against Nocardia tenirefensis. Anti-fungal activity, which was tested against five fungal species, was absent in all extracts of the plant parts [35].

Hepatoprotective activity

In hepatotoxic rats, Hussain et al. evaluate the hepatoprotective effect of DD roots Ethanolic extract. Animals were given orally with alcohol (3.75 g / kg) for ten consecutive days every day, 1 hour after the dose of DD. By using biochemical parameters, the protective effect was
assessed. The result showed that ethanolic extract treatment significantly improves alcohol-induced changes, including AST, ALT, ALP, Direct Bilirubin, Total Bilirubin, and Cholesterol. The dose of an extract of 400 mg/kg produced the best result, similar to Silymarin. Treatment with DD restored the altered parameters in a dose-dependent manner [39].

**Nephroprotective activity**

Siddique et al. evaluated In-vitro and In-vivo nephroprotective activity of aqueous root extract. The in-vitro nephroprotective study was investigated using the method of GGT assay. The in-vivo nephroprotective potential of the DD aqueous root extract (300,600 and 800 mg/kg) has been screened in rats. Cisplatin (5mg / kg BW) had induced nephrotoxicity. The root extract IC50 was found to be 189.3, where standard drug mesna (Sodium 2mercaptopethanesulfonate) was produced in GGT assay as IC50 61.29. The aqueous extract at a dose of (300,600 and 800 mg/kg) showed a significant dose-dependent reduction in elevated blood urea, uric acid, serum creatinine, and normalized histopathological changes. It is concluded that aqueous extract of DD possesses nephroprotective activity and can offer a promising role in treating renal injury caused by nephrotoxins such as cisplatin [34].

**Cardiovascular activity**

Asif et al. investigated the effect of DD’s aqueous extract on the cardiovascular system and its possible action mechanism. The aqueous extract of DD exhibited chronotropic and inotropic effects on normal, hypodynamic frog heart. The drug had initially shown tachycardia in dogs, followed by bradycardia. Significantly marked tachycardia has been observed after atropinisation, suggesting that bradycardia was due to reflex action. Alpha and β-blockers blocked the drug’s effect on the heart. The dog blood pressure study has also shown that the drug directly affects α and β-blockers [37].

**Miscellaneous**

Babak Daneshfard 2019, evaluated DD’s effect on fatigue by a randomized double-blind placebo-controlled clinical trial between healthy normal participants. For 15 consecutive days, participants were given either 500 mg of Jadwar root powder or placebo. The result showed that Jadwar has the potential to reduce fatigue in the normal Population [31].

**Toxicity**

The DD aqueous root extract has been evaluated for acute oral toxicity in mice. Oral doses were not fatal up to 14,000mg / kg, some of the CNS depression was observed, and the LD was found at 16,100mg / kg [30]. Other studies have shown that Dd single dose (2000 mg/kg) has little or no acute behavioural effects [32].

**CONCLUSION**

It is one of the effective medicines in India, particularly Unani medicine. The plant roots are helpful in a wide range of conditions, including aconite poisoning, brain diseases, fungal infection, piles, and toothache. DD has many bioactive constituents, including flavonoids, triterpenoids, alkaloids, including delphocurarine, staphisagrine, delphine, condelphine, denudatin, delnudine, delmune, vilmorri anonymous, vilmorrianone, diterpinoid alkaloid. The scientific analysis of Jadwar demonstrates many of the activities mentioned in Unani literature. Further research is needed to identify the mechanism, active constituent, and usefulness of Jadwar in clinical practice. Given the encouraging results against neurological disorders in the prefaces, this aspect should be thoroughly investigated to make it a standard medicine.

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**Conflict of interest**

The authors declare no conflict of interests

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