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Pharmacological Properties and Chemical Constituents of *Murraya paniculata* (L.) Jack

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Abstract

Murraya paniculata (L.) Jack belongs to the family *Rutaceae* and is mostly distributed throughout South Asia to Australia. Many pharmacological effects of the plant have been reported, and range from antinociceptive, antioxidant, anti-diabetic, antimicrobial to analgesic activities. A wide range of different compounds consisting of coumarins, alkaloids, phenols, terpenoids and flavonoids have been identified from different parts of the plant and have been evaluated for various biological activities. The aim of this review is to cover the biological activities and the active compounds derived from M. *paniculata* to provide more insights and spur further investigations that would lead to production of more effective and economical alternative medicine from the plant.

Keywords: *Murraya paniculata*, Chemical constituents, Biological activities

Introduction

Murraya is a genus of flowering plants, closely related to citrus. It is in the subtribe *Clauseninae,* which are known technically as the remote citroid fruit trees. *Murraya paniculata* (L.) Jack, commonly known as Orange Jessamine, is a tropical, evergreen plant with tiny, white, scented flowers, which is cultivated as an ornamental tree or hedge (Figure 1). It belongs to the family *Rutaceae* and can be commonly found in South Asia and Australia. Various parts of this plant have been used in traditional medicine. In Bangladesh M. *paniculata* leaves extract is orally used to alleviate pain [1]. In the Philippines, leaves were also used to treat diarrhea and dysentery because of their stimulant and astringent activities [2]. In India, people sometimes used root bark of M. *paniculata* as remedy for coughs, hysteria and rheumatism [3]. Furthermore, cooked leaves and boiled twigs applied to assuage inflamed joints and stomachache respectively in India [4].

There are many reports on pharmacological effects of the plant including antinociceptive [1,5], antioxidant [6,7] and anti-diabetic [4], to antimicrobial [4] and analgesic activities [8]. Several research groups have reported isolation of effective substances like alkaloids [9], phenols [4], terpenoids [10] and flavonoids [4,11-13] from leaves, fruits, flowers and root barks of M. *paniculata* as health remedy. In view of the importance of M. *paniculata*, we describe its antinociceptive, antioxidant, anti-diabetic, antimicrobial and analgesic properties.

Figure 1: The morphology of *Murraya paniculata* (L.) Jack.

Chemical Constituents of *Murraya paniculata* (L.) Jack

M. *paniculata* has been investigated for its bioactive compounds by many research groups. To date, various compounds were identified, ranging from indole alkaloids, coumarins, phenols, terpenoids to flavonoids. Besides, 60 compounds have been identified from volatile and essential oil extracted from M. *paniculata* leaves. The chemical components from different parts of M. *paniculata* were identified using chromatographic techniques and the structures were elucidated using spectroscopic techniques. A number of these compounds exhibited significant biological activities, which serve as the scientific evidence for the traditional usage of M. *paniculata*.

In 1986, an anti-implantation alkaloid, called Yuehcukene, 1β-(3,-indolyl-7,9α,9β-trimethyl-5β,8,9,10β-tetrahydroindano-[2,3-b] indole was also isolated from M. *paniculata* leaves [14]. Moreover, the two indole alkaloids, murrayacarine [15] and murrayaculatine [16] were isolated from root bark and flowers of M. *paniculata* respectively.

In early 1980s, different research groups isolated 3',4',5,5',7,8-hexa-methoxyflavone (Figure 2a) and 3,3', 4',5,5',7,8-heptamethoxyflavone (Figure 2b) from the methanolic extract of M. *paniculata* leaves [17,18]. Later, a flavone named 3,5,7,3',4',5'- hexamethoxyflavone, was isolated from M. *paniculata* flower [16]. Other research groups isolated eight flavonoids from M. *paniculata* leaves [12,19] and ten flavonoids from the peel and pulp of the fruits of the plant [20].

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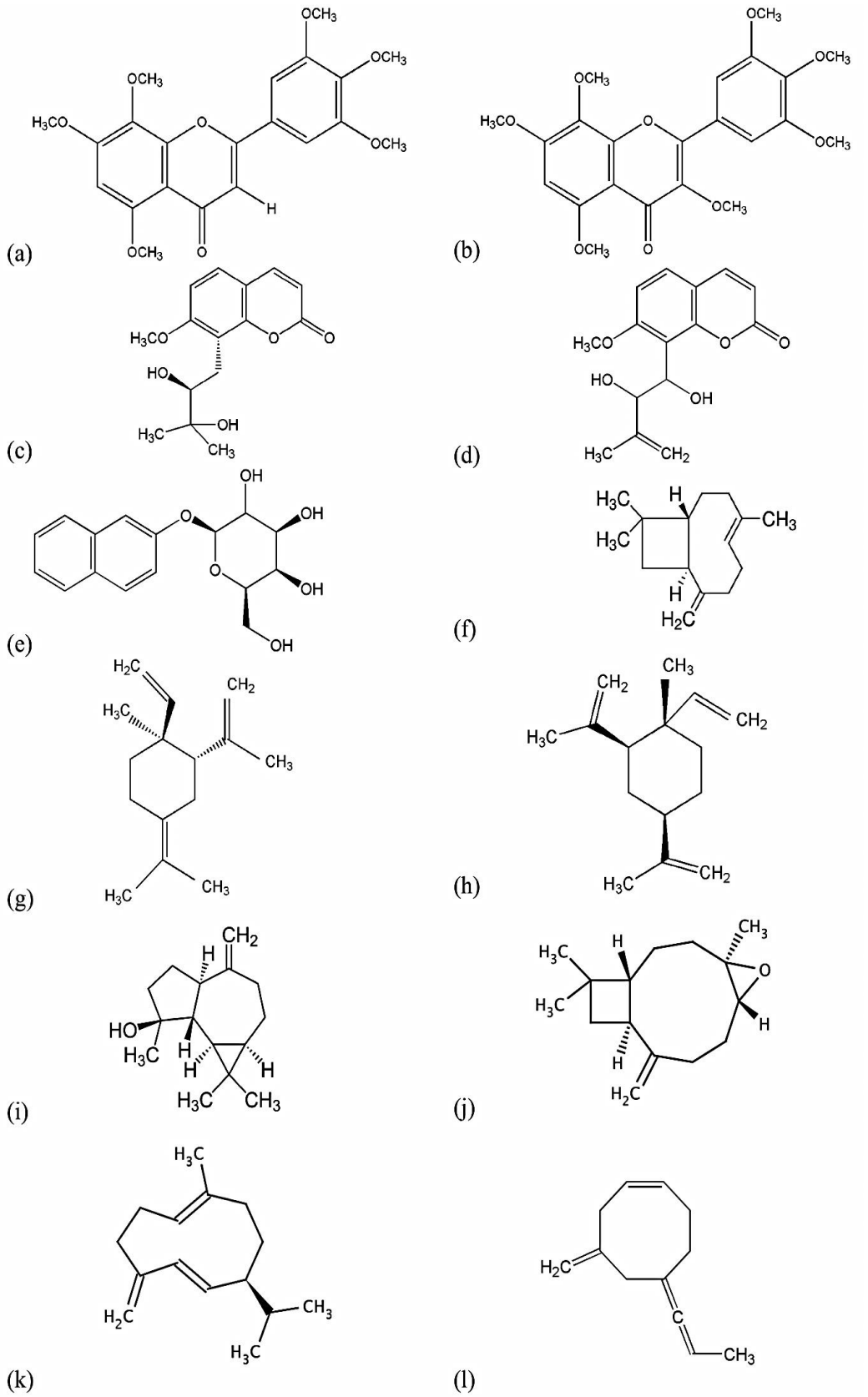

Figure 2: Chemical structure of major compounds identified in *Murraya paniculata* (L.) Jack.

Furthermore, three coumarins known as meranzin hydrate (Figure 2c), murpanidin (Figure 2d) and murragatin (Figure 2e) were isolated from M. *paniculata* leaves extract [18]. Other coumarins including 3-formylindole,omphalocar-pin,5,7-dimethoxy-8-(3'-methyl-2'-oxobuty coumarin, coumurrayin, murragleinin, omphamurin, murraol, (-)- murracarpin, (±)-murracarpin, mupanidin, mexoticin, murrangatin, and ferulyl esters were also isolated from M. *paniculata* root bark [15]. While from the fresh flowers of this plant, yuehgesin-A, yuehgesin-B, yuehgesin-C, and 22 compounds were characterized [21]. Besides nine coumarins, omphamurrayone, murralongin, isomurralonginol isovalerate, murrangatin, minumicrolin (murpanidin), coumurrayin, toddalenone, auraptene and toddasin were also identified from M. *paniculata* leaves acetone extract [22] and methyl 2,5-dihydroxycinnamate and murrayatin from methanolic extract [23].

As mentioned, 60 compounds have been aslo identified from volatile and essential oil extracted from M. *paniculata* leaves. The major components were t-caryophyllene (Figure 2f), γ-elemene (Figure 2g), perolidol, β-elemene (Figure 2h), spathulenol (Figure 2i), caryophyllene oxide (Figure 2j), β-caryophyllene, germacrene D (Figure 2k) and 4-methylene-6-(1-propenylidene)-cyclooctene (Figure 2l) [10,24,25].

Antioxidant Activities

Reactive oxygen species (ROS) are natural products of oxygen metabolism in biological systems which comprise in energy production, defense mechanism against infection and phagocytosis [26,27]. However, catastrophic biological oxidation can be observed while the production of ROS is enhancing. When cells have been exposed to excess ROS, some of the oxidative conversions like DNA affliction, lipid peroxidation and enzyme inactivation cause detrimental modification in cell function [27-29].

In recent years the utilization of substances from natural sources with antioxidant properties have been boosted because the preservation toward multitudinous disease [30-32]. Some problems concerning the conservation and toxicity of synthetic antioxidants lead to contributing more investigations on natural antioxidants derived from plant sources. Strong potential of plant antioxidants make them a crucial area of research [30-34]. Some plant source antioxidants are beta-carotene, selenium (Se) and flavonoids including flavanols, flavanones, flavones, iso-flavones, catechins, anthocyanins and proanthocyanidins [27].

Zhang et al. (2011) reported the antioxidant property of M. *paniculata* for the first time [7]. They detected seventy polymethoxylated flavonoids (PMFs) in the leaves extract and thirty nine PMFs in the branches extract of M. *paniculata* (Table 1) [35]. PMFs include a particular group of flavonoids responsible for numerous biological properties including antioxidant activity [36].

In 2005, Rohman and Sugeng reported significant antioxidant activity of the ethanol extract of M. *paniculata* leaves in linoleic-thiocyanate and 2,2-diphenyl-l-picryl hydrazyl (DPPH) methods [6]. They showed that the IC50 of M. *paniculata* leaves extract is 126.17μg/mL whereas, the IC50 of vitamin E the positive control is 8.27μg/mL. Furthermore, Chen et al. (2009) found that the 500μg/mL acetone extract of M. *paniculata* leaves displayed 72% inhibitory effect towards tyrosinase activity [37]. Besides, the 100μg/mL extract was able to inhibit 62% of lipoxygenase (LOX) and 10% of xanthine oxidase (XO) activities.

In 2011, Shaikh et al. isolated the secondary metabolite 2'-O-ethylmurrangatin from the leaves of M. *paniculata* by using spectroscopic techniques [38]. They found its significant activity towards lipoxygenase. 2'-O-ethylmurrangatin displayed the IC50 of 28.1 (mM) which was more than the IC50 of baicalein the positive control 22.7 (mM). In 2012, Gautam et al. reported that antioxidants significantly increased in Sprague-Dawley rats after 14 days oral administration of ethanol extract of M. *paniculata* leaves [4]. They found administration of 100, 200 and 400mg/kg of M. *paniculata* leaves extract increased superoxide dismutase (SOD) from 80.43 to 109.31 U/mg protein, catalase (CAT) from 36.17 to 59.18 U/mg protein and glutathione peroxidase (GPx) from 1.51 to 2.12 U/mg protein. They mentioned antioxidant activity of M. *paniculata* leaves extract is due to presence of alkaloids, flavonoids and phenolic compounds [4].

Identified PMFs in the leaves	Identified PMFs in the branches
Dihydroxy-dimethoxyflavone	Heptamethoxyflavone
Monohydroxy-trimethoxyflavone	Trihydroxy-dimethoxyflavone glycoside
Trihydroxy-dimethoxyflavone	Tetrahydroxy-dihydroxyflavone glycoside
Tetramethoxyflavone	Monohydroxy-dimethoxyflavone glycoside
Dihydroxy-trimethoxyflavone	Monohydroxy-trimethoxyflavone glycoside
Tetramethoxyflavanone or Tetramethoxychalcone	Heptamethoxyflavanone or Heptamethoxychalcone
Monohydroxy-trimethoxyflavone	Monohydroxy-tetramethoxyflavone glycoside
Monohydroxy-tetramethoxyflavanone or Monohydroxy-tetramethoxychalcone	Monohydroxy-trimethoxyflavanone or Monohydroxy-trimethoxychalcone
Trihydroxy-trimethoxyflavone	Monohydroxy-pentamethoxyflavone
Pentamethoxyflavone	Monohydroxy-trimethoxyflavone
Pentamethoxyflavanone or Pentamethoxychalcone	Pentamethoxyflavanone or Pentamethoxychalcone
Dihydroxy-tetrahydroxyflavone	Monohydroxy-trimethoxyflavone
Monohydroxy-pentamethoxyflavone	Pentamethoxyflavone
Monohydroxy-pentamethoxy or Monohydroxy-pentamethoxychalcone	Hexamethoxyflavanone or Hexamethoxychalcone
Trihydroxy-tetramethoxyflavone	Tetramethoxyflavone
Hexamethoxyflavone	Hexamethoxyflavonem
Hexamethoxychalcone	Dihydroxy-dimethoxyflavone
Monohydroxy-hexamethoxyflavanone or Monohydroxy-hexamethoxychalcone	Tetramethoxyflavanone or Tetramethoxychalcone
Monohydroxy-hexamethoxyflavone	Heptamethoxyflavone

Table 1: Polymethoxylated flavonoids (PMFs) detected in *Murraya paniculata* (L.) Jack.

The results obtained in these in vitro and in vivo studies clearly demonstrate the high potential of M. *paniculata* as a source of natural antioxidants. Further investigations are still required to confirm the antioxidant activity of the compounds and also to go through detailed mechanism of their activity.

Anti-diabetic Activities

Diabetes mellitus (DM) is a metabolic disorder caused by direct or indirect insulin inadequacy. Stimulation of glucose uptake into muscles and adipocytes determined by blood glucose level is under insulin control [39,40]. The glucose transporter Glut 4 can transport glucose from intra cellular pool to the plasma membrane in muscles and adipose tissues [41]. The glucose uptake can be measured by a fluorescent analogue of D-glucose, 2-[N-(7-Nitrobenz-2-oxa-1,3-

diazol-4-yl)amino]-2-deoxy-D-glucose (2-NBDG) [42,43]. Another vital mechanism which assures glucose hemostasis is insulin secretion from pancreatic β-cells [44]. Inordinate insulin secretion may cause life menacing hypoglycaemia hence, deficient secretion influence perceptive or chronic damaging lead to DM [45]. Furthermore, hypoglycemic agents like alpha glycosidase inhibitors and sulphonylure as found in some medicinal plants extracts are considerable compounds for the treatment of DM type 2 by stimulating insulin secretion [46-48].

In 2012 Gautam et al. reported that oral administration of M. *paniculata* leaves extract included hypoglycemic agents such as sulfonylures significantly declined the glucose level in diabetic Sprague-Dawley rats. They showed 400 mg/kg of M. *paniculata* leaves extract significantly reduced the glucose level (62.52 mg/mL) in diabetic rats compared to normal control group (94.78 mg/mL). In addition, they mentioned M. *paniculata* leaves extract can augment β-cell structure, cell membrane and nucleus in pancreas. Hypoglycemic action can be potentiating the insulin by enhancing the pancreatic secretion of it from β-cells of Langerhans islets or emancipating insulin from the bound form. Other studies showed that flavonoids in the M. *paniculata* leaves extract such as 5,7,3',4'-tetramethoxy-flavone, 5,7,3',4',5'-pentamethoxy-flavone, 5,6,7,3',4'-pentamethoxy-flavone, 5,6,7,3',4',5'-hexamethoxy -flavone, and 7-hydroxy-5,3', 4'-trimethoxy-flavone [49]. In 2009, Yongri et al. reported that the flavonoids in M. *paniculata* leaves extract evidently diminished the blood sugar level in ICR mice by increasing the insulin content and ameliorating the islet β-cells secretion index. However, the insulin resistance index significantly decreased [50]. Taken together, these in vivo results clarify that M. *paniculata* leaves extract could have eminent therapeutic effect on the Diabetes Mellitus (DM).

Antimicrobial Activity

Various antimicrobial agents, either synthtic or natural, are employed against pathogenic microbes to reduce the risks of common infections [51]. The repeated or continued use of antibiotics had led to widespread antimicrobial resistance [52]. On one hand there are serious infections that need to be cured using antibiotics and on the other hand the side effects of available commercial drugs, highlight the urgent demand for investigation on antimicrobial activities of natural antimicrobial compounds.

Plant extracts have shown to be a potential source of the novel antimicrobial agents [53]. However, as Plants produce bioactive compounds for their defense mechanisms which can be toxic in nature [54], not only the antimicrobial properties of the plant extract but possible toxicity should also be considered for their safety/safe use.

M. *paniculata* extract has been traditionally used as an antimicrobial medication and is believed to demonstrate significant antimicrobial activities [4,55]. The leaves extract has been reported to be safe in its oral effective dose as it did not indicate toxicity when tested on rodents [4]. According to the research conducted on 50% ethanolic leaves extract of M. paniculata, acute oral administration of M. *paniculata* extract (2000 mg kg–1, single dose) did not cause any mortality, CNS and ANS toxicities in rats.

The extract of M. *paniculata* leaves revealed the presence of alkaloids, flovonoids, phenolic compounds, which are all reported to have growth inhibition against gram positive and gram negative bacteria [4].

One of the mechanisms of phenolic compounds, that are known to possess antimicrobial activity, is by causing the leakage of cytoplasmic constituents such as protein, glutamate or potassium and phosphate from bacteria, which may occur as the result of disruption of cell peptidoglycan or damage of the cell membrane [56]. Flavonoids which are classified under phenolic groups have also demonstrated antimicrobial activity by inhibition of nucleic acid synthesis, cytoplasmic membrane function, and energy metabolism [57].

According to the research by Gautam et al., total phenolic and flavonoid content of different leaves extract of M. *paniculata* including petroleumether extract, methanolic extract, ethanolic extract and hydro-alcoholic extract were studied for their antibacterial activities [4]. At a concentration of 200mg/mL the inhibition zone of ethanolic extract and hydro-alcoholic extract tested on several human pathogenic bacteria, including E. coil, K. *pneumoniae*, S. *typhi*, E. *faecalis*, P. *aeruginosa*, S. *flexinerrii*, S. *aureus* and S. *sonneii* showed mild to moderate activity of 8-11mm. Petroleumether extracts indicated 8-12 mm of inhibition zone and the methanolic extract had highest antibacterial activity of 9-14 mm among other compound [4].

Analgesic and Antinociceptive Activity

Scientific exploration of new pain relieving herbal drugs with minimum side effects are in high demand [58]. Oral administration of M. *paniculata* leaves extract was used in traditional medicine in many places of Bangladesh for abatement of pain [1,59]. According to the study conducted by Podder et al., analgesic activity of M. *paniculata* bark extract has been practically proven [8]. They applied a method to indicate antinociceptive activity by testing the inhibitory ability of the sample against acetic acid induced writhing [60]. In their investigation, M. *Panuculata* bark extract was administered to mice at an oral dose of 200 and 400 mg/kg body weight. At the given doses, the extract indicated 37 ($p<0.001$) and 45% ($p<0.001$) inhibition of writhing respectively by reducing the frequency of acetic acid. Besides, the 19% ($p<0.05$) elongation of flicking time after 120 min was also observed [8]. This study concurred with the previous investigation by Chevallier (1996), indicating significant analgesic effect of M. *paniculata* bark extract in albino mice [61].

In 2009, Sharker et al. used a similar method to measure the antinociceptive activity of M. *paniculata* leaves ethanol extract [1]. They injected the 0.7% of acetic acid solution to the Swiss albino mice and then oral administration of 250 and 500 mg/kg of M. *paniculata* leaves extract produced significant antinociceptive activity of 26.27 and 66.67 writhing inhibitory percentage in mice in a dose dependent manner. In addition, Narkhede et al. reported oral administration of ethanol extract of M. *paniculata* leaves at the doses of 50, 100 and 200 mg/kg significantly inhibited the writhing at the rate of 28.84%, 54.93% and 67.91%, respectively in Swiss albino mice, which has been intraperitoneally administrated with acetic acid [5]. On the basis of these results it can be suggested that M. *paniculata* bark and leaves extracts might possess analgesic and antinociceptive activity. Besides, according to Sharker et al., M. *paniculata* extract indicated cytotoxic effects and it has to be taken into consideration as well [1].

Anticancer Activities

The major compound found in M. *paniculata* oil, (E)-caryophyllene, was found to posses cytotoxic activity against MDA-MB-231 (IC50= 31.6 μg/mL) and Hs 578T (IC50= 78.3 g/mL) human tumor cells [62].

As there are few studies on anticancer properties of M. *paniculata*, having a comparison of its chemical constituents with other plant extracts that have shown significant cytotoxic effects, might be useful as a clue for further investigations. A plant extract that is comparable to

M. *paniculata*, is *Juniperus phoenicea* leaves and berries extract which is rich in the same Monoterpene hydrocarbons (e.g. Sabinene) that are also found in M. *paniculata* [24]. J. phoenicea extract has indicated significant cytotoxic activity against U251, HeLa, H460, HepG2 and MCF-7 cell lines.

Valko et al. investigated cytotoxic effect of water extracts from leaves and branches of *Philadelphus coronaries* L. (Hydrangeaceae) against A431 (human skin carcinoma cell line) and MCF-7 (human breast adenocarcinoma cell line), where both extracts from the leaves and branches showed significant cytotoxic effects against the two cancer cell lines. The cytotoxicity of these extracts might be due to the presences of umbelliferone and scopolin, two coumarins that were also found in M. *paniculata* extract [21].

Conclusion

Different medicinal potentials of M. *paniculata* in various diseases have been reported by many investigators. However, there is a definite requirement of more detailed studies on the mechanisms of these properties. The current state of research on M. *paniculata* implicates great potential of the isolated bioactive compounds in treating diseases. With the advancement in medicinal chemistry and bioinformatics, the ethnomedicinal usage of M. *paniculata* can be scientifically explained and proved through in vitro or in vivo studies and may consequently be developed as potential plant-based drugs.

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