Chapter

Therapeutic Role of Natural Products Containing Tannin for Treatment of Constipation

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Abstract

Many herbal plants and medicinal foods with laxative effects have been reported as novel therapeutic strategies for the treatment of constipation and its related diseases. Indeed, several natural products containing tannins exhibit remarkable laxative effects in a constipation model. Therefore, we reviewed the laxative effects and the mechanism of action of natural products containing tannins because tannins have a wide range of pharmacological activities against human diseases. These products improved the excretion parameters, histological structure, mucin secretion and the downstream signaling pathway of muscarinic acetylcholine receptors (mAChRs) in the constipation model. This review provides strong evidence that various medicinal plants containing tannins are important candidates for improving chronic constipation.

Keywords: laxative effects, tannin, natural products, excretion parameters, constipation

1. Introduction

Chronic constipation is a complex gastrointestinal disease that is characterized by infrequent bowel movements, difficult defecation, sensation of incomplete bowel evacuation, sensation of anorectal obstruction, and the need for excessive straining [1–3]. This disease can be roughly classified into three groups: (i) constipation in the elderly and cancer patients; (ii) constipation related to neuromuscular diseases and (iii) functional constipation [1]. Constipation can be caused by a variety of factors including insufficient dietary fiber or fluid intake, decreased physical activity, drug administration, colorectal cancer obstruction, and hypothyroidism [4].

Meanwhile, the most common types of drugs used to treat patients with chronic constipation can be classified into bulk laxatives, osmotic laxatives, emollient laxatives, and prokinetic and prosecretory agents [1, 5, 6]. Among these, stimulant laxatives such as bisacodyl and natrium picosulfate are commonly administered to chronic patients although they have some limitations including high costs and undesirable side effects [7]. These laxatives significantly enhance the motility and secretion of the intestine by regulating electrolyte transport by the intestinal mucosa [8]. Many bulking agents and osmotic laxatives successfully treat constipation in elderly and cancer patients and in neuromuscular diseases, while prokinetic and prosecretory agents are prescribed to patients with functional constipation (Table 1) [9].
Constipation

To date, the laxative activities of natural products containing various bioactive compounds have been investigated in terms of the regulation of intestinal motility, ileum tension, frequency of defecation, and number of stools. Leaf extracts of *Aloe ferox* Mill., agarwood (*Aquilaria sinensis, A. crasna*), and common fig (*Ficus carica*) paste are reported to significantly increase the total stool weight and intestinal motility and to normalize body weight in constipated rats treated with loperamide (Lop) [10–12]. The water extract of Cactus (*Opuntia humifusa*) successfully improves the stool number and water content, as well as the histological parameters of the intestine [13]. High laxative activity and improvement of constipation symptoms were also observed after treatment with *Mareya micrantha* (Benth.) Mull. Arg. (Euphorbiaceae) in the Lop-induced constipation model [14]. A laxative effect compared to the standard drug (bisacodyl) was also detected with the methanol and hexane extracts of *Senna macranthera* leaves [15].

Furthermore, an aqueous extract of *Liriope platyphylla* recovered the frequency and weight of stools, villus length, crypt layer thickness, muscle thickness, mucin secretion, and accumulation of lipid droplets in crypt enterocytes [16]. The laxative effects of *L. platyphylla* correlated with the signaling pathway of mAChRs [16]. Although the laxative activity of many natural products has been reported, a relationship between natural products containing tannin and laxative effects has never been focused until now.

In the present review, we focused on the laxative effects and mechanism of action of natural products containing tannin in a constipation model. This study is the first to

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| Drug class                                      | Generic name          | Comments                                      | Dose                                    |
|------------------------------------------------|-----------------------|-----------------------------------------------|-----------------------------------------|
| Bulking agents                                 | Psyllium/ Ispaghula   | Effective                                    | 25–30 g daily in divided doses          |
|                                                |                       |                                                | 3.5 g to three times daily              |
| Osmotic laxative                               | Polyelethylene glycol | Effective Unpalatable taste                   | 17 g in 237 ml solution daily           |
|                                                | Lactulose             | Effective May causes bloating, flatulence and cramping | 13–30 ml (667 mg/ml) daily             |
| Stimulant laxatives                            | Bisacodyl             | Effective, but the effects subside with time, can cause cramping | 5–20 mg daily                          |
|                                                | Natrium picosulfate   |                                               | 5–10 mg daily                          |
| Emollient laxative                             | Mineral oil           | Effective                                     | 5–10 cm³ daily                         |
|                                                | Glycerin suppositories| Effective Initiates evacuation by distending the rectum | On demand                              |
| Prokinetic and prosecretory agents             | Prucalopride          | Effective May cause headache, nausea, abdominal pain and diarrhea. These adverse events occur within the first 24 h of treatment and are short lived | 2 mg daily                             |
|                                                | Linaclotide           | Diarrhea is the most common side effect       | 290 μg daily                           |

Table 1. Classification of drugs used to treat patients with chronic constipation [1].
suggest that natural products containing tannin may be as effective at alleviating constipation as commercial drugs such as bisacodyl, sennoside calcium, and docusate sodium.

2. Laxative effects and mechanism of action of natural products containing tannin

2.1 Role of tannin as health-benefiting biomolecules

Tannins are the most abundant secondary metabolites in plants and are well known as one of the major groups of antioxidants polyphenols. These compounds are found in various foods and beverages including coffee, tea, wine, grapes, blueberries, pomegranate, and strawberries [17]. They are abundantly distributed in leaves, wood, tree bark, fruit, and roots. Indeed, tannin accounts for 5–10% of the dry weight of plant leaves (Table 2) [18].

Tannins have been classified into three major groups: hydrolysable tannin (HT), phlorotannins (PT), and condensed tannin (CT). HTs are compounds with polyol (\(\beta\)-glucose) esterified by phenolic groups and include gallic acid and ellagic acid [19]. CTs are oligomers or polymers of polyhydroxy flavan-3-ol unit (polyphenolic bioflavonoids) and include catechin and epicatechin. HTs are usually distributed in low amounts in plants, while CTs are abundantly or widely distributed in plants (Table 2) [20].

Tannins have a wide range of biological and pharmacological activities including antioxidative, anticarcinogenic, anti-inflammatory, antibacterial, cardioprotective and anti-mutagenic activities [17]. Tannin also decreases the blood glucose level in diabetic rats and inhibits adipogenesis in adipose cells [21, 22]. These therapeutic effects are thought to be attributed to the ability of tannins to act as free radical scavengers and to activate antioxidant enzymes, although further studies are needed to confirm this [17]. Because of the versatility of tannins, novel functions of tannins in various chronic diseases have received a great deal of attention because they have great economy and potential ability as therapeutic drugs.

| Category            | Hydrolyzable tannins | Phlorotannins | Condensed tannins |
|---------------------|----------------------|---------------|------------------|
| Structure of basic unit | ![Structure of basic unit](image) | ![Structure of basic unit](image) | ![Structure of basic unit](image) |
| Name of basic unit | Gallic acid | Phloroglucinol | Flavan-3-ol's scaffold |
| Sources | Pomegranate, strawberries, raspberries, clove, barley, oat, rye, etc. | Brown algae | Coffee, tea, wine, grapes, cranberries, apples, rosemary, etc. |
| Major compounds | Gallotannins, ellagitannins, punicalagin, ellagic acid, hexahydroxydiphenic acid | Diphloethol, trifluhalol A, difucophloethol A, dieckol | Catechin, epicatechin, galocatechin, epigallocatechin, luteolin, quercetin, arbutin, vanillic acid |

Table 2. Three classifications of tannin [23].
2.2 Laxative effects of natural products containing tannin

2.2.1 Laxative effect of Mareya micrantha Mull. Arg

*M. micrantha* is a shrub tree that grows in west and central regions of Africa. The leaves of this plant have been used traditionally to treat several diseases including tapeworm infections, gonorrhea, leprosy, and constipation [24, 25]. However, scientific evidence for the therapeutic effects of this plant in several chronic diseases has also been reported. The aqueous extracts of *M. micrantha*’s leaf inhibited cardiac contractibility in the hearts of frogs and rats [26, 27], but induced contraction of longitudinal muscle in the guinea pig [28]. The methanol, aqueous, and ethanol extracts of leaves also showed anti-bacterial effects against some pathogens and antiplasmodial activity against *Plasmodium falciparum* [25, 29]. Also, these aqueous leaf extracts of *M. micrantha* had 566.66 kg/body weight of LD$_{50}$ and were classified as low toxic substance [30]. Meanwhile, the aqueous leaf extract of *M. micrantha* contained various phytochemicals including alkaloids, tannins, flavonoids, polyphenols, sterols and polyterpenes although their concentrations were low [31].

Furthermore, the aqueous leaf extract of *M. micrantha* enhanced the gastrointestinal motility, intestinal water secretion, intestinal ion secretion, and stool output in a dose-dependent manner (100, 200 and 400 mg/kg) in Wistar rats. Similar effects were observed in the loperamide (Lop)-induced constipation model. The total stool number and weight were significantly increased after treatment with the aqueous leaf extract of *M. micrantha* (Table 3). The laxative effects of this product at 400 mg/kg were very similar to those of 5 mg/kg of sodium picosulfate [31].

2.2.2 Laxative effects of A. ferox Mill

*A. ferox* is an arborescent perennial shrub that is widely distributed in Southern Cape, Eastern Cape, Southern parts of KwaZulu Natal, the Free State and Lesotho [10]. This plant has been widely used in traditional medicine because of its healing properties against several human diseases [32], particularly tooth abscesses [33], sexually transmitted infections [34], wound healing [35], arthritis and rheumatism [36], conjunctivitis and eye ailments [37] and as an insect repellent [38].

The acetone extract of the whole leaf of *A. ferox Mill.* contained phenols (70.33%), flavonols (35.2%), proanthocyanidins (171.06%) and alkaloids (60.9%), while the ethanol extract contained the same compounds at values of 70.24%, 12.53%, 76.7% and 23.76%, respectively. Their concentrations in aqueous extract were lower than those in acetone and ethanol. In contrast, tannin levels were consistently 0.014–0.027% in all the solvent extracts [39].

| Treatment    | Dose    | Weight of feces (g) |
|--------------|---------|---------------------|
| Control      | 5 mL/kg | 0.938 ± 0.45        |
| Sodium picosulfate | 5 mg/kg   | 3.84 ± 0.62”       |
| MAR          | 100 mg/kg | 2.602 ± 0.33      |
| MAR          | 200 mg/kg | 2.806 ± 0.42”      |
| MAR          | 400 mg/kg | 3.507 ± 0.45”      |

Values are expressed as mean ± S.E.M (n = 5).

"p < 0.05 compared to control group.

**p < 0.01 compared to control group.

Table 3. Laxative effect of *M. micrantha* aqueous extract (MAR) on Lop-induced constipation model [30].
Although various effects of this plant have been reported previously, scientific evidence for laxative effects of *Aloe ferox* was reported recently. The aqueous extract of *A. ferox* remarkably enhanced the water intake and the number, water content and weight of stools in the Lop-induced constipation model (Table 4). Also, a significant increase in the gastrointestinal transit ratio was induced by the administration of aqueous extract of *A. ferox*. These effects of this plant at 200 mg/kg were comparable to those of senokot [10]. Moreover, this extract was not induced any significant toxic effect on the hematological parameters for kidney and the liver function at 50, 100 and 200 mg/kg body weight for 7 days [40].

2.3 Laxative effects of *Urginea indica* Kunth

*U. indica* belongs to family Liliaceae and is distributed in western Himalayas and Coromandel Coast [41]. This plant was traditionally used to treat skin diseases, asthma, cough, bronchitis, calculous affections, rheumatism, leprosy, paralytic affection, internal pain, and scabies [42–44]. The bulbs of this plant were applied to relieve constipation and indigestion, to prevent burning sensations, and to remove corns and warts [41, 44, 45]. Also, its antifungal, antiangiogenic and pro-apoptotic effects were reported previously [46, 47]. Various phytochemical components including alkaloids, tannins and coumarins were detected in the crude aqueous-methanol extract of *U. indica* [48].

Laxative effects of *U. indica* have been examined in rabbits, guinea pigs and mice. The charcoal meal transit was accelerated in the small intestine of mice treated with *U. indica*. The total number of stools also increased in a dose-dependent manner in *U. indica*-treated mice. Furthermore, concentration-dependent spasmogenic effects of crude extract of *U. indica* were detected in guinea-pig ileum and rabbit jejunum (Figure 1) [48]. Moreover, this study provided the first evidence that the stimulant effect of *U. indica* was mediated by the activation of muscarinic receptors initiating the prokinetic effect [48].

| Parameters                      | Normal control | Constipated control | Constipated + *A. ferox* (mg/kg body weight) | Senokot |
|--------------------------------|----------------|---------------------|---------------------------------------------|---------|
|                                |                |                     | 50  | 100 | 200 |                |
| Feed intake                    | 17.18 ± 1.36   | 19.23 ± 3.86        | 19.90 ± 1.61      | 20.54 ± 1.38 | 17.80 ± 1.60 | 19.97 ± 3.31 |
| Water intake                   | 19.62 ± 2.22   | 11.72 ± 2.47        | 16.57 ± 2.05      | 17.24 ± 0.17  | 19.79 ± 2.33  | 18.14 ± 0.61  |
| Number of fecal pellet         | 73.57 ± 4.39   | 38.20 ± 2.21        | 45.43 ± 1.90      | 57.57 ± 1.62  | 69.83 ± 4.49  | 63.00 ± 3.11  |
| Water content of fecal pellet  | 14.40 ± 0.08   | 1.04 ± 0.09         | 1.75 ± 0.21       | 1.95 ± 0.11   | 2.25 ± 0.21   | 2.09 ± 0.06   |
|                                |                |                     | 7.14 ± 0.23       | 3.34 ± 0.38   | 5.72 ± 0.18   | 7.42 ± 0.33   | 8.10 ± 0.72   | 7.31 ± 0.25   |
| Weight of fecal pellet (g)     | 15.30 ± 1.00   | 33.80 ± 2.16        | 14.20 ± 0.71      | 13.20 ± 1.85  | 12.50 ± 1.53  | 15.35 ± 1.21  |

Data are mean ± SD values (n = 4). Row values with different superscripts than the control are significantly different (P < 0.05).

Table 4. Laxative effect of aqueous extract of *A. ferox* in constipated rats [31].
2.4 Laxative effects of *Fumaria parviflora*

*F. parviflora* is an annual flowering plant and is widely distributed in many parts of the world including the Middle East and South Asia [43, 49]. The aqueous-methanol extract of this plant contained alkaloids such as adlumidine, coptisine, fumariline, parfumine, protopine [50], fumaranine, fumaritine, parfumicin, parrarine [51], fumarophycine, cryptopine, sanactine, stylopine, bicuculline, adlumine, perfumidine and dihydrosanguirine [52]. Also, the aqueous-methanol extract of *F. parviflora* contained alkaloid, saponins, anthraquinones and tannins [53].

In Greco-Arab traditional medicine, this plant was used to treat indigestion, constipation, abdominal cramps and diarrhea [43, 49]. Recently, the laxative and prokinetic activity of this plant were investigated in three different animals. The charcoal meal GI transit, defecation and number of wet stools were enhanced in a dose-dependent manner in mice. Also, this plant induced a concentration-dependent, atropine-sensitive stimulatory effect both in mouse tissues (jejunum and ileum) and rabbit jejunum (Figure 2) [14].

2.5 Laxative effects of *Phyllanthus emblica*

*P. emblica* is a natural plant distributed in most areas of the Sind and Punjab provinces of Pakistan [43]. Most parts of this plant including the fruit, seed, leaves, root, bark and flowers are used in the herbal preparations due to their high phenolic contents [54].

The leaves of *P. emblica* contain tannins like glucogallin, corilagin, chebulagic acid, tannins emblicanins A and B [55], and apigenin glucoside [56]. The roots of this plant
contain norsesquiterpenoid glycosides (4′-hydroxyphyllaemblicin B, phyllaemblicins E and F, phyllaemblic acid, phyllaemblicin A, B and C) [57], quercetin and β-sitosteryl [58]. The leaves are known to have multiple health benefits including gastroprotective, anti-ulcerogenic, hypolipidemic and antidiabetic [59], antioxidant [60], hepatoprotective [61], antihypertensive [62], anti-inflammatory [63], antidiarrheal and antispasmodic [64] activities. But, the crude extract of dried fruits showed laxative effects that increased charcoal meal GI transit, the mean weight of defecation, and the number of stools. The crude extracts and aqueous fraction induced dose-dependent and partially atropine-sensitive contraction in isolated guinea-pig ileum and rabbit jejunum, while the petroleum fraction showed full atropine-sensitive contraction. In contrast, spasmolytic activity was detected in the ethyl acetate and chloroform fractions of this plant (Figure 3) [54]. Furthermore, extracts from the leaves of P. emblica showed 9.911 g/kg of LD50 and the indexes of thymus and spleen in the P. emblica extract–treated groups had no markedly difference [65].

2.6 Laxative effects of Galla Rhois

The laxative effect of Galla Rhois as a natural product containing high concentrations of tannin was investigated by Kim et al. [66]. Galla Rhois is an excrescence formed by parasitic aphids, primarily Schlechtendalia chinensis Bell, on the leaf of sumac, Rhus javanica (Anacardiaceae) (Figure 4) [67]. This product has been widely used for treatment of various diseases including diarrhea, seminal emissions, excessive sweating, boil, some skin diseases, bleeding, and chronic cough because of its

Figure 2.
Laxative effects of F. parviflora (Fp.Cr) crude extract on travel of charcoal meal through small intestine of mice, in the absence and presence of atropine. *p < 0.05 compared with control, **p < 0.01 compared to control and ***p < 0.001 compared to control [52].
Figure 3.
Stimulant and relaxant effects of several extracts and fractions of *P. emblica*. The concentration of acetylcholine (Ach) was measured in rabbit jejunum after treatment with (A) the crude extract (Pe.Cr), (B) the aqueous extract (Pe.Aq) in the absence and presence of atropine, hexamethonium, pyrilamine and indomethacin, (C) the effect of petroleum fraction (Pe.Pet) in the absence and presence of atropine, (D) the ethyl acetate (Pe.EtAc) and chloroform (Pe.CHCl₃) fractions. Values shown represent mean ± SEM of 6–7 determinations. *p < 0.05 compared with control, **p < 0.01 compared with control, and ***p < 0.001 compared with control [54]. Abbreviations: Spont., spontaneous.

Figure 4.
Living and dry forms of Galla Rhois [76].
ethnopharmacological properties [67–69]. In particular, the antibacterial effects of Galla Rhois have been detected against many pathogenic bacteria such as *Salmonella* spp., *Escherichia coli* and *Eimeria tenella* [70–72], while anti-inflammatory activity is observed in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages [73]. Also, Galla Rhois shows anticancer activity against nasopharyngeal carcinoma cells [74] and improves sensorimotor function in a cerebral ischemia rat model [75].

Meanwhile, the ingredients in gallotannin-enriched Galla Rhois (GEGR) have been measured by UV-Vis spectra and HPLC analyses. They consist of gallotannin (69.2%), gallic acid (26.6%) and methyl gallate (4.2%) (Figure 5) [66].

![Figure 5](image-url)

**Figure 5.** Ingredients of GEGR. Concentration of major components. (A) The levels of gallotannin, gallic acid and methyl gallate in GEGR were analyzed based on their UV-vis spectra. (B) HPLC chromatograms of pure gallic acid (commercial chemical), pure methyl gallate (commercial chemical), pure gallotannin (commercial chemical), and GEGR extract [66].
In the Lop-induced constipation model, the number and weight of stools was almost recovered in the GEGR-treated groups compared to those in the untreated and vehicle-treated groups. Also, significant alterations in the thickness of the...
mucosa, muscle, and flat luminal surface, as well as in the ability to secrete mucin, were detected in the transverse colon of constipated SD rats (Figure 6) [66].

Furthermore, the mechanism of GTEGR action during the laxative effects was investigated on the downstream signaling pathway of the muscarinic acetylcholine receptor. The Lop + GTEGR-treated group was remarkably recovered compared to the Lop + vehicle-treated group. A similar pattern was detected for the phosphorylation levels of protein kinase C (PKC) and phosphoinositide 3-kinase (PI3K), the levels of Gα expression and the inositol triphosphate (IP3) concentration after GTEGR treat-

ment (Figure 7) [66]. However, GTEGR did not induce any significant toxic effect on liver and kidney organs of ICR at doses of 1000 mg/kg body weight/day [69].

![Figure 7](image-url)

**Figure 7.** Recovery effects of GTEGR and mACHRs transcript and their downstream effectors. (A) The levels of mACHR M2 and M3 transcripts were measured by RT-PCR using specific primers. (B) The expression of Gα was measured by Western blotting using HRP-labeled anti-rabbit IgG antibody. (C) The IP3 concentration in total tissue homogenates was quantified by enzyme-linked immunosorbent assay. The relative levels of protein and transcript of mACHRs were calculated based on the intensity of actin protein and mRNA [66]. Abbreviations: No, no treated group; BS, bisacodyl-treated group; LoGTEGR, low level of GTEGR-treated group; MiGTEGR, medium level of GTEGR-treated group; HiGTEGR, high level of GTEGR-treated group; mAChR, muscarinic acetylcholine receptor.
3. Conclusions

Various bioactive molecules with therapeutic effects on human diseases have been isolated from many traditional plants including medicinal plants, aromatic plants, vegetables, and fruits [77]. Among these, tannins are some of the many

| Name of natural products | Constituents | Laxative effects | Reference |
|--------------------------|--------------|------------------|-----------|
| *M. micrantha* (Benth.) Mull. Arg. | Alkaloids, tannins, flavonoid, polyphenols, sterols and polyterpenes | - Increase the gastrointestinal motility  
- Increase the intestinal water secretion  
- Increase the intestinal ion secretion  
- Increase the stools parameters | [31] |
| *A. ferox* Mill. | Phenols, flavonoid, proanthocyanidins, alkaloids and tannins | - Increase the stools parameters  
- Increase the gastrointestinal transit ratio | [10] |
| *U. indica* Kunth. | Alkaloids, tannins and coumarins | - Increase the gastrointestinal transit ratio  
- Increase the stools parameters  
- Show the concentration-dependent spasmogenic effects | [48] |
| *F. parviflora* | Alkaloids, saponins, anthraquinones and tannins | - Increase the gastrointestinal transit ratio  
- Increase the stools parameters  
- Show the concentration-dependent spasmogenic effects | [52] |
| *S. macranthera* | Flavonoids, tannins and coumarins | - Increase the gastrointestinal motility  
- Increase the stools parameters | [15] |
| *P. emblica* | Alkaloids, saponins, tannins, terpenes, flavonoid, sterol and coumarins | - Increase the gastrointestinal transit ratio  
- Increase the stools parameters  
- Show the concentration-dependent spasmogenic effects | [54] |
| Galla Rhois | Gallic acid, methyl gallate and gallo-tannin | - Increase the stools parameters  
- Recovery the histopathological structure  
- Increase the mucin secretion ability  
- Recovery the mAChRs downstream signaling pathway | [66] |

Table 5. Summary of natural products containing tannin and their laxative effects.
phytochemicals and have various pharmacological activities against many chronic diseases such as cardiovascular disease, inflammatory diseases, cancer, obesity and diabetes due to their high antioxidant activity [17]. Tannins have also received a great deal of attention as novel therapeutic drugs for use in the treatment of chronic constipation and its related conditions. In an effort to identify candidate drugs for the treatment of chronic constipation and verify the role of tannins as key laxatives, this review describes some of the evidence supporting the use of natural products containing tannin as laxatives in several constipation models. Excellent laxative effects were detected for extracts of *M. micrantha*, *A. ferox*, *U. indica*, *F. parviflora*, *S. macranthera* and *P. emblica*. In particular, Galla Rhois, which contains a high concentration of gallotannin (69.2%), remarkably improved the symptoms of constipation (Table 5).

In conclusion, this review provides evidence correlating the laxative effects with natural products containing tannin, although the mechanism of action has not been completely verified. Therefore, tannins may be a viable laxative treatment of humans. However, more research is needed to verify the molecular mechanism and long-term effects of each tannin type.

Acknowledgements

I would like to express my gratitude to my students, including JE Kim, ML Lee, JJ Park, BR Song, HR Kim, JW Park, MJ Kang, HJ Choi and SJ Bae, for helping to compile this paper and for helping with the graphics and charts herein. This review was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2017R1D1A3B03032631).

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