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A Recent Review on Phytochemical Constituents and Medicinal Properties of Mangosteen

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ABSTRACT
Garcinia mangostana L. (mangosteen, Clusiaceae) has a long history of use as a medical plant, mostly in Southeast Asia. This review is focused on nutritional benefits and beneficial properties of mangosteen. Many tropical plants have interesting biological activities with potential therapeutic applications. Garcinia mangostana Linn. (GML) belongs to the family of Guttiferae and is named "the queen of fruits". It is cultivated in the tropical rainforest of some Southeast Asian nations like Indonesia, Malaysia, Sri Lanka, Philippines, and Thailand. People in these countries have used the pericarp (peel, rind, hull or ripe) of GML as a traditional medicine for the treatment of abdominal pain, diarrhea, dysentery, infected wound, suppuration, and chronic ulcer. Experimental studies have demonstrated that extracts of GML have antioxidant, antitumoral, antiallergic, anti-inflammatory, antibacterial, and antiviral activities. The pericarp of GML is a source of xanthones and other bioactive substances. Prenylated xanthones isolated from GML have been extensively studied; some members of these compounds possess antioxidant, antitumoral, antiallergic, anti-inflammatory, antibacterial, antifungal and antiviral properties. Xanthones have been isolated from pericarp, whole fruit, heartwood, and leaves. The most studied xanthones are alpha-, beta-, and gamma-mangosteens, Garci none E, 8-deoxygartanin, and gartanin. The aim of this review is to summarize findings of beneficial properties of GML's extracts and xanthones isolated from this plant so far. The phytochemicals found in mangosteen make it a natural remedy for a range of health conditions, including inflammation, cancer, diabetes and microbial infection. Mangosteen supplements, such as mangosteen extract and mangosteen juice, are also available and marketed as natural remedies.

KEYWORDS: mangosteen (garcinia mangostana L.), xanthones, Chemical Constituents, phytochemistry, medicinal properties, traditional medicine, pharmacology

I. INTRODUCTION

The purple mangosteen (Garcinia mangostana) is a tropical tree most famous for its dark purple mangosteen fruit. The origin of the mangosteen tree is not clearly understood however, it may have possibly originated in Malaysia and can now be found in hot and humid regions throughout Southeast Asia, Central America, and Africa

A notable feature of the mangosteen fruit is its sweet taste and different formulations of the mangosteen, including teas, ointments, tinctures, and other preparations have been used in traditional Eastern medicine to treat skin infections, urinary tract infections, dysentery, inflammation, abdominal pain, diarrhea, and fevers. The mangosteen plant, including the fruit, rind, roots, and leaves, contains a class of phytochemicals called xanthones, and more than 70 different xanthones have been isolated from the mangosteen.

These naturally occurring compounds have a flat planar structure that includes tricyclic aromatic ring systems with different functional groups attached to the A and C rings (commonly methoxy, hydroxy, or isopropyl groups). More recently, studies have used mangosteen xanthones, specifically α-mangosteen, the most abundant xanthone, as well as some of the less abundant isoprenylated xanthones and reported them to have antioxidant, anti-inflammatory, antibacterial, antifungal, anticancer, and antitumor activities.

Early reports of the traditional uses of infusions and decoctions of its peels and seeds to treat gastrointestinal and urinary tract infections, and as anti-scorbutic, laxative and anti-fever agent, date from almost two hundred years ago. Modern uses of the species comprise the alleviation of infection-related symptoms, such as diarrhea, abdominal pain, and fever, and also complains linked to inflammatory and immunological diseases, like acne, food allergies and arthritis (Wang et al., 2017). Nowadays, fruit derivatives demand has increased exponentially

Furthermore, mangosteen contains bioactive compounds such as xanthones, terpenes, anthocyanins, tannins, phenols, and some vitamins10. The nutritional value of mangosteen per 100 g includes 80.9 g of water, 0.5 g of protein, 18.4 g of carbohydrates, 1.7 g of fiber, 9 mg of calcium, 14 mg of phosphorus, 0.5 mg of iron, 2 mg of vitamin C, 0.09 mg of vitamin B1 (thiamin), 0.06 mg of vitamin B2 (riboflavin), and 0.1 mg of vitamin B5 (niacin)11. In fact, mangosteen's pericarp has many important benefits for health12,13,14. The main compounds in the content of mangosteen's pericarp are xanthones15; such as α-mangostin16, γ-mangostin17, 8-deoxygartanin, Garci none E, mangostanol18, βmangostin19, podophyllin A and B20, mangostenin21, and Mangostenone C, D, and E22. The main xanthone derivative is α-mangosteen, this compound has a variety of pharmacological activities such as antidiabetic23,24, antioxidants, and anti-inflammatory12,13,14,25. Therefore, this study aims to generate mangosteen's ethnobotany, toxicology, pharmacology, and phytochemistry of and its future prospects for a further scientific investigation for developing the effective therapeutic compounds.

Taxonomy:

Kingdom: Plantae; Subkingdom: Tracheobionta; Superdivision: Spermatophyta; Division: Magnoliophyte; Class: Magnoliopsida; Subclass: Dilleniidae; Order: Malpighi ales; Family: Clusiaceae; Tribe: Garcinia; Genus: Garcinia L.6; Species: Garcinia mangostana L.

Geographical Distribution:

Mangosteen is a tropical origin plant and native to Malay Peninsula and South East Asia, including Indonesia. Mangosteen is only known as a cultivated species. It was long known that the cultivation has been limited to Southeast Asia, ranging from Indonesia eastwards to New Guinea and Philippines, and north via Malay Peninsula into the southern parts of Cambodia, Vietnam, and Thailand. Only during the last two centuries has the crop spread to other tropical areas, including Brazil, Sri Lanka, Central America, South India, and Queensland. Mangosteen tree can grow in lowlands. The best growth is achieved in the area with the altitudes of 500-600 m a.s.l. In Indonesia, mangosteen tree's planting centers are West Sumatra, Central Kalimantan, Riau, East Kalimantan, North Sumatra, and North Sulawesi. In Java, the mangosteen production centers are Blitar, Bogor, Banyuwangi, Purwakarta, Cia mis, Cilacap, Purworejo, Sukusuma, Banjar Negara, Wanayasa, and Subang29.

ethnopharmacology:

Mangosteen is an important medicinal plant with several medicinal uses in traditional medication system. It has been used to cure many health problems in different parts of the world. The different parts of mangosteen, which are mostly the fruit hull, the bark, and the roots have been utilized for hundreds of years in Southeast Asia as a medicine within the great variety of medical conditions. In China, India, Thailand and other parts of Asia, the dried and powdered fruit hull is used as antimicrobial agents and antiparasitic treatments in dysentery as well as externally for healing the wounds and chronic ulcers. Mangosteen's leaves and bark are recognized to have strong anti-inflammatory properties and applied for treating hyperkeratosis, eczema, and other skin disorders. The rind decoction is administered to relieve gonorrhea, gleet, diarrhea, and cystitis. In addition, the decoction also can be applied externally as an astringent lotion. The astringent qualities of mangosteen are also employed for preventing dehydration and the loss of essential nutrients from the gastrointestinal tract. In Thai traditional medicine, the fruit hulls have been in use for the treatment of skin infections, wounds and a relief of diarrhea. In the Philippines and Malaya, a tea made from the rind and decoction of the leaves and bark are adopted as a febrifuge as well as in the treatment of dysentery, diarrhea, and various urinary disorders. A root's decoction is administered by women with menstrual disorders. Similarly, mangosteen has also been used for medical purposes in Caribbean and Latin America. A tea made from mangosteen's fruits is popularly applied as a tonic for fatigue and low energy states. Brazilians use similar tea as a digestive aid30. Pedraza-Chaverri et al. reported that traditional medicinal properties of mangosteen is employed for hemorrhoids, food allergies, arthritis, tuberculosis, mycosis, mouth aphthae, fever, thrush, abdominal pain, suppuration, leucorrhea, and convulsant.

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Fig.1: Mangosteen fruit and showing a mangosteen tree.

XANTHONE:

Xanthones are the major bioactive component found in mangosteen. At least over 68 xanthones derivatives isolated from mangosteen fruit were reported [1,3]. Some xanthones of mangosteen included α-mangostin, β-mangostin, ɣ-mangostin, gartanin, 8-deoxygartanine, Mangostenone, 11α-mangostin, Mangostanol, 1-isomangostin, 3-isomangostin, and garcinone E. The most abundant xanthones in mangosteen pericarp and bark are α- and γ-mangostin [6]. α-mangostin is the major xanthones derivatives isolated from mangosteen and have been drawnattention in the medicinal plant research area due to its extensive biological and pharmacological activities.

Phytochemical Composition:

Phytochemical screening, based on ethnomedicinal data, is considered as an effective approach for the discovery of new therapeutic agents. The major bioactive secondary metabolites of mangosteen are xanthone derivatives.

Table1: Mangosteens secondary metabolites

Number	Compound name	type	Plant part
1	α-Mangosteen	xanthones	Pericarp, whole fruit, stem, seed
2	β-Mangosteen	xanthones	Pericarp, whole fruit, stem
3	γ-Mangosteen	xanthones	Whole fruit
4	(16E)-1,6-Dihydroxy-8-(3-hydroxy-3-methyl but-1-enyl)-3,7-dimethoxy-2-(3- methyl but-2-enyl)-xanthone	xanthones	Whole fruit
5	1,3,6,7-Tetrahydroxy xanthone	xanthones	Pericarp
6	1,3,6-Trihydroxy-7-methoxy-2, 8-(3-methyl-2-butenyl) xanthone P2	xanthones	Leaves
7	1,3,8-Trihydroxy-4-methyl-2,7-diisoprenylxanthone	xanthones	Heartwood
8	1,3,7-Trihydroxy-2,8-di-(3-methyl but-2-enyl)-xanthone	xanthones	Leaves
9	1,3-Dihydroxy-2-(2-hydroxy-3-methyl but-3-enyl)-6,7-dimethoxy-8-(3- methyl but-2-enyl)-xanthone	xanthones	Heartwood

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10	1,5-Dihydroxy-2-(3-methyl but-2-enyl)-3-methoxy-xanthone	xanthones	Heartwood, stem
11	1,5-dihydroxy-2-isopentyl-3-methoxy xanthone	xanthones	Heartwood
12	1,5,8-Trihydroxy-3-methoxy-2-(3-methyl but-2-enyl) xanthone	xanthones	Heartwood
13	1,6-Dihydroxy-2-(2-hydroxy-3-methyl but-3-enyl)-3,7-dimethoxy-8-(3- methyl but-2-enyl)-xanthone	xanthones	Pericarp
14	1,6-Dihydroxy-3-methoxy-2-(3-methyl-2-butenyl)-xanthone	xanthones	Pericarp
15	1,6-Dihydroxy-3,7-dimethoxy-2-(3-methyl but-2-enyl)-8-(2-oxo-3-methylbut3-enyl)-xanthone	xanthones	Whole fruit
16	1,6-Dihydroxy-3,7-dimethoxy-2-(3-methyl but-2-enyl)-xanthone	xanthones	Heartwood
17	1,7-Dihydroxy-2-(3-methyl but-2-enyl)-3-methoxy-xanthone	xanthones	Pericarp
18	1,7-dihydroxy-2-isopentyl-3-methoxy xanthone	xanthones	Pericarp
19	11-Hydroxy-1-isomangostin	xanthones	Not stated
20	1-Isomangostin	xanthones	Pericarp
21	1-isomangostin hydrate	xanthones	pericarp
22	3-isomangostin	xanthones	pericarp
23	3-isomangostin hydrate	xanthones	Pericarp
24	6-Deoxy-7-demethylmangostanin	xanthones	Whole fruit
25	Calabaxanthone	xanthones	Arils
26	cudraxanthones	xanthones	Pericarp
27	Demethylcalabaxanthone	xanthones	Whole fruit, stem, arils
28	Garcimangosone a	xanthones	Fruit hull
29	Garcimangosone b	xanthones	Pericarp
30	Garcimangosone c	xanthones	Pericarp
31	gartanin	xanthones	Pericarp, whole fruit
32	mangosharin	xanthones	Stem
33	Mango statin	xanthones	Pericarp
34	Mangostanol	xanthones	Whole fruit, stem
35	Mangostenol	xanthones	Pericarp
36	Mangostenone A	xanthones	pericarp
37	Mangostenone B	xanthones	Pericarp
38	Mangostenon C	xanthones	Whole fruit

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39	Mangostenone D	xanthones	Whole fruit
40	Mangostenone E	xanthones	Whole fruit
41	Tovophyllin A	xanthones	Pericarp
42	Tovophyllin B	xanthones	Pericarp
43	Euxanthones	xanthones	Pericarp
44	Caloxanthone A	xanthone	Pericarp
45	Garcimangosone D	benzophenone	Pericarp
46	Maclurin	benzophenone	pericarp
47	Epicatechins	Flavonoids	Pericarp
48	Chrysanthemum	Anthocyanins	Pericarp
49	Cyanidin-3-O-glucoside	Anthocyanins	Not stated

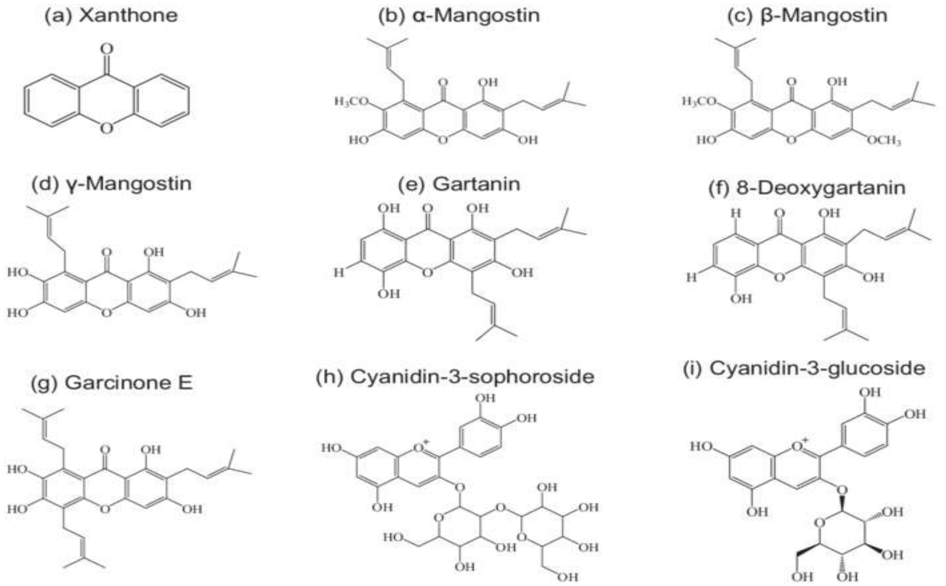

Fig: chemical structure of xanthone and its derivatives

Pharmacological Studies:

Studies of mangosteen's pharmacological has started inthe 1990's. Mangosteen is an important medicinal plant in the family of Clusiaceae. In recent history, this plant is reported for various medicinal properties (see Figure 3). Antibacterial Activity: Suksamrarn et al. stated that γ-mangostin, garcinone D, mangostanin, α-mangosteen, and demethylcalabaxanthone have a strong inhibitory effect on Mycobacterium tuberculosis21. α-mangostin has antimicrobial activity against vancomycin-resistant Enterococci (VRE) and methicillin-resistant Staphylococcus aureus (MRSA)36. As reported by Voravuthikunchai and Kitpipit, the ethanol extract from mangosteen has antimicrobial activity against methicillin-resistant Staphylococcus aureus37. Furthermore, Chomnawang et al. found that the crude extract of mangosteen can inhibit the growth ofPropionibacterium acnes and Staphylococcus epidermidis.

Antihyperglycemic and Antidiabetic Activities:

Several studies showed the antihyperglycemic and antidiabetic activity of mangosteen. Husen et al. stated that the extract of mangosteen's pericarp has been proven to be effective for decreasing the fasting blood cholesterol level and lipid peroxidation in the type-2 diabetic mice12. In addition, Husen et al. also tested the antioxidant and antidiabetic activity from the extract of mangosteen's pericarp in the streptozotocin-induced diabetic mice13. Moreover, Ansori et al. demonstrated the Reno protective effect from the extract of mangosteen's pericarp in the streptozotocin-induced diabetic mice14.

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Furthermore, Husen et al. reported an antioxidant activity assay of the alpha-mangostin for amelioration of kidney's structure and function in the diabetic mice16. Moreover, Husen et al. also mentioned that the hepatoprotective effect of γ-mangostin for amelioration of the impaired liver's structure and function in the streptozotocin-induced diabetic mice.

Wound Healing Activity:

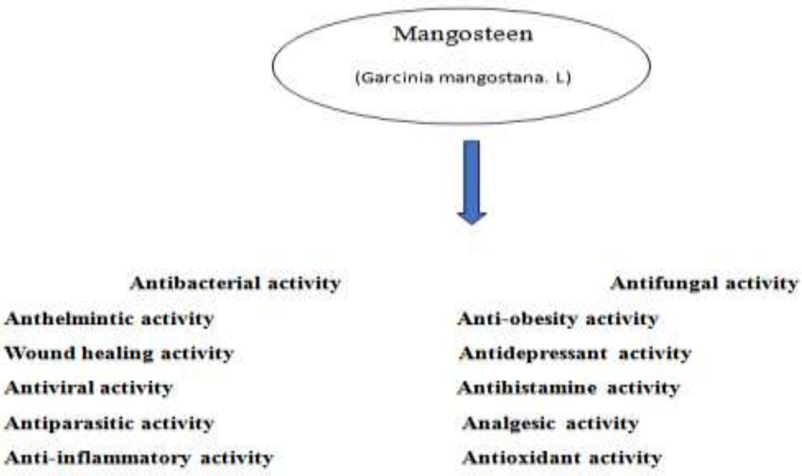
Nganlasom et al. confirmed that the mangosteen's folkloric utilization and suggested the beneficial effects of mangosteen's extracts for treating diabetic wounds in human being. Interestingly, the further studies with purified constituents were required to understand the complete mechanism of wound healing promotion induced by the mangosteen.

Anticancer, Anti-tumorigenic, and Antiproliferative Activities:

α-Mangostin induces the apoptotic cell death against canine osteosarcoma D-17 cells46. It also α showed the potent effects against HCT 116 colorectal carcinoma in an in vitro and in vivo47. Nakagawa et al. reported that αmangostin also is able to induce the cell death via caspase-independent apoptosis with the release of endonuclease-G from mitochondria and increases miR143 expression in human colorectal cancer DLD-1 cells48. In addition, Wang et al. stated that α-mangostin has a potential cytotoxic effect against human melanoma SK-MEL-28 cell line49. Meanwhile, Suksamrarn et al. argued that α-mangostin leads cell death in breast cancer and epidermoid carcinoma of the mouth cell lines through apoptosis, as gartanin also causes apoptosis in small cell lung cancer cell lines22. Furthermore, Matsumoto et al. reported that α-mangostin, βmangostin, and γ-mangostin are particularly effective for the significant inhibition against human leukemia HL60 cell growth50. While, Moongkarndi et al. argued that methanol extract of mangosteen's pericarp can induced the apoptosis of SKBR3 human breast cancer cell line51. Additionally, α-mangostin and γ-mangostin can induces cell-cycle arrest and apoptosis in human colon cancer DLD-1 cells52. Yu et al. said that immunomodulatory and anticancer activities can be found in phenolics which is derived from the mangosteen's fruit pericarp53. Mohamed et al. showed that new xanthones and cytotoxic constituents from mangosteen's fruit hulls can induce the apoptosis against human hepatocellular, breast, and colorectal cancer cell lines54. Moreover, Li et al. claimed that polyphenols from mangosteen fruit can induce apoptosis against breast and prostate cancer55. In addition, Doi et al found that in vivo antitumorigenic activity that uses panaxanthone (75%-85% α-mangostin, 5%-15% γ-mangostin) is effective in suppressing the tumor volume and lung metastasis56 . Lastly, Johnson et al revealed that α-mangostin decreases the tumor growth in human prostate carcinoma

Antiviral Activity:

α-Mangostin and γ-mangostin from mangosteen inhibited HIV-1 with IC50 values of 5.1 and 4.8 μM, respectively63. Furthermore, Vlietinck et al. discovered that the role of α-mangostin as a non-competitive inhibitor of HIV-1 protease by inhibiting the HIV virus replication cycle.



Antihistamine Activity:

α-Mangostin and γ-mangostin are histaminergic and serotonergic receptor blocking agents18. In addition, αmangostin inhibits allergic mediators in bone marrow-derived mast cell60. Furthermore, Nakatani et al. presented that ethanol extract of the mangosteen's pericarp inhibits both histamine release and prostaglandin E2 synthesis.

Antiparasitic and Anthelmintic Activities:

α-Mangostin and β-mangostin were reported to be inhibitory for the growth of Plasmodium falciparum clone D6. Several modified derivatives were prepared based on the skeleton of α-mangostin. Among these compounds, xanthone derivatives with alkylamine groups exhibits the most potent inhibitory activity against P. falciparum in an in vitro assay.

Anti-obesity Activity:

α-Mangostin has in vitro cytotoxicity against 3T3-L1 cells as well as inhibiting the fatty acid synthase.

Antimalarial:

Antimalarial activity of α-mangostin was demonstrated by virus titer assay through plaque assay method. Alpha-mangostin was tested against the dengue virus infection (DENV2) in human peripheral blood mononuclear cells (PBMC). Alpha-mangostin could potentially inhibit virus replication due to its higher concentration. The results showed 50% viral reduction after treatment using 10 and 20 μM of α-mangostin at 24- and 48-h post-infection, in which the 48-h treated group had a more percentage reduction effect. The IC50 values were 5.47 and 5.77 μM for 24- and 48-h treatments, respectively [52]. Another in vitro study was conducted on the antimalarial activity of α-mangostin in DENV infection in hepatocellular carcinoma HepG2 and Huh-7 cell lines. The results demonstrated that α-mangostin inhibited both DENV production and cytokine/chemokine expression in HepG2 cells.

Inflammatory bowel disease:

Mangosteen extract and α-mangostin reduced the degree of ulcerative colitis (UC) induced by dextran sulfate sodium (DSS) in mice. Furthermore, a recent study revealed that this mechanism occurred by suppressing nuclear factor-kappa B (NF-kB) activation due to mangosteen's anti-inflammatory and antioxidant effect

Antioxidant:

The fresh and frozen peel (pericarp) and the flesh (pulp) of G. mangostana were extracted by ultrasound-assisted extraction method for 15-, 30- and 60-min. Ethanol within 20%, 40%, 70% and 96% (v/v) concentrations were used as solvent. The antioxidant activity was measured using 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2′-azino-bis-(3- ethylbenzothiazoline-6-sulfonic acid (ABTS), cupric reducing antioxidant capacity (CUPRAC), ferric reducing antioxidant power (FRAP) and ferrous ion chelating (FIC) methods, whereas the total phenolic content was measured using the Folin-Ciocalteu (F-C) method. The result indicated that a higher antioxidant activity in fresh peel extracts corresponds to several antioxidant compounds. The F-C technique measured the highest polyphenol content from the fresh plant material extract [8]. Pectin was isolated from the mangosteen peel extract and the antioxidant potential was observed by the DPPH method. The result showed a moderate antioxidant activity with the IC50 of about 161.93 ± 31.57 μg/ml.

II. CONCLUSION:

The mangosteen (G. mangostana L.) contained several chemical compounds, especially xanthones, benzophenones, flavonoids, and anthocyanins. These components were proven to generate beneficial human health conditions through various pharmacological activities such as antioxidant, anti-acne, anti-aging, anti-hyperpigmentation, antibacterial, antidiabetic, antiobesity, anti-inflammatory, antimalarial, antiparasitic, and antitumor. Furthermore, chemical compounds isolated from mangosteen have shown advantageous outcomes for multiple pathological conditions includes Alzheimer's, various cancers, bipolar disorder, schizophrenia, neuropathic pain, CKD, and pulmonary fibrosis. This review indicated that xanthone in mangosteen has the potential to be developed as a promising drug candidate. Further exploration of mangosteen as drug candidates may include pharmacokinetic, pharmacodynamic, and xanthone targeting effects that possible to be carried out in the future study.

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