

Review

Review of pharmacological properties of *Channa striatus* (Haruan) in diabetes and cardiovascular complications

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Simple Summary: This review was carried out following previous reports on the hypoglycemia, hypolipidemia, antioxidant, and anti-inflammatory activities of *Channa striatus*. The fact that there are relationships between diabetes, oxidative stress, and inflammation processes has also triggered the authors to determine the potential of *C. striatus* against diabetes and cardiovascular disease. For information, *C. striatus* is a traditional medicine that widely used in Malaysia to treat ailments related to wound, pain, and also ulcers. This present review aims to assess the potential of *C. striatus* to use in the prevention and/or treatment of diabetes and cardiovascular complications.

Abstract: Diabetes mellitus remains a major risk factor for developing cardiovascular diseases, resulting in increased morbidity and mortality associated with cardiovascular complications. Given the burden of diabetes-related cardiovascular complications, there is a need to identify strategies, safe and effective therapeutic agents that could effectively prevent and control diabetes. Presently, many patients living with diabetes depends on traditional medicines as an alternative cure. *Channa striatus* (Haruan) is a freshwater fish traditionally used to treat wounds, inflammations, and pains. Several pharmacological investigations have supported the folkloric claims of *C. striatus* extracts, including hypoglycemic, hypolipidemic, antioxidant, anti-inflammatory, and pro-platelet aggregation activities. The therapeutic potentials of *C. striatus* were demonstrated to be associated with the presence of high content essential amino acids and good fatty acids known to improve cell growth and facilitate wound healing. Therefore, *C. striatus* bioactive compounds have great potentials to serve as lead candidates in developing novel therapeutic agents for the management of diabetes and related cardiovascular diseases. This review aims to provide a comprehensive overview of the pharmacological properties and therapeutic potentials of *C. striatus* for the management of diabetes and associated cardiovascular complications.

Keywords: antioxidant; anti-inflammatory; cardiovascular; *Channa striatus*; diabetes

1. Introduction

Diabetes mellitus has emerged as one of the rapidly increasing chronic non-communicable diseases with a substantial public health burden globally [1]. The World Health Organization (WHO) have estimated that over 450 million adults lived with diabetes globally in 2017, and it is projected to increase to over 690 million by 2045 in the absence of effective prevention and control strategies [1–4]. Diabetes is a metabolic disorder of several etiologies characterized by chronic hyperglycemia resulting from absolute or relative lack of insulin. Cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality among people living with diabetes [5]. Diabetes increases the risk of developing coronary heart disease, ischemic stroke, and death by many folds [6]. A substantial burden of diabetes is related to vascular complications, including coronary heart disease, peripheral artery disease, stroke, neuropathy, nephropathy, and retinopathy [5]. Given the progressive burden of diabetes-related cardiovascular disorders, it is imperative to identify and institute new strategies to prevent and control diabetes.

Despite the advancements in technologies and health, many patients still live in traditional ways that influence their health-seeking behaviors. To date, in many parts of the world, the majority of the population continues to rely on traditional medicine as the primary source of care [7]. Worldwide, plant-based traditional medicines received more attention in the medical literature compared to animal-based natural medicines. Several medicines are driven from animal sources, including those used in diabetes, many of which have been documented with their pharmacological properties. Animal-based natural products have become an essential source of new bioactive compounds that can potentially lead to drug development [8]. Specific animal-based natural products like *Channa striatus* (Haruan) have been demonstrated to have therapeutic effects against several diseases, particularly diabetes, with fewer side effects, lower cost, and are more accessible locally.

The *C. striatus* is a freshwater fish that serve as a host for the animal-based natural product known for wound healing and antidiabetic properties [9,10]. *C. striatus* has been demonstrated to exert several pharmacological activities [11,12], majorly attributed to its high content of essential amino acids and fatty acids [13,14]. Previous studies have reported *C. striatus* to have hypoglycemic [15], antioxidant [16], anti-inflammatory [11,17–19], antinociceptive [12,20–22], anti-bacterial [23,24], wound healing [25–29], and anti-ulcer [8,30] properties. Therefore, this review aims to provide an overview of the pharmacological properties of *C. striatus* related to diabetes and cardiovascular complications. The study will provide useful information for conducting further investigations and translating *C. striatus* compounds into drug development.

2. Methods

A non-systematic search of academic databases (PubMed and Google Scholar) and grey literature (Google) was performed to extract and synthesize relevant studies that describe the potential roles of *C. striatus* in the management of diabetes and related cardiovascular complications. The search terms used include *C. striatus*, Haruan, diabetes, and cardiovascular diseases.

3. *Channa striatus*

3.1 Scientific classification

Kingdom: Animalia; Phylum: Chordata; Class: Actinopterygii; Order: Anabantiformes; Family: Channidae; Genus: *Channa*; Species: *C. striatus*; Binomial name: *Channa striatus* (Bloch, 1793).

3.2 Animal description

C. striatus (Haruan), known as snakehead murrel, is an obligate air-breathing freshwater fish found mostly in tropical and subtropical Asian countries. *C. striatus* is consumed all over the Asia Pacific region and is considered a valuable source of protein with several therapeutic benefits [31]. *C. striatus* has high protein content, mainly albumin and essential amino acids, good fatty acids, minerals, and vitamins [13,14]. The fish is known to have nutritional benefits over other types of fish responsible for its therapeutic benefit.

3.2 Animal morphology

C. striatus has a large and slightly flattened scaled head like a snake with a big mouth and sharp teeth, a round body shape, and an extended dorsal fin and a rounded tail fin (Figure 1a). The upper side of the body is dark, brownish, or greenish; the underside of the body is white, while the sides part of the body have thick lines [32] (Figure 1b). The fish grows up to one meter in length, although bigger sizes are rarely found in the wild because of continuous fishing.



Figure 1. This is a figures of *C. striatus*. (a) Healthy adults *C. striatus*; (b) *C. striatus* mid-line fillets

3.3 Chemical composition

The common bioactive compounds attributed to *C. striatus* therapeutic effects are amino acids and fatty acids. The high protein and fat content of the fish make it an important dietary source of essential amino acids like lysine and methionine, as well as a good source of omega-3 fatty acids, particularly docosahexanoic acid (DHA) and

eicosapentanoic acid (EPA) [33]. These compounds have been shown to have a beneficial effect in preventing diabetes and cardiovascular complications [33]. In addition, the fish is also known to contain polyunsaturated fatty acids that regulate prostaglandins synthesis and hence wound healing [34,35]. Amino acids and fatty acids are also major biochemical components of the healing process, and deficiency could delay full recovery [13].

A study by Mat Jais et al. reported several fatty acids and amino acids in *C. striatus* fillet [13]. In the study, the mid-line fillet of *C. striatus* (Figure 1b) was found to contain fatty acids such as arachidonic acid (12.70%), palmitic acid (26.90%), stearic acid (10.30%), oleic acid (15.01%), (DHA; 16.43%), and EPA (1.29%). The study had also shown the presence of amino acids, which include aspartic acid (4.19%), glutamic acid (8.46%), glycine (9.77%), alanine (8.40%), proline (9.17%), leucine (10.51%), phenylalanine (5.04%) and lysine (5.89%).

Another study by Gam et al. has shown that *C. striatus* fillet comprises certain amino acids as the major chemical component, including glutamic acid, aspartic acid, lysine, arginine, leucine, alanine, valine, threonine, and glycine [36]. The study also demonstrated that *C. striatus* contain higher quantities of amino acids in *C. stratus* than Keli (a freshwater catfish), Rainbow trout, and the salmon fish [36].

A study on Malaysian *Channa* species, including *C. striatus*, reported amino acids and fatty acids as major compound compositions [14]. From the study, the proximate analysis revealed that the protein content of *C. striatus* fillet was 23.0%, 5.7% crude fat, and 1.8% crude ash (% of dry weight). The fatty acids contained in *C. striatus* fillet include palmitic acid (30.39%), stearic acid (15.18%), oleic acid (12.04%), arachidonic acid (19.02%), linoleic acid (8.34%), and DHA (15.18%). The amino acids contained in *C. striatus* fillet include aspartic acid (11.4%), glutamic acid (21.7%), arginine (5.9%), glycine (4.3%), lysine (9.7%), leucine (7.5%), and alanine (5.8%). In this fish, the presence of amino acids, particularly DHA, may contribute to the pain reduction, anti-inflammatory, and wound healing properties [14].

Zakaria et al., in another study, had also reported amino acids and fatty acids composition in the aqueous extract of *C. striatus* fillet. Amino acids in the extract includes aspartic acid (8.53%), glutamic acid (4.59%), glycine (35.77%), arginine (4.09%), proline (6.86%), lysine (9.44%), leucine (2.91%), phenylalanine (2.48%) and threonine (4.07%). While the fatty acid composition in *C. striatus* extract comprises palmitic acid (35.93%), stearic acid (15.31%), oleic acid (22.96%), linoleic acid (11.45%), and arachidonic acid (7.44%) [37].

Studies have demonstrated the antioxidant effect of amino acids extracted from *C. striatus*, such as aspartic acid, glutamic acid, leucine, and valine [38–40]. Fatty acids such as DHA has been shown to possess antioxidant activity [41,42]. Other studies have reported hypoglycemic [43,44], hypolipidemic [43,45], and anti-inflammatory [46] properties of the amino acids (arginine) and fatty acids (DHA, EPA, oleic acid).

4. Pharmacological properties of *C. striatus*

Cardiovascular complications are the primary cause of morbidity and mortality in patients with diabetes. Hyperglycemia leads to increased glucose autoxidation, lipid peroxidation, and non-enzymatic protein glycosylation, leading to an increase in reactive

oxygen species (ROS), advanced glycation end products (AGEs), and endothelial dysfunction [47]. The details of studies demonstrating the pharmacological properties of *C. striatus* via hypoglycemic, hypolipidemic, antioxidant, and anti-inflammatory are highlighted in the following sections.

4.1 Hypoglycemic and hypolipidemic properties

Only a single study was identified to demonstrate the hypoglycemic effect of *C. striatus*. The *in-vivo* study showed the antidiabetic activity of *C. striatus* in an alloxan-induced diabetic mice model. Administration of the ethanol extract of *C. striatus* powder at a dose of 300 mg/kg reduced blood glucose concentration after 12 days of treatment [15]. The hypoglycemic effect of the crude extract of *C. striatus* was linked to certain amino acids and fatty acids in *C. striatus*, such as palmitic acid, oleic acid, and arginine.

An *in-vivo* study by Lee et al. reported the hypoglycemic property of palmitic acid in type 2 diabetic db/db mice [48]. In this study, administration of palmitic acid-modified exendin-4 (Pal-Ex4) directly into the trachea of type-2 diabetic db/db mice at a dose of 150 nmol/kg using micro sprayer delayed the time to blood glucose rebound to >150 mg/dL compared to Ex4 (18.1 hours vs 5.2 hours). The degree of hypoglycemia caused by Pal-Ex4 was shown to be 3.4 and 2.3-fold greater than that caused by native Ex4 at 75 and 150 nmol/kg, respectively. From the findings, prolonged hypoglycemia demonstrated by Pal-Ex4 was due to the delayed absorption in the lungs and albumin binding in the circulation. This finding showed that palmitic acid-modified exendin-4 should be viewed as a long-acting candidate for treating type-2 diabetes [48].

Another *in-vivo* study by Obici et al. demonstrated the hypoglycemic effect of oleic acid [49], a fatty acid present in *C. striatus*. The infusion of oleic acids in the third cerebral ventricle of rats produced a reduction in plasma insulin level (0.9 ± 0.1 vs 2.1 ± 0.4 ng/mL) and plasma glucose levels (139 ± 2 vs 152 ± 3 mg/dL) compared with ICV vehicle. ICV administration of oleic acid also demonstrated a marked decrease in food intake compared with baseline and vehicle after 24h (-11 ± 2 g) and 48h (-9 ± 3 g). The oleic acid signals 'nutrient abundance' to discrete areas within the central nervous system. This signal, in turn, activates a chain of neuronal events apparently designed to promotwitch in fuel sources from carbohydrate to lipids and limit the further entry of exogenous and endogenous nutrients in circulation. The unveiling of this nutrient-activated neuronal circulatory may lead to innovative approaches to treating obesity and type-2 diabetes [49]. Oleic acid may also improve insulin and leptin sensitivity to their respective receptors, resulting in reduced blood glucose and food intake observed in the animal model. Shimura et al. has demonstrated that the hypoglycemic and hypolipidemic effects of DHA in a diabetic mice model. Oral administration of DHA for 10 hours significantly reduced blood glucose concentration compared to the control rats [43]. The hypoglycemic effect of DHA was associated with increased insulin sensitivity [43].

Although there are no experimental studies on the hypolipidemic property of the crude extract of *C. striatus*, an *in vivo* study by El-Kirsh et al. reported that arginine, an amino acid present in *C. striatus*, exhibited hypolipidemic properties. El-Kirsh et al. has shown that arginine supplementation in high fat and high cholesterol-fed rats reduced total cholesterol, triglycerides, LDL-C, very-low-density lipoprotein cholesterol (VLDL-C),

atherogenic index, and increased high-density lipoprotein cholesterol (HDL-C) [45]. Supplementation also produced marked increases in serum NO levels [46]. Shimura et al. demonstrated that administration of DHA in a diabetic mice model reduced triglycerides and free fatty acids levels compared to control rats [43].

The hypoglycemic and hypolipidemic effects of *C. striatus* extract, with its amino acid and fatty acid composition, could prevent glucose autoxidation, reducing ROS production, particularly superoxide anion, thereby improving NO bioavailability and attenuate endothelial dysfunction in diabetes. The attenuation of endothelial dysfunction in diabetes may prevent the development of atherosclerosis as well as other cardiovascular complications.

4.2 Antioxidant property

The presence of excess free radicals around the cells can be harmful [16]. Cell damage caused by ROS appears to be a major contributor to vascular complications in diabetes [50]. Chronic hyperglycemia in diabetes induces mitochondrial overproduction of ROS, particularly in the endothelium of both large and small vessels [51]. Overproduction of ROS, particularly superoxide anion, led to increased oxidative stress. Oxidative stress is the condition where the high production of ROS overwhelms endogenous antioxidant defence mechanisms. Antioxidants could be an integral approach in reducing atherosclerosis in cardiovascular diseases and play a significant role against vascular endothelial dysfunction. An antioxidant's function is to scavenge free radicals by preventing and repairing damage caused by ROS. It, therefore, can enhance the defence system and lower the risk of diabetes-accelerated cardiovascular diseases.

Few studies report the antioxidant property of *C. striatus* extracts [16,30]. An *in-vitro* study by Radzak et al. has reported that aqueous extract of *C. striatus* fillet exhibits antioxidant activity via the total phenolic content (TPC), ferric-reducing antioxidant power (FRAP), 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, and 2,2'-azino-Bis (3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) scavenging activity assays [17]. This study demonstrated that aqueous extract of *C. striatus* showed high TPC (12799 ± 237.90 mg GAE/100g dry weight), FRAP (1250 ± 0.617 mg FeSO₄/1mg dry weight), DPPH (0.2804 ± 0.035 µg/ml; EC₅₀) and ABTS (4687 ± 0.67 µg/ml; EC₅₀) [16].

A study by Khan et al. reported the effect of *C. striatus* aqueous extract on oxidative stress markers in gastric ulcers of a rat model [30]. This study demonstrated that treatment with lower dose (30% w/v) of aqueous extract of *C. striatus* reduced malondialdehyde (MDA; 0.088 ± 0.0034 moles/mg of tissue) levels, while higher dose (50% w/v) of *C. striatus* extract increased superoxide dismutase (SOD; 0.055 ± 0.013 units/mg of tissue) and catalase (0.072 ± 0.012 units/mg of tissue) activity [30]. The antioxidant effect of crude extract of *C. striatus* might be associated with the presence of certain amino acids and fatty acids. Amino acids such as aspartic acid, glutamic acid, and leucine possess antioxidant effects [38–40]. Previous studies have also reported the antioxidant effect of fatty acids such as DHA [41,42].

A few mechanisms may contribute to the potential effects of *C. striatus* in attenuating vascular oxidative stress in diabetic vasculopathy. Firstly, it may be due to the hypoglycemic effect of *C. striatus*. The hypoglycemic effect of *C. striatus* might prevent

glucose autoxidation, thus reduces free radical generation. The reduction of free radicals increases the antioxidant enzyme SOD activity, which decreases the oxidative stress level. Secondly, the high radical scavenging activity by *C. striatus* extract may contribute to reducing oxidative stress status in diabetes. *C. striatus* extract demonstrated high DPPH, FRAP, and ABTS radical scavenging activity. These effects may increase the level of the antioxidant enzyme such as SOD. These properties were supported previously with the treatment of *C. striatus* extract, which increased SOD and reduced MDA levels. The attenuation of lipid peroxidation (MDA level), potentiating antioxidant (SOD), and high radical scavenging activity of *C. striatus* attenuate vascular oxidative stress, slowing down the pathogenesis of atherosclerosis in diabetes.

4.3 Anti-inflammatory property

Inflammation is a normal response to tissue injury or pathogen exposure and a critical factor in the body's ability to heal itself or fight off infection. The inflammatory response involves the activation of leukocytes and is mediated, in part, by a family of cytokines and chemokines. Although inflammation is beneficial, it can have a detrimental effect [52]. Diabetes has been considered a state of chronic and low-level inflammation. Some evidence has suggested that this immune activation may precede insulin resistance in diabetic and pre-diabetic conditions. These effects may be the factor that initially increases cardiovascular risk in this disease process [52–54].

Previous studies have shown reduced NO bioavailability (a potent vasodilator) and increased vasoconstrictor and growth factor endothelin-1 in subjects with metabolic syndrome. These abnormalities not only increase vasoconstriction but are associated with the release of pro-inflammatory cytokines [52,55]. The increase in pro-inflammatory cytokines is directly proportional to the cells' oxidative status or tissues in question. These imply that there will be an increase in oxidative status due to the rise in the production of ROS by the endoplasmic reticulum (ER) stress, mitochondria, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and other sources of ROS. ER stress can also activate inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukins-4 (IL-4), and IL-6.

Pro-inflammatory cytokine induces or exacerbates injury by various mechanisms, including enhanced vascular permeability, programmed cell death (apoptosis), recruitment of invasive leukocytes, and the promotion of ROS production [52,56]. In the diabetic condition, augmented pro-inflammatory cytokines contribute to endothelial dysfunction and atherogenesis. Studies have shown increased pro-inflammatory cytokines, particularly TNF- α in aortas and cardiac tissue of diabetic rat models [57,58]. TNF- α regulates vascular permeability to control inflammation, since increased permeability of micro-and macro vessels allow blood molecules and inflammatory cells to enter the injured vascular tissue. The increased micro and macrovascular permeability contribute to the formation of atherosclerotic plaques initiated by sub-endothelial accumulation of blood lipids and inflammatory cells [59]. In a diabetic state, increased TNF- α activates NADPH oxidase that increases the generation of free radicals, particularly superoxide anion. The overproduction of superoxide anion scavenges NO to form peroxynitrite, disrupting eNOS activity, thus reducing NO bioavailability [60]. Therefore, studies on the effects of *C.*

striatus on inflammatory cytokines, mainly TNF- α would be beneficial to observe it can prevent/or slow diabetic vasculopathy progression.

A study by Somchit et al. has reported the effect of an aqueous extract of *C. striatus* and methanol-chloroform extract of *C. striatus* on cotton-pellet granuloma test in rats [11]. This study demonstrated that aqueous extract of *C. striatus* showed marked inhibition of the transudative and proliferation components of chronic inflammation (42.9% and 31.2%, respectively) when compared to non-steroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid (25.1% and 21.3%), and piroxicam (36.1% and 26.2%). In the same study, the methanol-chloroform extract of *C. striatus* did not show any anti-inflammatory effects. This study showed that NSAIDs decreased granuloma (cotton pellet) size by inhibiting granulocyte inflammation, preventing the generation of collagen fibers, and suppressing mucopolysaccharides [11,61]. Monocyte infiltration, fibroblast proliferation, and exudation take place in chronic inflammation. This proliferation may spread to small vessels or granuloma [11,62]. Therefore, the aqueous extract of *C. striatus* could inhibit monocyte infiltration and fibroblast proliferation; these may potentially prevent atherosclerosis development.

An *in-vivo* study by Abedi et al. reported on the anti-inflammatory property of *C. striatus* based cream on acute inflammation in the croton oil-induced mice's ear-edema model [17]. Administration of *C. striatus* cream at different doses (1%, 5%, and 10%) significantly reduced ear edema; and this effect was comparable to 1% hydrocortisone (positive control). At 4 hours of treatment, *C. striatus* at these three doses reduced ear edema by 76%, 89%, and 95%, respectively. At 24 hours of treatment, *C. striatus* based cream reduced edema by 68%, 78%, and 98%, respectively, compared to vehicle control (basic cream). All three doses of *C. striatus* based cream significantly reduced myeloperoxidase (MPO) activity to 3.7%, 3.24%, and 2.7%, respectively, compared to vehicle control. MPO is a pro-inflammatory enzyme released by activated neutrophils and macrophages (markers of polymorphonuclears accumulation) [17].

Another *in-vivo* study by Isa et al. reported the anti-inflammatory effect of *C. striatus* cream on 12-tetradecanoylphorbol-13-acetate (TPA)-induced chronic dermatitis in mice [18]. Administration of *C. striatus* cream at doses 1%, 5%, and 10% reduced mouse-ear thickness to 0.547 ± 0.025 mm (19.4%), 0.556 ± 0.018 mm (18.1%), 0.489 ± 0.015 mm (28%) respectively; these effects were comparable to 1% hydrocortisone administration of these doses of *C. striatus* cream also down-regulated TNF- α gene expression level to 34, 54, and 112-fold respectively, with significant reduction as compared to TPA (negative control) alone [18].

A clinical study reported by Shafii et al. has indicated changes in inflammatory markers with supplementation of freeze-dried *C. striatus* extract in women who had lower segment Caesarean section [19]. Supplementation with 500 mg of freeze-dried *C. striatus* extract capsule exhibited a significant reduction in high-sensitivity C-reactive protein (hsCRP;) and total white cell count (TWCC;) and increased platelet counts from day 1 to day 3 of treatment. This effect was comparable to the control group. This study proved that *C. striatus* extract could induce platelet aggregation during wound healing in normal people and diabetic patients [19,63].

Besides the anti-inflammatory effect of crude extract of *C. striatus*, fatty acids present in *C. striatus* may assist in attenuating inflammatory cytokines. Vassiliou et al. had shown that oleic acid effectively reverses the inhibitory effect on insulin production by the inflammatory cytokine TNF- α . Significant increases in insulin production by INS-1 cells were seen when grown in mediums containing glucose and treated with oleic acid at 10 μ M and 5 μ M [46].

Based on the studies highlighted, it could be deduced that the anti-inflammatory effects of *C. striatus* is attributed to the inhibition of the pro-inflammatory cytokine, TNF- α production. Thus, a reduction of TNF- α may impair ROS production as well as oxidative stress. Therefore *C. striatus* have the potential to prevent vascular endothelial dysfunction and atherosclerosis development in diabetes.

5. Conclusion

Studies have established the ethnopharmacological uses and therapeutic potentials of *C. striatus* against diabetes and cardiovascular complications. Limited studies have shown *C. striatus* to have hypoglycemic, hypolipidemic, antioxidant, anti-inflammatory potentials in diabetes models. The therapeutic potentials of *C. striatus* were demonstrated to be associated with the presence of bioactive compounds, particularly high content essential amino acids and good fatty acids known to improve cell growth and wound healing. Therefore, the biochemical composition and pharmacological effects of *C. striatus* suggested its therapeutic potential in managing diabetes and cardiovascular complications. Further studies would be required to fully elucidate the molecular mechanisms in which *C. striatus* exerts its pharmacological effects. Therefore, there is also a need for further bioassay-guided fractionation, isolation, and characterization of the extracts and fractions of *C. striatus* are necessary to understand the bioactive compounds responsible for the pharmacological activities fully and to enable the discovery of novel antidiabetic agents. Since the fish is generally consumed, further clinical trials should also be performed to establish the clinical safety and efficacy of *C. striatus* for use in the treatment of diabetes and other diseases. Besides, more studies are required to standardize the appropriate dosage of *C. striatus* compounds.

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