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Betanin: a promising molecule for biomedical applications

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ABSTRACT

Plants with medicinal properties possess beneficial influences on health and disease. Different plant parts and extracts carry valuable active ingredients with pharmacological properties that lead to developing new drugs. *Terminalia bellirica* is among those plants that have been formulated as pharmaceutical products. This is attributed to its biologically active phenolics and tannins exhibiting analgesic, anti-hypertensive, anti-microbial, anti-diabetic, anti-oxidant, as well as, other pharmacological properties. Beetroot has been shown to be rich in nitrates with a positive impact on the cardiovascular system. Beetroot contains a number of useful ingredients as the free-radical scavenger ascorbic acid, the anti-inflammatory flavonoids and the anti-oxidant carotenoids. Moreover, beetroot is rich in the natural colorant betalains that are further classified into betacyanins and betaxanthins. Betanin, is one of the major constituents of beetroots that have been postulated to possess significant beneficial therapeutic effects in a number of conditions and diseases. However, several studies have demonstrated the relatively poor bioavailability of betanin upon oral administration. In the current review we aim to highlight some of the latest researches dealing with the therapeutic properties of betanin in different disease conditions, the possible mechanistic pathways beyond such beneficial effects and plausible strategies capable of enhancing its stability and bioavailability.

Keywords: *Betanin; medical plant; nanoencapsulation; Terminalia berillica; oxidative stress; autophagy; inflammation.*

1. INTRODUCTION

Plants with medicinal properties support in providing healthiness. Knowledge of medical plants then using them for curing various illnesses valorized them among modern and ancient civilizations [1,2]. The plant part leaf was employed in preparing medicines. Afterward, the use of the fruit, root, seed, stem bark, flower, as well as whole plants and oil extract took places [3-7]. Plants with the highest usage indicate the presence of possible precious metabolites. For related pharmacological activities, they should be investigated. This has lead and may further lead to the development of new drugs. Hence, such plants are viewed can be considered as potent materials for curing various diseases [2, 8, 9]. It is also known that herbs exhibit a safer profile in pharmacology with lower adverse effects [10]. The elderly people of rural areas have adequate ethnomedicinal knowledge [11]. They knew how to choose medicative plants for practice in healing some ailments. Unfortunately, the ethnobotanical knowledge is gradually weakening in the urban areas due to modern health facilities. Accordingly, documenting the traditional knowledge of medicinal plant usage has become essential. Hence, it is proposed to investigate and document the ethnomedicine. The latter accounts for the status of contemporary knowledge using quantitative indices [12,13]. Preliminary plant extracts phytochemical screening of *Terminalia bellirica has* shown biologically active phenolics and tannins [14-16]**.** *Terminalia bellirica* Roxb, also known as Bahera, belongs to the *Combretaceae* family. Gallic, chebulanic and ellagic acids, glucoside, tannins, ethyl galate and gallyl glucose are the major active phytoconstituents of *Terminalia bellirica* [17]. They are medicinally important and responsible for many pharmacological functions. Different parts of Bahera have various medicative properties. Bahera exhibits analgesic, anti-hypertensive, anti-microbial, anti-diabetic, anti-oxidant, and anti-urolithiatic properties [18-20]. It possesses anti-psychotic potential as well [21]. Such pharmacological properties support in preventing and delaying clot formation and provide an immunostimulant action. It has traditional uses including cough relief, asthma, indigestion, dental problems, throat problems and wounds [22]. Fruits are found to possess anti-inflammatory, anti-helminthic, anti-pyretic, anti-emetic, and expectorant properties [23,24]. They may assist in curing diseases like asthma, bronchitis, dyspepsia, cardiac disorder, skin disease, leprosy and ulcer. Ripe fruits are used as astringents [25,26]. Thus, the treatment of hypertension, diabetes and rheumatism can be achieved using *Terminalia bellirica* [27,28]. Moreover, *Terminalia bellirica* has been previously shown to possess anti-HIV-1, anti-malarial, anti-bacterial and anti-fungal activities [29,30]. Accordingly, *Terminalia bellirica* active ingredients have been marketed as capsules together with other approved medicinal plants [31].

Another plant that has recently gained significant attention, is Beetroot (*Beta vulgaris L.*). Beetroot is the taproot portion of the beet plant. Beetroot has been shown to be rich in nitrates with a positive impact on the cardiovascular system [32,33]. It has been postulated that 25% of beetroot nitrates are reduced into nitrite by the aid of salivary bacteria. Upon ingestion, gastric reductases help convert these nitrates into nitric oxide (NO), which is known for its blood pressure lowering effects [34,35]. Additionally, beetroot has been depicted to contain a number of useful ingredients that play an important role in health and disease. Among those ingredients are the free-radical scavenger ascorbic acid, flavonoids that are known for its anti-inflammatory properties, as well as, carotenoids that possess antioxidant traits [36,37]. Moreover,

beetroots represent the main source of the water-soluble nitrogen pigment betalain with an illustrated chemical structure in Figure 1.

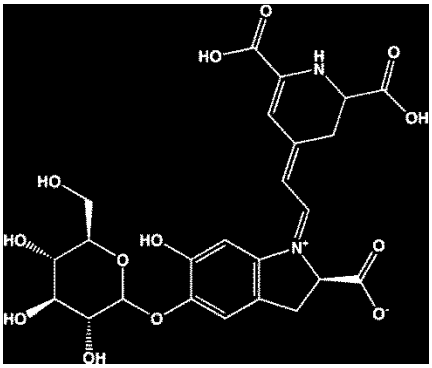

Figure 1. Betalain structure

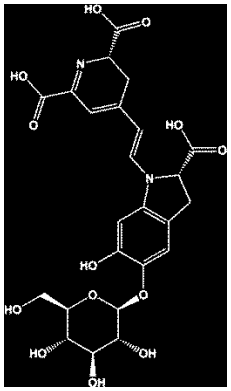

Figure 2. Betanin structure

Betalains, a group of heterocyclic compounds, are present in the tuberous part of beetroots, conferring its red-purple coloration. Betalains are further classified into betacyanins having a red-violet color and betaxanthins, having an orange-yellow color. Betanin (betanidin 5-*O*-β-d-glucoside) is the most abundant betacyanin found in beetroots, and is used as a natural colorant in food products, cosmetics and pharmaceuticals [38]. Betanin is formed by β-glycosylation of the aglycone betanidin C5 [39] as shown in Figure 2, with a molecular weight of 550 g/mol [40]. A marked number of studies have asserted the potential beneficial therapeutic effects of betanin in a number of conditions and diseases, among which are renal fibrosis, atherosclerotic diseases, and cancers [32,41,42], in addition to its well documented antioxidative properties in Parkinson's disease, peripheral artery vasospasm models and others [43-46].

Betanin has gained further attention as well, due to its anti-inflammatory properties [47]. After extracting betanin from plants other than beetroots, Sutariya & Saraf were able to depict that betanin ameliorated the mRNA and protein expression levels of transforming growth factor-β (TGF- β), as well as, collagen IV in a rat model of streptozotocin-induced diabetic nephropathy [41]. Additionally, betanin has been shown to exhibit hepatoprotective properties against acetaminophen-induced hepatic injury in a rat model, which was confirmed by histopathological data [48]. Moreover, betanin has also been demonstrated to possess anti-apoptotic properties [46]. Last but not least, betalain-rich concentrates have been shown to improve running, cycling and exercise performances [49,50]. However, it should be noted that betanin beneficial effects are challenged by its relatively low bioavailability [40,51-53].

In the current review, we aim to demonstrate the potential beneficial therapeutic and protective properties of betanin that have been elaborated in a number of conditions and diseases, and the postulated mechanisms for enhancing its stability and bioavailability.

2. THE ROLE OF BETANIN IN DEALING WITH SOME DISORDERS

2.1. Betanin and oxidative stress.

Several studies have pointed out the ability of betanin to scavenge free radicles, hence, reduce oxidative stress that affects cultured cell lines, as well as, experimental animals [54-57]. Some studies were able to depict that betanin pretreatment of differentiated rat pheochromocytoma PC12 cells prior to exposure to 6-hydroxydopamine (6-OHDA) or hydrogen peroxide was able to significantly reduce oxidative stress [58,59]. This was done through pretreating the cultured cells with different concentrations of betanin followed by exposing the cells to the prooxidants 6-hydroxydopamine or hydrogen peroxide. After which the cells were exposed to 2′,7′-dichlorodihydrofuorescein diacetate capable of interacting with reactive oxygen species to produce a fluorescent signal. The authors have depicted that pretreatment with different concentrations of betanin ranging from 5-200 μM was able to significantly lower the level of the fluorescent signal indicating a lower level of reactive oxygen species. The results were further augmented by having significantly better cell viability and survival with betanin pretreatment, especially in light of the fact that exposing the cultured cells to such concentrations of betanin was ultimately safe as assessed by cytotoxicity studies [46]. Relevant results were illustrated in primary rat hepatocytes exposed to organophosphate poisoning and in Huh7 human liver hepatoma cells [60,61]. Tural *et al*. have illustrated the capability of post-operative betanin administration for 1 week to revert markers of oxidative stress towards normal in a rat model of femoral artery vasospasm [45]. However, it should be noted that betanin is unlikely to have direct vasorelaxant effects [38]. Vascular rings from porcine coronary, mesenteric and pulmonary arteries' responses to betanin were examined in the absence and presence of the vasoconstrictor prostaglandin $F_{2\alpha}$. The authors concluded that, at physiologic concentrations, betanin is neither capable of inducing vasorelaxation, nor capable of providing a protective effect against the induced vasoconstriction. They were only able to depict an endothelium-dependent vasorelaxation of the coronary arteries in response to concentrations of betanin much higher than the physiological ones, a finding that limits the clinical significance of such an effect [62]. *In vivo* mitigations of betanin against oxidative stress have also been demonstrated in a number of models among which are rats with diabetic nephropathy and those on hyperlipidemic diets. Different concentrations (25, 50, 100 mg/Kg) of oral betanin were able to normalize lipid peroxidation, and superoxide dismutase activity, and improve catalase activity in blood and renal tissue homogenates. Markers of oxidative stress were also improved in liver tissues [41,43]. Betanin effects have illustrated a dose dependent pattern with

higher doses providing better outcomes. In an attempt to unravel the mechanism behind the antioxidative properties of betanin, it was depicted that betanin normalized TGF-β, type IV collagen, E-cadherin, and α-smooth muscle actin both on the mRNA expression levels, as well as, the protein levels [41]. An earlier study has also demonstrated significant antioxidative properties of betanin against paraquat-induced acute renal injury in rodents. Betanin was administered three days before and two days after a single dose of paraquat. There has been marked improvement in catalase, superoxide dismutase and lipid peroxidation parameters, delineating the protective potential of betanin [56].

Recently, pretreatment with betanin has been reported to attenuate the cytotoxic effects of (6-OHDA) in PC12 cells. 6-OHDA leads to the development of a Parkinson's similar syndrome, via impairing mitochondrial function in response to the elevated oxidative stress resulting from dopamine oxidation. Cells exposed to betanin in concentrations ranging from 5 to 200 μM prior to exposure to 6-OHDA have demonstrated better survival, and cell viability as compared to those without prior treatment with betanin. Betanin (20 and 50 μM) pretreatment was also able to significantly diminish the apoptotic signal in response to 6-OHDA exposure in PC12 cells as assessed by flow cytometry. In an attempt to unravel the mechanistic pathway beyond these potential protective effects, the authors have examined the protein levels of survivin and cytochrome c. It appeared that pretreatment with betanin has resulted in an increased protein level of survivin with a concomitant reduction in cytochrome c when compared to the 6-OHDA treated cells. Moreover, 6-OHDA resulted in an increased Phospho SAPK/JNK46/54 to SAPK/ JNK46/54 proteins relative to the control group, a finding that was reverted as a consequence of betanin pretreatment [46]. However, it should be noted that these beneficial protective effects of betanin against a Parkinson's like model are only demonstrated *in vitro*. Further studies showing the ability of betanin to exhibit such protective effects in the central nervous system *in vivo* are still warranted. Betanin, has also been demonstrated to exhibit a significant protective effect against cisplatin-induced kidney injury via a mitochondrial pathway. Ardalan and coworkers have depicted that capability of betanin pretreatment to confer moderate protection against cisplatin-induced kidney injury in rats. They were able to show that betanin treatment prohibited mitochondrial lipid peroxidation, banned the induced ameliorations in dehydrogenase activity, and enhanced mitochondrial indices functionality [63].

In a rat model of ethanol-induced gastric ulcer, oral betanin administration one hour prior to ethanol consumption has conferred significant protection as evidenced by the smaller size and fewer number of lesions revealed via histopathological examination. These effects were dose dependent with the highest concentration of betanin (200 mg/Kg) providing maximum protection. Moreover, it was depicted that betanin administration has significantly banned the reduction of NO and malondialdhyde levels in response to ethanol insult, further demonstrating the antioxidative properties of betanin in a different pathological model, an effect that was comparable to that achieved in response to ranitidine treatment [64]. Noteworthy that, not only beetroots are rich in betalains among which is betanin, but also beet leaves. Beet leaves were recently shown to act as antioxidants in an alloxan-induced diabetic rat model [65]. Hence, plenty of existing evidence demonstrates the notable antioxidative properties of betanin both *in vitro* and *in vivo* pointing out its possible future use for scavenging free radicals and antagonizing its hazards.

2.2. Betanin and inflammation.

Several studies have depicted the anti-inflammatory properties of betanins. These properties have been demonstrated in both the experimental and the clinical levels [56,66,67]. Rahimi and colleagues have illustrated that betalains administration has resulted in a prominent activation of Sirtuin-1 (SIRT1), with a concomitant decrease in Lectin-like Oxidized LDL Receptor 1 expression level, and plasma concentration of the inflammatory marker high sensitive C Reactive Protein (hs-CRP), in a group of patients experiencing coronary artery disease. Hence, the authors concluded that betalains are capable of providing some protection against the development of cardiovascular diseases. However, the exact mechanism beyond these effects, and whether betanin plays a specific role in such findings, or alternatively, they are attributed to the nitrate content of beetroots, was not demonstrated [66]. In an attempt to dig further beyond these effects, Bhaswant and coworkers examined oral beetroot juice in comparison to sodium nitrate in rats fed a high-carbohydrate, high-fat diet, hence, exhibiting cardiometabolic, as well as, hepatic changes. Similar positive outcomes were observed among the two groups regarding the cardiovascular functionality and structure, as well as, hepatic changes. In light of the limited bioavailability of betanin and the administered dose, the authors attributed the ameliorative effects of beetroot juice to its nitrate content rather than its betanin content [68]. Another study that aimed at examining the protective effects of betanin against ischemic injury has been performed in male Wistar rats. Rats were subject to ischemia-reperfusion injury of the superior mesenteric artery after a single 50 mg/Kg dose of intraperitoneal betanin administration. Post-ischemia inflammatory response was documented in jejunal and lung tissues. The inflammatory response was lower in the betanin pretreated group as demonstrated by the significant decrease in the number of the myeloperoxidase positive cells in the betanin group at 4- and 24-hours post perfusion, as compared to their level at 1-hour, showing a different pattern from the stable elevation observed with the control group. However, it should be noted that at 1-hour, the myeloperoxidase cells of the betanin-treated rats were significantly higher in the betanin group relative to its control counterpart. In addition, it was also demonstrated that the mast cells infiltration was significantly lower with betanin pretreatment from the very beginning. These findings were supported by histopathological and histomorphometric analyses, demonstrating much less injury of jejunal mucosa and lung parenchyma with betanin pretreatment [69]. Furthermore, Tan and coworkers, have illustrated that oral betanin administration was capable of protecting against or reducing the level of the potent inflammatory marker Nuclear factor kappa B (NFkB), with its downstream signaling molecules cyclooxygenase 2 (COX2) and the inducible nitric oxide synthase (iNOS), in a rat model of acute kidney injury. The conclusions were supported by a significantly lower histopathologic score in the presence of betanin. The authors have proposed that the anti-inflammatory properties of betanin could be explained in light of its anti-oxidative properties, knowing that oxidative stress is a potent trigger and inducer of inflammation [56]. Similar results were reported in a rat model

with paraquat-induced lung injury, where betanin administration was able to attenuate paraquat-induced toxicity via reducing the level of the pro-inflammatory cytokines NFkB, interleukin-1β (IL-1β), and tumor necrosis factor α (TNF-α), while increasing the level of the anti-inflammatory mediator interleukin-10 (IL-10), especially with the higher (100 mg/Kg) dosing regimen. The authors also correlated the protective effects of betanin in the face of inflammation to its antioxidative properties. Histopathological examination has also revealed that betanin ameliorated lung damage with significantly lower level of edema, hemorrhage, neutrophil infiltration and alveolar septa thickening [70]. Comparable findings as well have been demonstrated in a model of acute myocardial infarction induced by three daily 100 mg/Kg isoproterenol doses. Infarct size was significantly smaller with betanin treatment. Similarly, NFkB and iNOS levels were significantly less, while catalase, superoxide dismutase and glutathione levels were significantly higher in heart tissues with betanin [71].

2.3. Betanin and fibrosis.

Several research articles have dealt with the possible antifibrotic actions of betanin [63,67]. In a cardiac fibrosis model induced by a high fructose diet in Wistar rats, Han and colleagues were able to show that oral administration of betanin in doses of 25 and 100 mg/Kg/day for sixty days was able to ban the observed cardiomyopathic changes in response to high fructose diet. They have illustrated that betanin was able to significantly minimize the production of advanced glycation endproducts (AGEs), and its receptors (RAGEs) expression levels, thus, reducing collagen production and its cross linking in left ventricular tissues. They have also demonstrated that these amendments could possibly have been executed via inhibiting NFkB production [67]. Comparable findings have been demonstrated in diabetic kidneys where betanin treatment was capable of halting fibrotic changes while reducing intracellular matrix proteins deposition in renal tissues [41].

2.4. Betanin and carbohydrate metabolism.

Betanin has been shown to play a significant role in regulating carbohydrate metabolism in streptozotocin-induced experimental diabetes model. Treatment with 20 mg/Kg betanin via the oral route was able to ameliorate the streptozotocin induced changes as evidenced by enhanced activity of the key glycolytic enzymes with a concomitant reduced activity of gluconeogenic enzymes. Such findings were further augmented by immunohistochemical examination of the pancreatic β-cells [72]. It has also been delineated that betanin is capable of inducing a significant dose-dependent improvement in the clinical manifestations of the metabolic syndrome via assessing plasma glucose, insulin, glycated hemoglobin levels and HOMA index values, in addition to NADPH oxidase and glutathione peroxidase activities, in a high fructose-fed rat model [67].

2.5. Betanin and autophagy.

Recently, betanin has been implicated to play a significant role in autophagy. Macias-Ceja and colleagues have induced colitis in Balb/Jc mice using intrarectal 2,4,6-trinitrobenzenesulfonic acid (TNBS), so as to resemble a model of Crohn's disease. Mice received i.p. betanin at a dose of 1 g/kg once daily starting on the day of TNBS administration either for 2 or 4 days. The authors have demonstrated that TNBS administration was able to increase the histological damage score in colon tissues, especially 2 days' post administration. TNBS treated mice have exhibited a reduced level of the autophagy marker LC3II, with a concomitant elevation in p62 protein level, thus, suggesting impaired autophagy. Moreover, the negative modulator of autophagy, phosphorylated mTOR was significantly higher with TNBS treatment relative to the control group. The authors revealed that betanin administration was able to significantly decrease the histological damage score. This was accompanied by a significant increase in LC3II expression level, with a parallel reduction in p62 protein level in colon tissue, suggesting a protective effect of betanin against the impaired autophagy induced via TNBS administration. The research results have also depicted a positive impact of betanin on the level of the anti-inflammatory cytokine IL-10 expression, while blocking the rise in the pro-inflammatory cytokines expression levels in colon tissues. In order to further validate the involvement of autophagy in mediating the protective effects of betanin, the authors have utilized the autophagosome formation inhibitor 3-methyladenine. Using this inhibitor has abolished the protective effects of betanin against TNBS-induced damage [73]. However, it should be noted that an earlier study on human breast cancer (MCF-7-treated) cells have illustrated that a betanin/isobetanin concentrate was able to stimulate autophagosomic cell death, thus, decreasing cancer cells proliferation, in the absence of any significant impact on normal cells [32].

2.6. Betanin and lipogenesis.

Two studies have been performed to investigate whether betanin plays a role in adipogenesis or not [74,75]. Both studies have depicted that treatment of 3T3-L1 cells with either betanin [74] or the ethanolic extracts of Djulis [75], which contains eleven ingredients in addition to betanin have resulted in the formation of a fewer number of oil droplets indicating reduced lipid accumulation. These manifestations were dose dependent with betanin concentrations in the range of 10-50 μM. The reduced triglycerides level in betanin treated cells ascertained such a finding. The authors were able to demonstrate a reduced expression levels of the adipogenic genes among which are PPARγ, C/EBPα and SREBP-1c [74].

3. SOME NANOBASED APPLICATIONS FOR PLANT EXTRACTS

Biosynthesis of nanoparticles is considered a rising zone of nanoscience improvement and examinations [76]**.** In the development of anti-bacterial surfaces, graphene-based nanomaterials are very much promising due to its biocidal activity. The effect of the physico-chemical features has yet to be clarified. Graphene nanoparticles performed significantly in inducing photo-thermal death of human glioma cells, *in vitro* [77]. Graphene-based nanomaterials as anti-cancer therapeutics can be applied in photo thermal therapy as a drug carrier, and also as nano-drugs by themselves [78]. Some leaf extracts including *Prunus serrulata*, *Magnolia kobus*, *Platanus orientalis*, *Diopyros kaki*, *Pinus desiflora*, *Acer palmatum* and *Ginkgo biloba* were compared to explore their efficiency in reducing graphene oxide. The highest

absorbance and reaction rate values were observed with *Prunus serrulata* from cherry leaf extract [79].

Similarly, some researchers have illustrated that nanoparticle formulation of betanin enhances its stability and bioavailability [51,80-83]. Moreover, encapsulating betanin in nanoliposome phospholipid bodies has been shown to provide an effective means by which the highly hydrophilic betanin can bypass the blood brain barrier. To this end, one might postulate that such a technique possibly promises an added value that encourages the use of betanins in the medical and pharmaceutical fields for their beneficial therapeutic effects rather than just a food colorant, especially in light of the fact that betanin safety profile cannot be abandoned [80]. Amjadi and coworkers have successfully demonstrated a significantly better response to oral betanin treatment, as evidenced by lower plasma glucose and a higher plasma insulin levels with betanin loaded nanoliposome as compared to free betanin in a streptozotocin-induced diabetic rat model. Such an encapsulation technique has resulted in a slower release of betanin with a better stability [84]. Moreover, attempts have been made to co-deliver betanin with the potent chemotherapeutic agent doxorubicin using PEGylated gelatin nanoparticles. The aim behind such an approach was to make use of the synergistic effects of the combined regimen, yielding lower survival of cancerous cells, accordingly, reducing doxorubicin dosing, thus limiting its threatening adverse events [51].

4. CONCLUSIONS

Plants with medicinal properties are gaining increasing attention due to their potential therapeutic effects with a relatively high safety profile as compared to their synthetic counterparts. Betanin, the hydrophilic molecule formed by β-glycosylation of the aglycone betanidin from beetroots (*Beta vulgaris L.*), has been shown to possess anti-oxidative and anti-inflammatory effects. Several studies have depicted the usefulness of using betanin in a number of pathological conditions among which are renal, hepatic and cardiac fibrosis, atherosclerotic diseases, neurological diseases, diabetes, ischemia-reperfusion injury as well as some cancers. These effects were demonstrated *in vitro* and *in vivo* models. In an attempt to unravel the possible mechanistic pathways potentiating betanin's therapeutic effects, a number of studies have illustrated that betanin is capable of inhibiting TGF- β mRNA and protein expression levels. Betanin administration is also capable of inhibiting NFkB production, with its downstream COX2 and iNOS enzymes. Hence, this links betanin's anti-inflammatory properties to its anti-oxidative ones. Recently, betanin has been linked to modulating autophagy in a number of diseases.

It has been demonstrated that betanin is capable of altering the mitochondrial function in response to elevated oxidative stress while promoting cell viability. This coincides with its regulatory role in lipids and carbohydrates metabolism. Some attempts have employed nanoliposome phospholipid bodies and PEGylated gelatin nanoparticles as delivery vehicles of betanin to overcome its low bioavailability. Such techniques, have proven to augment betanin stability and boost its bioavailability. Moreover, it paves the way to enhance betanin use in the medical and pharmaceutical fields besides its use as a safe food colorant.

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