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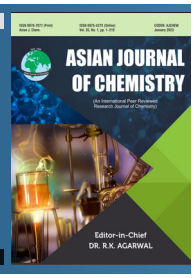

Anti-Glycation and Phytochemical Properties of Cinnamon Stem-Bark Water Extract

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The study evaluated the ability of cinnamon stem-bark water extract (CWE) to break established cross-links formed between proteins and advanced glycation end-products (AGEs) as well as its anti-glycation effect. The extract showed a dose-dependent anti-glycation effect against total fluorescent AGEs (FAGEs) derived from both glucose and fructose. The CWE recorded a uniform IC_{50} value of 0.13 mg/mL for both glucose and fructose-derived FAGEs while aminoguanidine, a well-known synthetic anti-glycative agent gave IC_{50} values of 0.14 mg/mL for glucose and 0.17 mg/mL for fructose derived FAGEs. The anti-glycative effect of CWE was also significantly higher than aminoguanidine against total immunogenic AGE (TIAGEs) in both sugar models ($p < 0.001$). While CWE and aminoguanidine showed weak protein crosslink breaking activity selectively on fructose-derived protein crosslinks already formed, none whatsoever was detected exerted on the established glucose-derived protein crosslinks. Phytochemical screening revealed the presence of several important secondary metabolites, which may have contributed to the anti-glycative effect of CWE. Gas chromatography mass spectrometry enabled the identification of (+)-α-tocopherol acetate, a chain breaker, in the methanol fraction of CWE. Although CWE showed great potential for inhibition of formation of major types of AGEs, it appears to be poor in breaking established cross-links formed between proteins and AGEs.

Keywords: Cinnamon stem, Anti-glycation, Advanced glycation end-products (AGEs), Aminoguanidine, Diabetes.

INTRODUCTION

Advanced glycation end-products (AGEs) have been found to play a role in the development of metabolic disorders, cardiovascular diseases, degenerative diseases and immunological diseases [1-3]. AGEs are produced through a non-enzymatic covalent interaction between the carbonyl groups found in reducing sugars like glucose or fructose and the free amino terminals present in proteins, lipoproteins and nucleic acids [3-5]. They are classified on the basis of their ability to fluorescence or form crosslinks into fluorescent crosslinking AGEs (*e.g.* pentosidine and crossline), non-fluorescent crosslinking AGEs (*e.g.* glyoxal lysine dimer [GOLD] and arginine-lysine imidazole [ALI]) and non-fluorescent non-crosslinking AGEs (*e.g.* N^{ε}-(carboxymethyl)lysine [CML] and N^{ε}-(carboxyethyl)lysine [CEL]) [3,6,7]. It has also been reported that different reducing sugars differ in their reactivity as glycating agents as well as in the type of AGEs formed [1,8]. For instance, the initial reaction of glucose with amino acid residue yields an Amadori product while that of fructose with the same amino acid residue results in two Heyns products, which eventually form AGEs that are different from those formed with glucose [9].

Several synthetic compounds that possess the capability to hinder the formation of AGEs have been reported in the scientific literature. Nevertheless, certain medicines, such as aminoguanidine, have been discovered to possess unfavorable side effects [10]. Given the challenges associated with synthetic medications, it is imperative to explore alternative anti-glycating agents that are both novel and safer. This exploration should particularly focus on natural sources, such as medicinal plants [5,10].

Cinnamon stem-bark plays a vital role as spice and its fragrance makes it an important components of products of aroma and essence industries [11]. The cinnamon stem-bark is frequently utilized in the preparation of culinary items, fragrances, and medical products due to its rich composition

of many essential elements. Several constituents of cinnamon stem-bark were found to exhibit important biological activities [11,12]. These activities include antimicrobial, antidiabetic, anti-inflammatory and anticancer. Some of its components are also reported to have cholesterol and lipid-lowering effects. Many of the compounds found in cinnamon have also found use in the treatment of cardiovascular diseases [11]. In addition, identified in cinnamon stem-bark are several compounds with free radical scavenging and antioxidant properties. Several compounds which can inhibit the progression of neurological disorders are already documented in literature [11]. While there are some reports about the anti-glycative effect of cinnamon [12], there is need for more supporting reports on this and the possible crosslink breaking effect of cinnamon.

A variety of polyphenolic chemicals, including catechin, epicatechin, procyanidin B2 and other proanthrocyanidins, have been extracted from the stem-bark of cinnamon. These compounds have been extensively studied and their anti-glycation properties documented [12,13]. The proanthrocyanidins reportedly behave in similar manner as aminoguanidine [12] Aminoguanidine is a reference drug and standard inhibitor of AGEs. This study provides further evidence of the anti-glycation effect of cinnamon as well as its effect on AGEs-protein crosslinks. Thus, the aim of the current research study was to screen cinnamon stem-bark crude water extract for both anti-glycation and AGEs-protein crosslink breaking activities and compare with aminoguanidine.

EXPERIMENTAL

Encapsulated stem-bark of cinnamon (Diabecinn, OTC Pharma SA (Pty) Ltd, Cape Town, RSA) was purchased from a local Clicks pharmacy in South Africa. Stem-bark powder (60 g) of cinnamon was extracted with boiled distilled water (100 mL) and filtered using Whatman No. 1 filter paper. The final weight of dry filtered cinnamon stem-bark water extract (CWE) was determined. The dry extract was stored at −20 ºC until further use. Part of the dry extract was redissolved in distilled water to a final concentration of 1 mg/mL for further analyses.

Phytochemical screening: Various phytochemical tests were conducted to determine the presence of alkaloids, phenols, coumarins, flavonoids, cardiac glycosides, quinones, steroids, and terpenoids in the cinnamon stem-bark water extract (CWE) by following known procedures [14-17].

Gas chromatography mass spectrometry (GC-MS): The water extract of cinnamon stem-bark was dissolved separately in *n*-hexane, ethyl acetate and methanol. The *n*-hexane, ethyl acetate and methanol fractions were analyzed with a Shimadzu gas chromatograph coupled to a QP2010 SE mass detector using GC-MS SOLUTIONS version 2.6 software according to the reported procedure [18]. A Zebron capillary column (ZB-Tm1), 30 mm in length with an internal diameter of 0.25 m ID and film thickness of 0.25 µm, was used in the investigation. The ionizing energy of 70 eV was applied for the analysis. The initial GC oven temperature was 50 ºC/ min. This was increased at a constant rated to 180 ºC, 240 ºC and 280 ºC at a rate of 20 ºC until the final temperature of 300 ºC was reached and held for 10 min. The temperature was maintained at 290 ºC for the injector and detector. The carrier gas utilized in this study was helium (5 µL) and employed at a flow rate of 2.21 mL/min. The mass detector operation was conducted at 230 ºC, utilizing a scan range of 0.30 scan/s spanning from 50 to 700 *m/z*. The solvent exhibited a delay time of 6 min and the overall duration of the sample run was 33.5 min.

AGEs formation inhibitory assay: The methodology employed in this study was based on the approach described by Ho & Chang [19], with modifications made according to the work of Adeniran & Mogale [20] to screen for the *in vitro* anti-glycation effect of CWE. In this experiment, 500 µL aliquot of bovine serum albumin (BSA) solution with a concentration of 10 mg/mL was subjected to incubation with 500 µL aliquot of either glucose or fructose solution, both with a concentration of 50 mg/mL. The incubation was carried out at 37 ºC for a duration of 40 days. Two conditions were tested: one with the presence and absence of CWE, serving as control. Additionally, a standard inhibitor called aminoguanidine (AG) was included as a positive control.

Determination of anti-glycation effect: At the end of the incubation period, spectrofluorometry was used to measure the amounts of fluorescent AGEs (FAGEs) and results were expressed in arbitrary units (ratio of emission and excitation light intensity) with excitation at 370 nm and an emission at 440 nm. Also, the amounts of total immunogenic AGEs (TIAGEs) was determined using enzyme immunoassay kits (STA-317 Oxiselect™, Cell Biolabs inc., San Diego, USA) and performed according to the manufacturer's instructions. Concentrations of 0.25, 0.5, 1, 2 and 4 mg/mL for both CWE and standard drug were used for the FAGEs investigation while a concentration of 1 mg/mL was used for the TIAGEs investigation. The results were presented as percentage anti-glycation activity calculated using the following formula:

$$\text{Anti-glycation activity (\%)} = \frac{A_{control} - A_{sample}}{A_{control}} \times 100$$

where $A_{control}$ = 100% AGEs-BSA, comprising of BSA and glucose or fructose; A_{sample} = BSA + glucose or fructose + test sample or standard.

Determination of crosslink breaking ability: The crosslink breaking ability of CWE and standard inhibitor, AG on AGEs-protein crosslinks were assessed according to the procedure described by Cheng *et al*. [21] and Adeniran & Mogale [20]. Briefly, aliquots (500 µL) of either glucose or fructose were incubated with an aliquot of BSA (500 µL) at 37 ºC for 80 days followed by the addition of 50 µL of this reaction mixture into each well of a 96-well collagen coated plate (Gibco®, Maryland, USA). In order to allow for the formation of collagen-AGEs-BSA crosslinks, the mixture was further incubated for 4 h at 37 ºC. Collagen-unbound AGEs-BSA were removed by washing the wells thrice using phosphate buffered saline solution containing 0.05% Tween-20 (PBST). Thereafter, 50 µL of CWE (1 mg/mL) or AG (1 mg/mL) was added to the mixtures in the plates in triplicate. Aminoguanidine solution (50 µL) served as a positive control whilst collagen-AGE-BSA

mixtures without test sample or standard inhibitor served as negative control. The 96-well plate were incubated for a further 24 h. Thereafter, the amount of BSA released was quantified using bovine albumin ELISA kit (E11-113 ELISA, Bethyl Lab., Texas, USA). Briefly, the wells were washed four times with PBST (Amresco Inc., Ohio, USA), then anti-BSA primary antibody was added and further incubated for 1 h at 25 ºC. Further washing and incubation with 100 µL of streptavidin-conjugated horseradish peroxidase secondary antibody was done. Next, 100 µL of 3,3′,5,5′-tetramethylbenzidine substrate was added to each well, incubated for 30 min before terminating the reaction with the addition of 0.18 M H_2SO_4 (100 µL) used as stop solution.

Absorbance measurement was obtained at 450 nm and the percentage crosslink breaking activity for CWE and aminoguanidine calculated using the following formula:

$$\text{AGE cross-link breaking activity (\%)} = \frac{A_{450}\text{control} - A_{450}\text{sample}}{A_{450}\text{control}} \times 100$$

where A_{450} control = absorbance of collagen-AGEs-BSA glucose or fructose; A_{450} sample = absorbance of BSA + glucose/fructose + collagen + test sample or standard.

Statistical analysis: Phytochemicals tested for are represented with plus sign (+) to indicate presence and minus sign (-) to indicate absence. Difference between the two groups were analysed using Student's t test and difference were deemed statistically significant at a *p* value less than 0.01. Chemdraw, ChemWindow Spectroscopy 6.0 Sadtler Suite version 1.0 was used to reproduce the GC-MS identified structure.

RESULTS AND DISCUSSION

Ever since its hypoglycaemic effect became known, cinnamon has seen widespread use as a diabetes supplement [22]. Findings from this study showed that the encapsulated cinnamon used for our investigation contains most of the major phytochemicals present in plants (Table-1). These metabolites include phenols, flavonoids, saponins, quinones, cardiac glycosides, steroids, coumarins and terpenoids. Although this study did not test for tannins, there are reports that attests to tannins as a secondary metabolite found in cinnamon stem-bark [19,23,24]. Most of these metabolites such as phenols, flavonoids, terpenoids and coumarins are observed with anti-glycation properties [5,25].

TABLE-1
QUALITATIVE PHYTOCHEMICAL COMPOSITION OF CINNAMON STEM-BARK WATER EXTRACT (CWE)

Phytochemicals	CWE
Phenols	Presence
Flavonoids	Presence
Alkaloids	Absence
Saponins	Presence
Quinones	Presence
Cardiac glycosides	Presence
Steroids	Presence
Coumarins	Presence
Terpenoids	Presence

Identification of the phyto-constituents of the cinnamon stem-bark water extract was further exploited by GC-MS analysis of *n*-hexane, ethyl acetate and methanol fractions of the extract. The compounds identified by GC-MS in the *n*-hexane and ethyl acetate fractions are listed in Table-2. These compounds include ketone, alcohol, fatty acid and hydrocarbons. A number of hydrocarbons, fatty acid, ketone and alcohol containing compounds were identified in both *n*-hexane and ethyl acetate fraction of encapsulated water extract of cinnamon stem bark used in this study. According to Abo-Dahab [26], one of the identified compounds, 1,3,5-cycloheptatriene, also known as 7-ethyl-1,3,5-cycloheptatriene or 7-ethylcycloheptatriene, has antimicrobial and antioxidant activities [27]. The GC-MS analysis of the methanol fraction of CWE enabled the identification of (+)-α-tocopherol acetate, a fat-soluble antioxidant. The chromatogram for the methanol fraction of the cinnamon stem-bark water extract revealed a distinct peak, among several peak, of (-)-α-tocopherol acetate as seen in Fig. 1. The total ion chromatogram (Tic) with its corresponding mass spectrometry of a compound identified as (+)-α-tocopherol acetate is shown in Fig. 2. Other names for (+)-α-tocopherol acetate are dl-tocopheryl acetate or vitamin E acetate, which is a stable form of vitamin E.

Moreover, the results obtained from this study indicate that CWE has the capacity to inhibit the formation of immunogenic and fluorescent advanced glycation end products (AGEs) originating from glucose or fructose to a greater extent than the conventional inhibitor, aminoguanidine. The percentage anti-glycation effects of CWE and aminoguanidine on BSA/glucose-derived and BSA/fructose-derived TIAGEs are presented in Table-3. The CWE demonstrated significantly higher

TABLE-2
SOME CHEMICAL CONSTITUENTS DETECTED BY GAS CHROMATOGRAPHY MASS SPECTROMETRY (GC-MS) FROM THE *n*-HEXANE AND ETHYL ACETATE STEM-BARK FRACTIONS OF CINNAMON WATER EXTRACT

S. No.	Compound name	Class of compound	*n*-Hexane	Ethyl acetate
1	4-Cyclohexyl-2-butanone	Ketone	+	–
2	2-Dodecyl-1,3-propanediol	Alcohol	–	+
3	2-Methyldecane	Hydrocarbon	–	+
4	3-Ethyltridecane	Hydrocarbon	–	+
5	1,3,5-Cycloheptatriene	Hydrocarbon	+	–
6	3-(Ethenyloxy)methyl heptane	Hydrocarbon	+	–
7	7-Propyltridecane	Hydrocarbon	–	+
8	3-hydroxy hydroxylauric acid (Dodecanoic acid)	Fatty acid	–	+
9	6-Methyl octadecane	Hydrocarbon	+	–
10	4,8-Dimethyl tridecane	Hydrocarbon	+	+

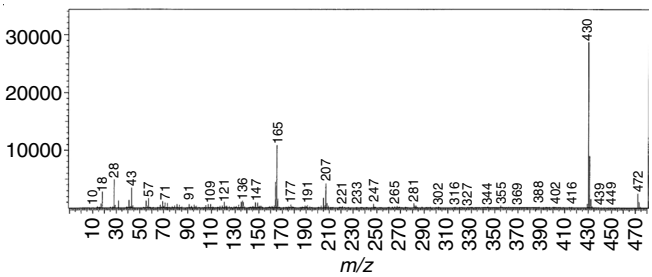

Fig. 1. Chromatogram for the methanol fraction of the cinnamon stem-bark water extract

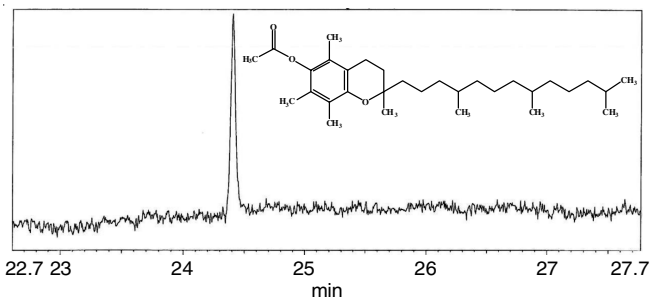

Fig. 2. Total ion chromatogram with its corresponding mass spectrometry

TABLE-3
PERCENTAGE ANTI-GLYCATION EFFECTS OF CINNAMON STEM-BARK WATER EXTRACT AND STANDARD INHIBITOR AMINOGUANIDINE ON BSA/GLUCOSE AND BSA/FRUCTOSE DERIVED TOTAL IMMUNOGENIC AGEs

Inhibition of TIAGEs (%)	CWE	AG
BSA-glucose	100	95.9
BSA-fructose	96	92.2

AG: Aminoguanidine; CWE: Cinnamon stem-bark water extract

anti-glycation activity than aminoguanidine against both BSA/glucose and BSA/fructose-derived TIAGEs ($p < 0.001$).

The percentage anti-glycation effects of CWE and standard drug, aminoguanidine against FAGEs are shown in Table-4. CWE exhibited higher percentage inhibition on AGEs formation than that of AG at investigated concentrations. Also, the 50% inhibition concentrations (IC_{50}) are shown in Table-5. With an IC_{50} of 0.13 mg/mL for both BSA-glucose and BSA-fructose derived fluorescent AGEs (FAGEs), CWE demonstrated significantly higher anti-glycation effect compared to aminoguanidine (0.14 and 0.17 mg/mL) at $p < 0.0001$. IC_{50} is the inhibitory concentration needed to prevent AGEs formation by 50%. The 50% inhibition concentration (IC_{50}) of the CWE (0.13 mg/mL) against AGEs formation were lower compared to that of aminoguanidine.

In addition to the anti-glycation effect, the result obtained in this study showed that cinnamon stem-bark water extract is mildly effective in reversing the crosslinks formed between proteins and fructose, but not glucose. As shown in Table-6, no crosslink breaking ability was observed with either CWE or AG on BSA/glucose-derived crosslinks. Both CWE and AG showed crosslink breaking effect on crosslinks derived from BSA/fructose. The crosslink effect was however less than 50%. CWE demonstrated less than 40% effectiveness in breaking AGEs-protein crosslinks. This breakage effect was only observed

TABLE-4
PERCENTAGE ANTI-GLYCATION EFFECTS OF CINNAMON STEM-BARK WATER EXTRACT AND STANDARD INHIBITOR AMINOGUANIDINE ON BSA/GLUCOSE-DERIVED FLUORESCENT AGEs (FAGEs) AND BSA/FRUCTOSE-DERIVED FAGEs AT VARYING CONCENTRATIONS

FAGEs inhibition (%)	BSA-glucose (%)		BSA-fructose (%)	
Concentrations	CWE	AG	CWE	AG
0.25 mg/mL	98	91	93	74
0.5 mg/mL	98	87	90	73
1 mg/mL	100	85	96	75
2 mg/mL	100	85	97	78
4 mg/mL	100	87	100	84

AG: Aminoguanidine; CWE: Cinnamon stem-bark water extract

TABLE-5
50% INHIBITORY CONCENTRATION (IC_{50}) OF CINNAMON STEM-BARK WATER EXTRACT AGAINST FAGEs (AG USED AS A POSITIVE STANDARD)

FAGEs	IC_{50} of CWE (mg/mL)	AG IC_{50} (mg/mL)
BSA-glucose	0.13	0.14
BSA-fructose	0.13	0.17

AG: Aminoguanidine; CWE: Cinnamon stem-bark water extract

TABLE-6
PERCENTAGE CROSS-LINK BREAKING EFFECTS OF CINNAMON STEM-BARK WATER EXTRACT AND STANDARD INHIBITOR AMINOGUANIDINE ON BSA/GLUCOSE AND BSA/FRUCTOSE-DERIVED AGEs-PROTEIN CROSS-LINKS

% Cross-link breakage ability	CWE	AG
BSA-glucose	0	0
BSA-fructose	35.9	12

AG: Aminoguanidine; CWE: Cinnamon stem-bark water extract

in the BSA-fructose model. None whatsoever was observed in the BSA-glucose model. Its effectiveness against the formation of AGEs and breaking of fructose-derived AGEs-protein cross-links were significantly greater than that of the standard inhibitor, aminoguanidine. Aminoguanidine is documented to prevent AGEs formation by trapping intermediates at the initial glycation stage [12,28] by capturing carbonyl compounds through its amino base [29].

Cinnamon has a long history of use as a pharmacological agent. Its antidiabetic, antioxidative and anti-inflammatory effects is documented [4,11,19,30]. Numerous polyphenolic compounds such as catechin, epicatechin, procyanidin B2 and other proanthrocyanidins have been isolated from cinnamon stem-bark and the anti-glycation activity of these compounds are reported in literature also [12,13]. Some of these compounds present in cinnamon stem-bark are documented to have insulin-potentiating properties [11,12,31]. Based on this, it is suggested that these compounds may be responsible for alleviating the signs and symptoms associated with diabetes and cardiovascular diseases related to insulin resistance and metabolic syndrome which they are known to exert [11]. Also, many of such compounds are credited with lipid-lowering and cardiovascular disease lowering activities against neurological disorders such as Parkinson and Alzheimer's disease [32].

The phenolic compounds are known to play a leading role in mediating anti-glycation activities [5]. Investigations

by Ho & Chang [19] showed that the concentration of both phenolic compound and flavonoid in a particular spice extract were significantly correlated with its anti-glycating capacity. Cinnamon bark extracts are known to have a high phenolic content as well as elicit high antioxidant activities [11]. A study by Saraswat *et al.* [32] found that crude extracts of cinnamon, amongst others, strongly inhibited AGEs formation. Also, another study reported the inhibitory effect of cinnamic acid, a compound present in cinnamon, against the formation of AGEs [4]. In the investigation by Adisakwattana *et al.* [4], cinnamic acid and its derivatives were found to inhibit the formation of AGEs significantly by approximately 11.96-63.36% at a concentration of 1 mM.

Formation of protein crosslinks are also consequences of AGEs [33]. Contrary to the result of Arachchige *et al.* [34], which reported the reversal of AGEs formation, using authenticated *Cinnamomum ceylon*, no AGEs-protein crosslink potential in a BSA-glucose model was detected in this study. Although slight crosslink breaking ability was detected in the BSA/fructose model, the percentage activity of both the cinnamon (35.9%) and aminoguanidine (12%) were too minimal to be considered as effective crosslink breakage. Recently, Adeniran *et al.* [18] highlighted the anti-glycation and protein crosslink breaking effects of different extracts from the stem-bark of *Sclerocarya birrea*. *Sclerocarya birrea* has been shown to share similar phytochemical contents such as procyanidins (catechin and epicatechin) with cinnamon stem-bark [12,13,18,35]. Although in the findings of Adeniran *et al.* [18], *Sclerocarya birrea* stem-bark water extract showed strong AGEs-protein crosslink breaking effect, this was not the case with CWE, also a stem-bark. The results obtained with Adeniran *et al.* [18] suggested that the phytochemical content in the polar extract might not work effectively in synergy for an elevated result regarding anti-glycation. This may also be the case for the effect of the recognised phytochemicals with anti-glycation effect in CWE whereby they are not effective in uncoupling AGEs-protein crosslinks. It is therefore considered that the ability of the compounds and phytochemicals in the tested CWE might just be limited to inhibiting formation of glycation products. Also, there might be other components of the extract that could suppress their ability to cleave AGEs-protein crosslinks. For instance, while vitamin E acetate is documented to be effective against skin ageing, acting as a chain breaker during lipid peroxidation [36], its effectiveness was not apparent in the AGEs-protein crosslink breakage investigation undertaken in this study. Vitamin E acetate was detected and identified by GC-MS in the methanol fraction of CWE used in this study. Based on the result of this study and other evidence regarding the effects of compounds present in cinnamon stem-bark, cinnamon should be considered only as having the ability to inhibit the formation of AGEs but not as a good candidate to reverse crosslinks. As such it may not be exploited further in investigation of protein crosslink breakage.

Conclusion

The aqueous extract derived from cinnamon stem-bark (CWE) exhibited the capacity to inhibit the production of various types of advanced glycation end products (AGEs). The anti-glycation activity exhibited by the substance is effective in inhibiting the formation of both fluorescent and immunogenic advanced glycation end products (AGEs) that are formed from glucose or fructose. However, it has been demonstrated that the effectiveness of cinnamon stem-bark in breaking advanced glycation end products (AGEs)-protein crosslinks is not ideal.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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