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In-vitro evaluation of khaya and albizia gums as compression coatings for drug targeting to the colon

Oluwatoyin A. Odeku and John T. Fell

Abstract

Khaya and albizia gums were evaluated as compression coatings for target drug delivery to the colon using indometacin (a water insoluble drug) and paracetamol (a water soluble drug) as model drugs. The core tablets were compression-coated with 300 and 400 mg of 100% khaya gum, 100% albizia gum and a mixture of khaya and albizia gum (1:1). Drug release studies were carried out in 0.1 M HCl (pH 1.2) for 2 h, Sorensen's buffer (pH 7.4) for 3 h and then in phosphate-buffered saline (pH 6.8) or in simulated colonic fluid for the rest of the experiment to mimic the physiological conditions from the mouth to colon. The results indicated that khaya and albizia gums were capable of protecting the core tablet in the physiological environment of the stomach and small intestine, with albizia gum showing greater ability than khaya gum. The release from tablets coated with the mixture of khaya and albizia gums was midway between the two individual gums, indicating that there was no interaction between the gums. Studies carried out using rat caecal matter in phosphate-buffered saline at pH 6.8 (simulated colonic fluid) showed that the gums were susceptible to degradation by the colonic bacterial enzymes, leading to release of the drug. The results demonstrate that khaya gum and albizia gum have potential for drug targeting to the colon.

Introduction

Target drug delivery to the colon is highly desirable for local treatment of diseases such as colon cancer and inflammatory bowel disease, and the systemic delivery of protein and peptide drugs. A colonic drug delivery system is expected to protect the drug during the transit time in the gastrointestine and to allow its release only in the colon. This delivery system has the advantages of more effective therapy, a reduced dose and reduced undesirable side-effects often associated with high doses (Ashford et al 1993a, b). The various approaches that have been studied for targeting orally administered drugs to the colon include the use of pH-sensitive polymers (Ashford et al 1993a, b; Khan et al 1999), time-dependent dosage forms (Davis et al 1986; MacNeil & Stevens 1990; Van den Mooter & Kinget 1995), and the use of carriers degraded by enzymes produced by colonic bacteria (Rama Prasad et al 1998; Sinha & Kumria 2002). Of these approaches, the use of materials that are degraded by the colonic microflora has been found to be the most promising because of their site specificity (Rama Prasad et al 1998).

A number of plant polysaccharides have been investigated as carriers for colon-specific drug delivery based on the activity of colonic bacteria on the carrier systems. The polysaccharides that have been investigated include pectin and its salts (Rubinstein et al 1993; Ashford & Fell 1994; Wakerly et al 1996a, b; Munjeri et al 1997), amylose (Milojevic et al 1996), chitosan (Tozaki et al 1997), and guar gum (Rama Prasad et al 1998; Krishnaiah et al 1998a, b). These polysaccharides are capable of protecting the drug from being released in the acidic environment prevailing in the stomach and small intestine: they are degraded by the colonic bacterial enzymes, thereby releasing the drug in the colon where there is local action and improved absorption. The fact that these polysaccharides are naturally available, inexpensive, non-toxic and biodegradable has also increased interest in developing them for pharmaceutical use.

Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria

Oluwatoyin A. Odeku

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester M13 9PL, UK

John T. Fell

Correspondence: Oluwatoyin A. Odeku, Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, University of Ibadan, Ibadan, Nigeria. E-mail: pejuodeku@yahoo.com

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In the present study, two naturally occurring plant gums, khaya and albizia gums, were evaluated for drug targeting to the colon. The gums were used as coating materials in compression-coated tablets with the hope that they would be degraded by the colonic microflora, thereby releasing the drug. Khaya gum is a polysaccharide obtained from the incised trunk of the tree *Khaya grandifoliola*, family Meliaceae. It is known to contain highly branched polysaccharides consisting of D-galactose, L-rhamnose, D-galacturonic acid and 4-*O*-methyl-D-glucoronic acid (Aspinal & Bhattacharjee 1970). Khaya gum has been shown to be useful as a binding agent in tablet formulations (Odeku & Itiola 1996, 1998, 2003). Further work has also shown its potential as a directly compressible matrix system in the formulation of controlled release tablets (Odeku & Fell 2004). Albizia gum is obtained from the incised trunk of the tree *Albizia zygia* (DC) J. F. Macbr, family Leguminosae. It consists of ß1–3-linked D-galactose units with some ß1-6-linked D-galactose units (Drummond & Percival 1993). Albizia gum has been investigated as a possible substitute for gum Arabic as a natural emulsifier for food and pharmaceuticals (Ashton et al 1975; US Academy of Science 1979). Recent studies on the binding properties of albizia gum have also shown that the gum produces tablets with greater mechanical properties and longer disintegration and dissolution times when compared with gelatin BP (O. A. Odeku, unpublished data).

In the present work, khaya gum, albizia gum and a mixture of both were used as compression coats and evaluated for their ability to prevent drug release under conditions mimicking the mouth to colon transit time using indometacin (a water insoluble drug) and paracetamol (a water soluble drug) as model drugs. The susceptibility of the gums to undergo biodegradation in the colon was assessed by conducting drug release studies in the presence of rat caecal contents in phosphate-buffered saline (PBS) at pH 6.8.

Materials and Methods

Materials

Indometacin and paracetamol were supplied by Sigma Chemical Co (St Louis, MO, USA), microcrystalline cellulose was received as Avicel PH 102 from FMC International (Cork, Ireland), magnesium stearate was obtained from BDH Chemicals Ltd (Poole, UK), hydrochloric acid with a specific gravity of 1.16 was supplied by Fisher Scientific (Loughborough, UK), and potassium dihydrogen orthophosphate and disodium orthophosphate were general purpose reagents obtained from BDH Chemicals Ltd (Poole, UK). Khaya gum was obtained from the incised trunk of *K. grandifoliola* at the Botanical Gardens, University of Ibadan, Nigeria, and Albizia gum was obtained from the incised trunk of *A. zygia* at the Forestry Research Institute of Nigeria, Ibadan, Nigeria.

Khaya and albizia gums were extracted using the method described by Tyler et al (1981) for the extraction of gums. The gums were hydrated in chloroform water double strength for 5 days with intermittent stirring, and extraneous materials were removed by straining through a calico cloth. The gums were then precipitated from solution using absolute ethanol. The precipitated gum was filtered, washed with diethyl ether and then dried in a hot air oven at 40°C (Tyler et al 1981; Odeku & Itiola 1998, 2003).

Swelling index

The swelling index of each polysaccharide after 1 h was determined by the European Pharmacopoeia method 2.8.4 and calculated by the equation:

$$\text{Swelling index} = [(\text{volume of polymer at time t} - \text{initial volume})/\text{initial volume}] \times 100$$

Preparation of compression-coated tablets

Indometacin and paracetamol core tablets of 6 mm diameter were prepared from 100 mg of powder mixture containing 50% drug and 50% avicel under a compression force of 20 kN using concave punches on a hydraulic press (Beckman model 16; Beckman, Buckinghamshire, UK). The die and punches were lubricated with a 1% dispersion of magnesium stearate in dichloromethane. To prepare the coated tablets, half the quantity of the coating material was placed in a concave die (10 mm), the core tablet was carefully positioned in the centre of the die and the remaining coat material added. The coat was compressed around the core at a compression force of 30 kN. The thickness of the tablets was measured using a micrometer screw gauge (Moore & Wright, Sheffield, UK). The composition of the coat material and the coat thickness are given in Table 1. The breaking load and friability of the core tablets and the compression-coated tablets were determined using a hardness tester (Type C50; Engineering Systems, Nottingham, UK) and the Roche Friabilator (Type TAR 100; Copley Scientific Ltd, Nottingham, UK), respectively.

Dissolution testing

The dissolution test was carried out using the US Pharmacopeia XXIII basket method (Erweka Dissolution Tester, Type DT 700; Copley Scientific Ltd, Nottingham, UK) rotated at 50 rev min^{-1} with 900 mL medium maintained at a constant temperature of 37 ± 0.5°C. The dissolution test for the core tablet containing indometacin was carried out in Sorensen's phosphate buffer (pH 7.4), while the dissolution test for paracetamol was carried out in 0.1 M HCl. The media used for the compression-coated tablets were 0.1 M HCl (pH 1.2) for the first 2 h, Sorensen's phosphate buffer (pH 7.4) for 3 h and then PBS (pH 6.8) to simulate the gastrointestinal environment. Samples (5 mL) were withdrawn and replaced with fresh medium at fixed time intervals. The sample was diluted and the amount of indometacin released was determined using a UV spectrophotometer (Cecil CE 1020; Cecil Instruments Ltd, Cambridge, UK)

Table 1 Composition of coated indometacin and paracetamol tablets (mean ± s.d., n = 3)

Drug	Coat type	Coating weight (mg)	Coat thickness (mm)	Crushing strength (N)	Friability (%)
Indometacin	Core tablet	–	–	85.44 ± 6.48	0.40 ± 0.04
	Khaya gum	300	0.85 ± 0.03	71.42 ± 0.29	1.15 ± 0.02
		400	1.30 ± 0.07	102.71 ± 6.18	1.02 ± 0.01
	Albizia gum	300	0.82 ± 0.04	98.67 ± 2.45	0.80 ± 0.05
		400	1.29 ± 0.03	115.90 ± 3.49	0.71 ± 0.03
	Khaya/albizia (1:1)	300	0.86 ± 0.06	51.99 ± 3.15	0.97 ± 0.05
		400	1.30 ± 0.005	90.06 ± 4.39	0.88 ± 0.02
Paracetamol	Core tablet	–	–	82.34 ± 2.82	0.58 ± 0.03
	Khaya gum	300	0.89 ± 0.02	68.54 ± 0.36	1.05 ± 0.05
		400	1.38 ± 0.06	98.22 ± 3.42	1.00 ± 0.02
	Albizia gum	300	0.89 ± 0.08	92.48 ± 1.47	0.89 ± 0.04
		400	1.39 ± 0.04	113.34 ± 2.64	0.66 ± 0.04
	Khaya/albizia (1:1)	300	0.92 ± 0.03	53.43 ± 1.67	0.94 ± 0.03
		400	1.41 ± 0.06	84.47 ± 2.47	0.73 ± 0.05

at a wavelength of 304 nm. The results are the means of three determinations.

Drug release in the presence of rat caecal contents

To assess the susceptibility of khaya and albizia gums to the colonic microflora, drug release studies were carried out in the presence of rat caecal contents because of its similarity to human intestinal microflora (Herberlin & Friend 1992). Male albino rats (100–150 g), maintained on a normal diet, were fed with 1 mL of a 2% w/v dispersion of khaya gum, albizia gum or a mixture of both (khaya/albizia 1:1), in water using gavage. The treatment was continued for 7 days in order to induce the enzymes acting on the polysaccharides. At 30 min before the drug release experiments, the rats were killed using carbon dioxide asphyxiation. The abdomen was opened, the caecum isolated and the caecal contents removed, weighed and suspended in PBS (pH 6.8), previously bubbled with CO_2, to give a final dilution of 4% w/v, which has been reported to provide the best conditions for assessing the susceptibility to colonic degradation (Rama Prasad et al 1998).

The drug release experiment was carried out using the US Pharmacopeia XXIII basket method (Apparatus 1, 100 rev min^{-1}, 37°C) with slight modifications. PBS (pH 6.8, 100 mL) containing the rat caecal matter in a 150-mL beaker was immersed in a water bath maintained at 37°C. To mimic the anaerobic conditions of the caecum, the experiment was carried out with continuous CO_2 supply into the medium (Rama Prasad et al 1998). Samples (1 mL) were withdrawn at various time intervals and replaced with 1 mL of PBS bubbled with CO_2. Then, 9 mL of PBS (pH 6.8) was added and centrifuged at 3000 rev min^{-1} for 10 min. The supernatant was filtered through a non-pyrogen filter and then assayed for indometacin. Blank runs done to assess the possible interference of the medium on spectrophotometric determinations showed that the medium did not interfere with the absorbance readings of the drug.

Statistical analysis

Statistical analysis to compare the effects of coat weights on the tablet properties and the effect of enzymes on the drug release from compression-coated tablets was performed with the Kruskal–Wallis test, a non-parametric multiple comparison test, using the software Graphpad Prism 4 (GraphPad Software Inc., San Diego, CA, USA). Individual differences between the formulations were performed using the Dunn's multiple comparison tests. At 95% confidence interval, P values less than or equal to 0.05 were considered significant.

Results and Discussion

Khaya gum and albizia gum (100% w/w) were used as compression coatings on indometacin and paracetamol tablet formulations for target drug delivery to the colon. A mixture of khaya and albizia gums was also used to assess whether there was enhanced protection due to the interaction of the two gums. The physical properties of the core tablet as well as the compression-coated tablets are given in Table 1. All tablets complied with pharmaceutical standards for compressed tablets. The dissolution test for indometacin core tablets was carried out in Sorensen's phosphate buffer (pH 7.4). Indometacin is a weakly acidic drug with a pKa value of 4.5, and thus it is insoluble in acidic pH. Paracetamol is a basic drug with a pKa value of 9.5, and so the dissolution test was carried out in 0.1 M HCl. The core tablets complied with the British Pharmacopoeia 1998 standard for compressed tablets, which is that more than 70% of the active ingredient is released within 45 min. The crushing strength of the compression-coated tablets increased with an increase in the coating material, while the friability decreased. Analysis using the Kruskal–Wallis test showed that the effect of the formulations on the coating thickness, crushing strength and friability was statistically significant ($P < 0.01$), but there was no significant difference ($P > 0.05$) between the

tablet properties of indometacin and paracetamol compression-coated tablets.

The ability of tablets coated with khaya and albizia gums to retain their integrity in the physiological environment of the stomach and small intestine was assessed by conducting the drug release studies in 0.1 M HCl for 2 h, then in Sorensen's buffer (pH 7.4) for 3 h, followed by PBS (pH 6.8) for the rest of the experiment. Representative plots of percent indometacin and paracetamol released against time for tablets coated with 300 mg of the polysaccharides are presented in Figures 1 and 2, respectively. On exposure to the dissolution fluids, the gums hydrate and form a viscous gel layer around the tablets, slowing down the diffusion of the dissolution fluid into the core tablets. The amounts of the drugs released after 5 and 12 h for the various formulations are given in Table 2. After 5 h, 21% of indometacin and 19% of paracetamol were released for tablets coated with khaya gum, while tablets coated with albizia gum released less than 4% of indometacin and 6% paracetamol. Tablets containing the khaya/albizia mixture released less than 5% of indometacin and 9% of paracetamol. This suggests that the khaya and albizia gums can effectively control the release of the drugs in the physiological environment of the stomach and small intestine. The amount of drug released depended on the thickness of the coating material, with tablets coated with 400 mg of the polysaccharides releasing lesser amounts (Table 2). The amount of drug released from the tablets coated with the khaya/albizia gum mixture was midway between the two individual gums. Thus, there does not appear to be an interaction between the two gums. Analysis using the Dunn's multiple comparison test showed that there was a statistically significant difference ($P < 0.05$) between the amount of drug released from tablets coated with khaya gum and those coated with albizia gum. This could be due to the difference in the swelling index values of the gums. The values of the swelling index for khaya and albizia gums in distilled water after 1 h were 250% and 450%, respectively (Odeku & Fell 2004). Gums are generally hydrophilic: they swell and form a gel layer around the coated tablet, serving as a barrier to the release of drug contained in the compression-coated core tablet. Since the swelling index of albizia is greater than that of khaya gum, the thickness of the swollen layer will be greater for tablets coated with albizia gum and thus the rate of diffusion of the drugs through the gel layer will be slower. It was also observed that the tablets were able to retain their physical integrity for up to 12 h in the dissolution studies. Furthermore, there was no statistically significant difference ($P > 0.05$) between the amount of indometacin and paracetamol released from the compression-coated tablets. Thus, the dissolution rate of the tablets was not affected by the difference in the water solubility of the model drugs or by the changes in the pH of the dissolution medium. Thus, only tablets containing the indometacin core were used for further studies.

In order to assess the susceptibility of the gums to degradation by the enzymes present in the colonic microflora, the dissolution studies were carried out in simulated colonic fluid (containing 4% w/v rat caecal content). The amounts of indometacin released after 5 and 12 h in simulated colonic fluid are given in Table 3. Statistical analysis using Dunn's multiple comparison tests indicates that there was no significant difference in the amount of indometacin released from tablets coated with 300 and 400 mg polysaccharides. On the other hand, analysis using the Kruskal–Wallis test showed that there

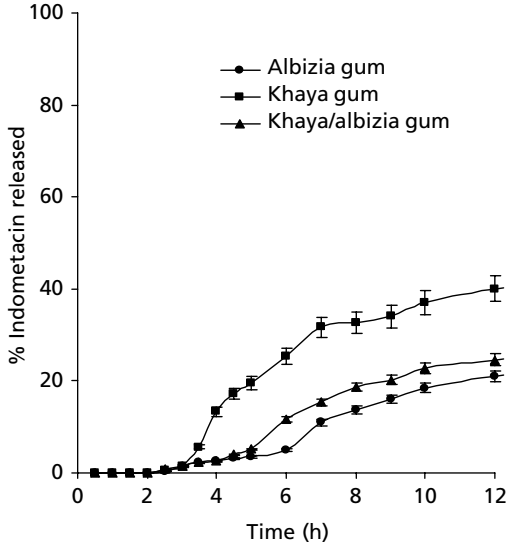

Figure 1 Percent indometacin released from tablets coated with 300 mg polysaccharide in 0.1 M HCl for 2 h, Sorensen's buffer (pH 7.4) for 3 h and then in phosphate-buffered saline (pH 6.8) (mean ± s.d., n = 3).

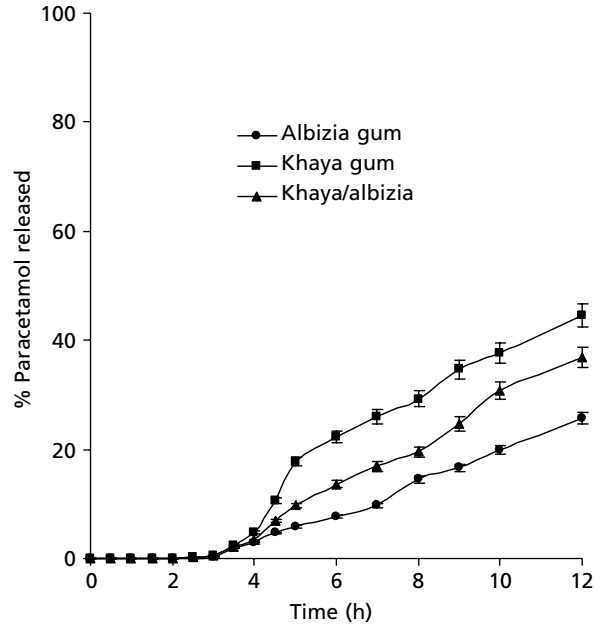

Figure 2 Percent paracetamol released from tablets coated with 300 mg polysaccharide in 0.1 M HCl for 2 h, Sorensen's buffer (pH 7.4) for 3 h and then in phosphate-buffered saline (pH 6.8) (mean ± s.d., n = 3).

Table 2 Percent indometacin and paracetamol released after 5 and 12 h (mean ± s.d., n = 3)

Coat type	Coating weight (mg)	% Released			
		Indometacin		Paracetamol	
		After 5 h	After 12 h	After 5 h	After 12 h
Khaya gum	300	20.69 ± 1.64	40.21 ± 1.52	18.83 ± 3.64	44.56 ± 1.92
	400	11.07 ± 2.86	33.09 ± 2.86	12.26 ± 1.46	36.10 ± 1.46
Albizia gum	300	3.47 ± 0.28	21.02 ± 1.98	5.92 ± 0.24	24.70 ± 0.98
	400	3.09 ± 0.28	15.15 ± 1.49	3.68 ± 0.16	17.01 ± 0.94
Khaya/albizia (1:1)	300	5.11 ± 0.69	24.60 ± 0.98	8.71 ± 0.82	28.98 ± 1.15
	400	3.29 ± 0.82	19.30 ± 2.46	4.21 ± 0.98	22.46 ± 1.26

Table 3 Percent indometacin released after 5 and 12 h in simulated colonic fluid (mean ± s.d., n = 3)

Coat type	Coating weight (mg)	% Released	
		After 5 h	After 12 h
Khaya gum	300	76.30 ± 1.86	104.72 ± 2.01
	400	69.63 ± 3.43	98.68 ± 2.34
Albizia gum	300	56.00 ± 2.36	99.87 ± 2.01
	400	50.43 ± 2.54	94.34 ± 1.87
Khaya/albizia (1:1)	300	71.20 ± 2.57	100.23 ± 2.12
	400	62.78 ± 2.24	97.34 ± 1.98

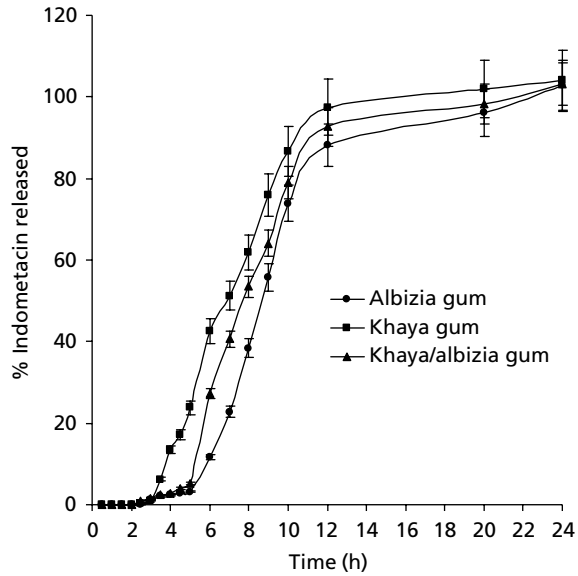

Figure 3 Percent indometacin released from tablets coated with 300 mg polysaccharide in 0.1 M HCl for 2 h, Sorensen's buffer (pH 7.4) for 3 h and then in simulated colonic fluid (mean ± s.d., n = 3).

was a statistically significant difference ($P < 0.001$) in the amount of indometacin released after 5 and 12 h in the dissolution study with simulated colonic fluid when compared with the dissolution study in the absence of the simulated colonic fluid. Furthermore, it was observed that the coat was almost completely degraded in the presence of rat caecal matter, thereby leading to complete release of the drug into the dissolution medium. This indicates that khaya and albizia gums were susceptible to enzymatic action of the colonic microorganisms present in the caecal matter.

The ability of the compression-coated tablets to release indometacin in conditions mimicking those from mouth to colon was assessed by performing the release studies in 0.1 M HCl for 2 h, Sorensen's buffer (pH 7.4) for 3 h and then in rat caecal content medium for the rest of the experiment. Representative plots of percent indometacin released from tablets coated with 300 mg polysaccharide are presented in Figure 3. Protection of the indometacin core tablet can be observed in the early stages of the dissolution process, followed by a marked acceleration in release when the tablet was exposed to the enzymes in the rat caecal content medium. This indicates the breakdown of khaya and albizia gum coats, allowing enhanced drug release. The release rate was greater in the presence of the enzymes due to the pre-exposure to the conditions in the upper gastrointestinal tract, which stresses the importance of hydration for enzyme activity. In all cases, the amount of drug released for tablets containing the 300 mg coat was greater than the amount released for tablets with the 400 mg coat. Thus, the greater the weight of the coating material, the lesser the rate of penetration of the dissolution medium into the tablet and hence a lesser amount of the drug is released. These results are in agreement with the results obtained for tablets coated with pectin (Ashford et al 1993a; Fernandez-Hervas & Fell 1998). Whereas other studies have used higher coating weights (700–1000 mg) to achieve a reduction in the release of the drug (Ashford et al 1993a), the weights of the coating materials used in the present study were 300 and 400 mg. This indicates that khaya and albizia gums are capable of effective protection of a core tablet in conditions mimicking the mouth to colon transit time.

Conclusion

The results indicate that khaya and albizia gums, and their mixtures, used in compression-coated tablets were capable

of protecting the drug from being released in the physiological environment of the stomach and small intestine. In-vitro studies in conditions mimicking the mouth to colon transit time indicate that the polysaccharides were degraded by the enzymes present in the caecal matter, leading to complete release of the drug within 24 h. The results demonstrate that khaya and albizia gums have potential for drug targeting to the colon.

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