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Synthesis and Encapsulation of *bis*-eugenol in a Mesoporous Solid Material: Enhancement of the Antioxidant Activity of a Natural Compound from Clove Oil

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Authors' contributions

This work was carried out in collaboration between all authors. Author VAG performed the experimental analysis and wrote the first draft of the manuscript. Author CAF designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors PMM and MNK managed the analyses of the study and reviewed the final manuscript. All authors read and approved the final manuscript.

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ABSTRACT

In the present work, microwave extraction conditions to recover high eugenol content in the crude extract from clove were investigated. The effect of factors like temperature, stirring, time, liquid: Solid ratio and solutions of solvent were evaluated with Taguchi's method. The eugenol content was determined by gas chromatography. From the isolated eugenol, the *bis*-phenol was synthesized by the dimerization of eugenol. The encapsulation of *bis*-eugenol on the mesoporous silica was carried out by a microwave assisted process. Previously, mesoporous silica SBA-15 was prepared by hydrothermal synthesis using Pluronic P123 triblock copolymer as a surfactant. The *bis*-eugenol

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encapsulated in SBA-15 was characterized by physicochemical techniques. The results indicated that the encapsulation of *bis*-eugenol in the pores of silica occurred through weak interactions of an electrostatic nature without producing chemical changes in the antioxidant property. The antioxidative activity of eugenol, *bis*-eugenol and *bis*-eugenol/SBA-15 system was examined by phosphomolybdenum assay. Among these materials, a remarkably high antioxidant activity was found in bis-eugenol encapsulated in SBA-15. These resultas suggest the possibility of applying this system as an antioxidant active packaging in the future.

Keywords: Antioxidant activity; encapsulation; mesoporous material; clove oil.

1. INTRODUCTION

Aromatic plants and their essential oils have been used since antiquity in flavor and fragrances, as condiments or spices, as medicinal, as antimicrobial/insecticidal agents, and to repel insects or protect stored products [1]. Essential oils are aromatic and volatile oil liquids extracted from different parts of plants (leaves, seeds, roots, fruits) by different methods [2,3]. These natural products have received increasing attention in the chemical, food and pharmaceutical industries because they can have a wide range of applications and can also replace several synthetic compounds [4,5,6]. For this reason, it is desirable to use natural compounds which have a decreased risk of side effects if compared to the synthetic components of drugs [7].

Vegetal species produce a diversity of secondary metabolites, which have multiple functions throughout the plant life cycle [8]. Many of these natural compounds are present in essential oils, as a complex mixture of components with low molecular weight [9] especially phenolic compounds from essential oils, such as acid-phenols and their esters, which have antioxidant properties. The antioxidant activity of aromatic plants is very attractive because in foods rich in unsaturated lipids they prevent or slow down the process of rancidity. This effect is important not only in terms of preservation but also because of their important health benefits. Antioxidants act as free radical stabilizing agents inhibiting the peroxidation lipid. This process is involved in the development of several common diseases, which include atherosclerosis and neurodegenerative disorders such as the Alzheimer's disease [10,11]. The antioxidant activity of phenolic compounds depends on the chemical structure, in particular, in the electron delocalization on the aromatic ring [12,13].

Clove (*Syzygium aromaticum*) is an important aromatic spice. Clove has a light yellow or brown colour, it produces a pleasant aroma, and has a wide spectrum of medicinal properties [14]. In fact, extracts from clove have antibacterial, antifungal, insecticidal, analgesic, anticoagulation, anti-inflammation and antioxidant properties and is used as a flavouring agent and antimicrobial material in some industries such as pharmacy, fragrance, cosmetics and food [15,16,17]. Its major constituent is eugenol as well as eugenyl acetate, α-humulene, and β-caryophyllene. Eugenol (4-allyl-2-methoxy-phenol) is a naturally phenolic compound widely used in food, pharmaceutical, cosmetics and active packaging applications, due to its effective antimicrobial and antioxidant properties [18,19,20,21]. However, most plant-derived bioactive compounds, including eugenol, are highly volatile, unstable, and sensitive to oxygen, light and heat during processing, utilization and storage.

Conventional methods of extraction such as, steam distillation and solvent extraction often require quite large solvent volumes and extended extraction times. This work focuses on the use of the microwave extraction method (MAE) for the extraction of eugenol from clove. MAE is more advanced than the traditional extraction method, it heats the matrix internally and externally without a thermal gradient and thus, functional compounds can be extracted in a careful and efficient manner [22,23]. MAE is based upon the selective and rapidly localized heating of moisture in the sample by microwave. Due to the localized heating, pressure builds up within the cells of the sample, leading to a fast transfer of the compounds from the cells into the extracting solvent [24]. MAE is gaining an important role in sample preparation techniques because it offers a considerably reduced usage of organic solvents and extraction times, and it increases sample numbers through the use of multi-vessel systems that allow the simultaneous extraction of multiple samples [25]. In this work, Taguchi's method was applied to know the best conditions of extraction by microwave. Taguchi´s methodology provides a complete knowledge of every factor affecting the performance by

employing a special set of orthogonal arrays which examines a huge quantity of variables [26].

Several studies have recently shown that encapsulation has become a technique of increasing interest since it offers numerous benefits, including ease of handling, enhanced stability, protection against oxidation, retention of volatile ingredients, taste masking, controlled release, consecutive delivery of multiple active ingredients, change in flavour character, long-lasting organoleptic perception, reduced toxic side effects, improved water solubility of hydrophobic ingredients, and enhanced bioavailability and efficacy revealed [27]. Microencapsulation allows getting microparticles with a size between 1-1000 μm comprising an active agent embedded in a natural or synthetic material. Microcapsules are composed of two parts, namely the core and the shell. The core (the internal part) contains the active agent, while the shell (the external part) protects the core from the outer environment. Encapsulation can be achieved by a wide range of methods or techniques, providing isolation, entrapment, protection or controlled release of sensitive or reactive materials from/across the surrounding matter. There are numerous industrial applications of microencapsulation and the microencapsulation technology has been extensively used in various food processing fields [28,29,30]. This technology can embed compounds and protect these ingredients against deterioration, volatile losses, or premature interaction with other ingredients [14]. In special, different research groups have investigated the utilization of essential oils or antioxidant agents encapsulation using different materials, such as chitosan nanoparticles [31,32], jelly-alginates complex microparticles [33], casein micelles [34] and β-cyclodextrin [27].

Another material that presents potential applications is mesoporous silica, such as SBA-15. This silica is a suitable inorganic support due to its uniform wide channels that can immobilize organic molecules. Its stability leads to better dispersion, biocompatibility and subsequent functionalization to obtain a useful system to be applied in the field of food, medical and cosmetics industries [35,36,37]. The specific surfaces of SBA can be used to provide sites for the adsorption and diffusion of targets and enhance the local concentration [38]. In fact, the possibility of using siliceous ordered mesoporous materials for controlled delivery systems has been reported for a wide range of drugs [39]. Previous investigations were based on supporting enzymes on ordered mesoporous solids [40] other studies used ordered mesoporous silica materials which are special for the architecture of fluorescence chemosensors to detect Pb^{2+} [41] and this material is employed in osseous regeneration technologies [42].

The aim of this study was to assay the antioxidant activity of eugenol and its related compounds. The *bis*-eugenol (BE) was synthesized by oxidative coupling from eugenol isolated from clove and then encapsulated in SBA-15 by hydrothermal conditions. The focus was on the evaluation of the antioxidant activity of this novel *bis*-eugenol/SBA-15 system compared with the antioxidant activity of eugenol and *bis*-eugenol.

2. MATERIALS AND METHODS

2.1 Eugenol Extraction from Clove

Commercial clove was dried at 40ºC and ground in a mortar. A microwave-assisted extractor (Anton Parr Monowave 300) equipped with 30 ml vessel was utilized to perform microwave assisted extraction. Sample extractions were carried out by manipulating the control panel for the adjustment of the parameters studied. The experiment was designed by 5-level L_{25} Taguchi´s orthogonal array. In the Taguchi statistical design, the introduced orthogonal arrays can supply efficient and suitable possibility to perform the practical tests with the minimum number of examinations [43]. Temperature, stirring, time, solution of ethanol and liquid:solid ratio were selected as important factors affecting the yield of essential oil and of eugenol. The controlling parameters and their levels were temperature (30-70ºC), stirring (240-1200 rpm), time (5-25 min), solution of ethanol (20-100%) and liquid:solid ratio (7-16 ml/mg). Analysis of variance was used for statistical analysis of the results to investigate which factors have the greatest influence on the optimum conditions.

Once the extractions were performed, the samples of essential oil (EO) were analysed with a Perkin Elmer gas chromatograph (GC). The peaks obtained by injecting the samples were identified and quantified using standard solutions of methyl salicylate, and the percent recovery of eugenol was determined. Details are given elsewhere [44]. Yields (Y) of the process were calculated by equations (1) and (2):

$$Yield\ of\ EO\ (\%) = (\text{mass of EO})/(\text{mass clove})\ \ x\ 100 \quad (1)$$

$$Yield\ of\ eugenol\ (\%) = (\text{mass of eugenol})/(\text{mass of EO})\ \ x\ 100 \quad (2)$$

Eugenol was extracted from clove essential oil according to [45] dried under anhydrous sodium sulphate. After filtration, the solvent was evaporated. The eugenol obtained was stored at 4 °C until use.

2.2 Synthesis of *bis*-eugenol and SBA-15

The BE was synthesized by the oxidative coupling of eugenol [46]. Eugenol (3 g, 18.27 mmol) was dissolved in acetone (60 ml) and distilled water (30 ml), then ammonium hydroxide 28% (40 ml) was added. The mixture was stirred until a yellow colour developed. Afterwards, a saturated solution of potassium ferricyanide was added dropwise for 5 hours. The mixture was then stirred for 12 hours, previous addition of ammonium hydroxide 28% (40 ml). The reaction was neutralized with diluted hydrochloric acid. The solid was filtered and recrystallized with ethanol absolute.

Mesoporous silica SBA-15 (SBA) was prepared by using Pluronic P123 triblock copolymer surfactant as a template in acid media according to the literature [47]. Polyethylene glycol acts as modifier and tetraethyl orthosilicate (TEOS) acts as source of silica. First, Pluronic P123 (4 g) was dissolved at room temperature in a 3.1 M aqueous hydrochloric acid solution (350 mL). Then, polyethylene glycol 400 (10 g) was added and the resulting solution was slowly stirred at 35ºC until the solution became clear. TEOS (22.5 mL) was then added to the solution and the resulting mixture was vigorously stirred at 40 °C for 24 h. Subsequently, the content was transferred to a microwave oven and kept at 100ºC for 12 h under static conditions. The resultant product was filtered, washed with water, and dried overnight at 80ºC. Finally, the surfactant was removed by calcination at 550ºC for 5 h in air.

2.3 Encapsulation of BE in SBA-15

The BE-SBA preparation was performed using an Anton Paar Monowave 300. BE (0.15 g) was placed in a vial, and SBA-15 (1.5 g) was added. Then, a solution of ethanol:water (50:50, v/v) (18 mL) was added to the mixture. The mixture was placed in a microwave oven. The reaction was carried out at 70ºC (with a controllable power system), 1200 rpm, for 20 min. After a slow cooling of the mixture, the resulting material was dried at 80ºC for 5 h.

2.4 Characterization of Materials

^{1}H NMR spectra were recorded using a Bruker DPX-300 (300 MHz) spectrometer. Nitrogen adsorption-desorption isotherms were measured at −196ºC on a NOVA-1000 Quantachrome. Prior to testing, the samples were treated at 100ºC in the degassing port of the adsorption analyser. Specific surface areas were evaluated using the Brunauer, Emmett and Teller (BET) method, while pore size distributions were calculated using the Barret-Joyner-Halenda (BJH) algorithm on the adsorption branches of the isotherms.

FTIR tests were performed on a Shimadzu FTIR Prestige-21 spectrophotometer in the region from 4000 to 1000 cm^{-1}. The samples were mixed with KBr (1% wt) and then pressed. The UV absorption measurements were carried out on a Perkin Elmer Lambda 20 spectrophotometer. Fluorescence studies were performed on a Perkin Elmer F7000 spectrofluorometer. Spectrofluorometric spectra were performed from a suspension of the sample in ethanol:water (50:50, v/v) and then brought into a quartz cell for measurement.

2.5 Encapsulation Efficiency of BE

The BE encapsulated in SBA-15 was removed using a mix of acetone:DMSO (50:50, v/v). For this purpose, 0.1 g of BE-SBA was mixed with 20 ml of the solvents at 500 rpm for 20 min and then sonicated during 30 min. After this procedure, the suspension was filtered out and the amount of BE was determined by UV spectrophotometry using a calibration curve obtained from standard solutions of BE (λ= 282 nm). The encapsulation efficiency (EE) of BE was calculated by the equation (3):

$$EE\ (\%) = (\text{amount of BE encapsulated})/(\text{initial BE amount})\ \ x\ 100 \quad (3)$$

The percentage of carbon in the BE-SBA samples was analysed by EA to verify the EE of BE in the SBA.

2.6 Antioxidant Activity

Antioxidant activity of free eugenol, free BE, free SBA, and BE-SBA was determined using the

phosphomolybdenum method [48]. BE was dissolved in a mix DMSO:ethanol (1:99, v/v) at 100 mg/ml, and free SBA and BE-SBA were dissolved in the same mix solvents, which contained approximately 100 mg/ml BE in the particles. Then, the samples were filtered and diluted with the same solvent to obtain solutions of known concentration. An aliquot of 1 ml of sample solution was combined in a tube with 9 ml of reagent solution composed of 0.6 M sulfuric acid, 28 mM sodium phosphate, and 4 mM ammonium molybdate. The tubes were capped and incubated at 95ºC for 90 min. After the samples had cooled to room temperature, the absorbance of the aqueous solution was measured at 695 nm against a blank. The control solution contained 1.0 ml of reagent solution and the appropriate volume of the same solvent used for the sample. It was incubated under the same conditions as the rest of the samples. Similar tests were carried out with a solution of butylhydroxytoluene (BHT) antioxidant. Antioxidant activity was expressed as inhibition (I) calculated by equation (4):

$$AAO\ (\%) = \left[1 - \left(\frac{A_S - A_{S90}}{A_C - A_{C90}}\right)\right]\ x\ 100 \qquad (4)$$

where A_S is initial absorbance, A_{s90} is the absorbance of the sample at 90 min, A_c is initial absorbance of the negative control and A_{c90} is the absorbance of the negative control at 90 min.

3. RESULTS AND DISCUSSION

3.1 Extraction of Essential Oil from Clove

We studied the extraction of EO assisted by microwave, in which different factors were evaluated independently. The highest yield of EO (Y = 45-52 %) was obtained at 50ºC, 750 rpm of stirring rate, 15 min of extraction, with a solution of ethanol of 40 wt. % in water and a liquid:solid ratio of 7 mL/mg. Under these conditions the yields of eugenol were between 35 and 48 %. The eugenol was isolated in the usual form. The rest of the constituents are those that are classical for this essential oil.

Considering the yield of the process as (mass of eugenol/mass of clove) %, the extraction assisted by microwave presented values of 16-25 %. In conclusion, the extraction assisted by microwave has technological advantages as it implies less extraction time and therefore lower energy consumption.

3.2 Characterization of Materials

The eugenol obtained from clove essential oil was a light yellow liquid with a strong-clove smell. The BE synthesized was a brown solid with a yield of 80 %. The characteristic bands presented in the ^{1}H RMN spectrum were: (acetone-d6, 300 MHz) d (ppm): 6.82 (s, 2H, H_{Ar}); 6.72 (s, 2H, H_{Ar}); 6.01 (m, 2H, HC); 5.11 (d, 2H, HC=C); 5.02 (d, 2H, HC=C); 3.87 (s, 6H, -CH_3); 3.35 (d, 4H, -CH_2-). The main bands identified by IR were: (KBr, cm^{-1}): 3530 (OH); 2885 (=CH); 2880 (-CH_2-); 2850 (-OCH_3); 1665 (C=C); 1620 (C=C_{Ar}); 1470 (C=C_{Ar}); 1370 (C=C_{Ar}).

The N_2 adsorption/desorption isotherms of SBA-15 and BE-SBA were determined to study their textural properties. Results are reported in Table 1. The values of the specific surface area, pore volume and pore diameter of SBA-15 agree with those reported in the literature [35,47].

Samples showed N_2 adsorption/desorption curves corresponding to type IV isotherms with H1 hysteresis loop at a relative pressure from 0.65 to 0.96, Fig. 1(A). The encapsulation of BE into SBA-15 caused a reduction of specific surface area and a slight increase of average pore diameter, while the pore volume remained almost unchanged, Fig. 1(B). Considering the molecular diameter of BE previously calculated by DFT [49] it is possible to understand that this molecule can be easily located within the pores of the SBA-15. Thus, the changes of textural parameters can be interpreted as BE molecules within the pores of silica reducing the adsorption of nitrogen.

Table 1. Textural properties of materials

Sample	Specific Surface Area (m^2/g)	Pore Volume (cm^2/g)	Average Pore Diameter(Å)
SBA-15	420	0.77	83
BE-SBA	264	0.61	100

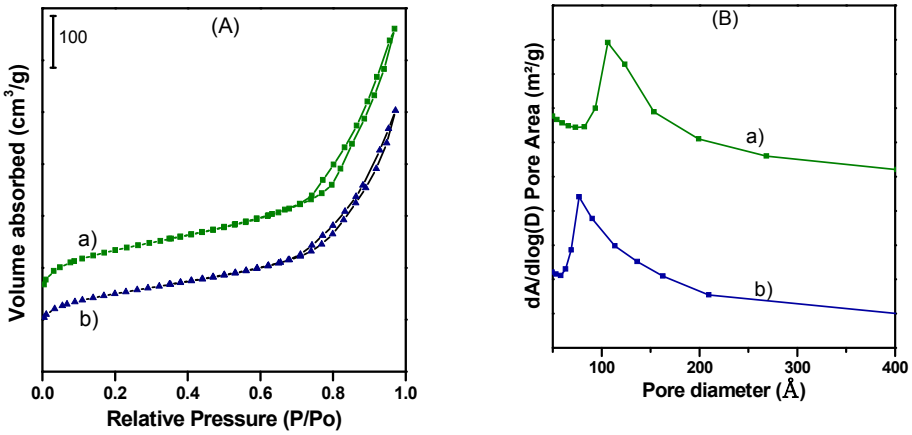

Fig. 1. (A) Nitrogen adsorption-desorption isotherms and (B) Pore size distribution of: a) SBA-15, b) BE-SBA

The FTIR spectra of SBA-15, BE, and BE-SBA is shown in Fig. 2(A). The characteristic bands reported in BE characterization were obtained from BE spectrum. In the spectrum of SBA-15, a peak near 1635 cm^{-1} is observed, mainly resulting from the bending vibration of the H_2O absorbed. The typical Si-O-Si bands appear in the OH bending region as three peaks: one broad and strong peak centred at 1033 cm^{-1}; two narrow and relatively weak peaks near 805 and 463 cm^{-1}, which are associated with the condensed silica network. Silanol groups of SBA-15 give the characteristic band at 964 cm^{-1}, but the encapsulation of BE produces the reduction of the intensity of the main bands of silica (spectrum of BE-SBA), which indicates a strong interaction between silanol groups of mesoporous silica with molecules of BE present in the SBA-15 pores.

To assess the interaction between BE and SBA-15, a study of fluorescence spectroscopy was carried out. The fluorescence spectrum of BE-SBA is shown in Fig. 2(B). Mesoporous silica SBA-15 itself showed no fluorescence, whereas BE presented an excitation band at 595 nm (under emission wavelength at 420 nm). The luminance phenomenon of BE is caused by the π electron conjugate system present in these molecules. The composite of BE-SBA gives a sensitive fluorescence response, under the same wavelength as the free BE. In these cases, the fluorescence of BE-SBA appears at a definite excitation length owing to the fluorescent of *bis*-eugenol molecules encapsulated in the mesoporous silica. However, the fluorescence intensity of the hybrid material of SBA decreases due to the lower amount of BE present in the suspension in the sample. In conclusion, the results suggest weak interactions of electrostatic nature (hydrogen bond) that connect BE molecules with Si-OH groups present on the porous wall of SBA-15. These interactions do not cause chemical changes in BE.

The BE content of BE-SBA, obtained by extraction with acetone:DMSO and quantified by UV spectroscopy, was 9.07 wt. %. Considering that the initial BE used was of 9.98 wt. %. These results indicate an encapsulation efficiency of 90.88 %. The percentage of carbon in BE-SBA was analysed by elemental analysis to calculate the amount of BE encapsulated in SBA-15 and in this way, verify the result obtained by extraction and analysis by UV. The carbon amount in the BE-SBA was 7.8 wt. %, which corresponds to a BE content of 10.61 wt. %. These results verify the amount of BE obtained by UV assay. Since the content of BE in this procedure is obtained by calculations, it is common to obtain higher amounts of BE than those reported by theoretical and experimental calculations [50].

3.3 Antioxidant Activity

Evaluation of the antioxidant activity of samples using the phosphomolybdenum method at two levels of molar concentration was carried out. The results are presented in Table 2. SBA-15 showed no antioxidant activity. On the other hand, the other samples presented antioxidant properties. Regardless of the concentration of

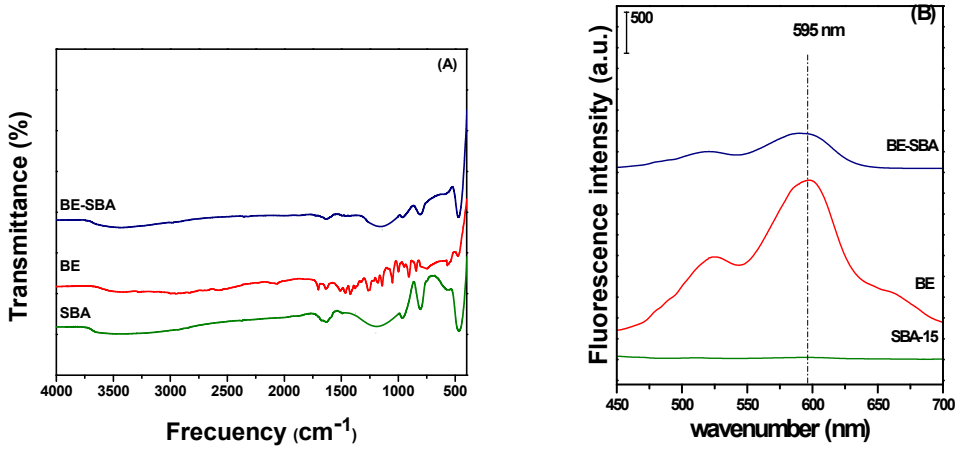

Fig. 2. (A) IR spectrum and (B) Fluorescence spectrum of SBA-15, BE, and BE-SBA

the free compound, antioxidant potency decreased in the order: BHT > BE > Eugenol. The inhibitory effect of dimerized eugenol is higher than that of monomeric eugenol [12]. At the same level of concentration, BE encapsulated in SBA presented higher antioxidant activity than that of free *bis*-eugenol. This was attributed to the increase in the solubility of BE in the BE-SBA system, as a result of their interaction with mesoporous silica [27].

Table 2. Antioxidant activity of samples by the phosphomolybdenum method

Sample	Concentration	
	2 mM	8 mM
Eugenol	6.1	11.0
BE	13.7	38.4
BE-SBA	19.0	42.2
BHT	12.3	34.5

4. CONCLUSIONS

The experimental results reported in this paper show that the extraction assisted by microwave proposes an efficient time saving and quality control strategy to obtain eugenol. From eugenol separated from essential clove oil, it was possible to synthesize a dimer *bis*-eugenol with high yield. The SBA-15 obtained by hydrothermal procedure is a mesoporous material with an excellent capacity for encapsulating *bis*-eugenol. The encapsulation methodology used in this work, i.e. encapsulation assisted by microwave, was an efficient procedure for embedding *bis*-eugenol in mesoporous silica SBA-15. The physicochemical characterization of *bis*-eugenol supported in SBA-15 showed a satisfactory encapsulation. The encapsulation of BE in SBA-15 increased the performance as antioxidant of *bis*-eugenol. A remarkable characteristic of this system is that the encapsulated BE presented a higher antioxidant activity than that of the free eugenol. This property could be used in the different applications.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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