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Original Article

FORMULATION AND EVALUATION OF DISPERSIBLE TABLETS OF FLAVONOID PGAL ISOLATED FROM *SARACA ASOCA* LEAVES

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ABSTRACT

Objective: The study aimed to design and evaluate a dispersible tablet of flavonoid PGAL isolated from *Saraca asoca* leaves for antidepressant activity.

Methods: The phytoconstituent was isolated from a methanolic extract of *Saraca asoca* leaves using silica gel column (60-120 mesh) chromatography. The dispersible tablets were prepared by direct compression and then evaluated for various tablet evaluation parameters and antidepressant activity, performing Tail Suspension Test (TST), Forced Swim Test (FST), Locomotion activity, Brain glutamate level and brain nitrite level.

Results: Hardness of 2.85±0.13 kg/cm^2 to 3.25±0.15 kg/cm^2 and friability of 0.35% to 0.48% indicate that the prepared tablets were mechanically sound. Test for weight variation was also within tolerance limits, i.e. 2.04% to 4.25% difference in weight of the tablet from the average weight of 10 tablets. The tablets also passed the test for drug content uniformity, 97.35% to 100.35%, i.e. always within the prescribed limits of 95% to 105%. Disintegration time, 2 min to 2.75 min, and dispersion time, 3.25 min to 3.75 min, were also exemplary. The antidepressant activity was displayed by the optimized formulation as indicated by a significant decrease ($p<0.05$) in immobility time in TST as well as FST; a significant decrease ($p<0.05$) in the level of brain tissue glutamate as well as nitrite in PGAL formulation treated mice when compared with negative control, as did by standard drug fluoxetine.

Conclusion: The formulation has been optimized based on dispersion time. The formulation with minimum dispersion time, i.e. F1, has been considered an optimized formulation. The prepared optimized formulation was found to comply with all physical parameters and antidepressant activity.

Keywords: Antidepressant activity, Dispersible tablets, Methanolic extract, *Saraca asoca* leaves, Phytoconstituent

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INTRODUCTION

Saraca asoca is a perennial evergreen tree. It is the most sacred tree in India. It has great respect in Hindu and Buddhist Mythology [1]. The IUCN (International Union for Conservation of Nature) has nominated this species as "vulnerable" due to its declining population and damaging habitat harvesting [2]. Therefore, this species must be preserved and multiplied to continuously benefit from its remarkable medical properties. It contains several alkaloids and flavonoids, having several therapeutic benefits [3].

In this sequence, the methanolic extract of the leaves was obtained, followed by isolation of `the probable compound Peonidin-3-O-β-galactopyranoside (PGAL) by column chromatography using various suitable solvents and combinations [4]. The antidepressant activity of PGAL has not been reported earlier, so, our aim of this study is to investigate the antidepressant activity of the isolated PGAL and its convenient delivery via a suitable formulation.

For checking the therapeutic activity, there is a need to develop a palatable formulation. Because of the formulation development, some solubility studies revealed that the isolated compound was poorly water-soluble. So, there is a need to develop a formulation that increases solubility as well as the rate of dissolution of the poorly soluble isolated compound [5].

The oral route is considered the most convenient route for drug administration [5]. Among various oral formulations, tablets have obvious advantages over other formulations like the ease of handling, picking and transportation [6].

The primary studies indicate that the isolated compound PGAL has poor solubility, and poorly soluble drugs need to be formulated to improve their solubility and rate of dissolution through formulation [7]. Out of various types of tablets, one such variety of tablets is fast disintegrating and dissolving tablets [8].

In the present research, to achieve fast disintegration, such ingredients like cross carmellose sodium and cross povidone are included as super disintegrants in tablets [9]; and to further increase the solubility, sodium lauryl sulphate (SLS) has been added as solubilizing agent [10].

As direct compression presents many advantages over granulation methods, like less cost, and less time consuming, the tablets have been prepared by direct compression method [9]. Microcrystalline cellulose is a highly compressible ingredient that has been used here as a filler and a directly compressible ingredient [9].

So, the objective of this study was to formulate and evaluate dispersible tablets of PGAL obtained as the isolated product from methanolic extract of *Saracca asoca* leaves.

MATERIALS AND METHODS

Collection and authentication

Saraca asoca (Roxb.), De. Wild leaves used in the study were collected and got the same validated from NISCAIR (National Institute of Science Communication and Information Resources). A sample specimen was submitted to the raw material Herbarium and Museum, NISCAIR Delhi (Ref No. NISCAIR/RHMD/Consult/ 2020/3620-21).

Chemicals and reagents

Methanol, chloroform, petroleum ether, ethyl acetate and toluene were purchased from Molychem, Mumbai, India. Silica gel G-60 F_{254} from EduDap, New Delhi. Polyvinylpyrrolidone (PVP), sodium lauryl sulphate (SLS), Microcryatalline cellulose (MCC) and Talc were procured from CDH, New Delhi. Rest of the chemicals were purchased from HiMedia, Mumbai.

Preparation of extract

The leaves harvested from *Saraca asoca* plant were cleaned, shade-dried and pulverized with the help of a suitable mill. The powder was then passed through a 40 mesh screen and stored in a well-closed container

until use. Dried powdered leaves were then used for successive extraction using Soxhlet apparatus with petroleum ether, chloroform, ethyl acetate and methanol. The extract was then concentrated using a rotatory evaporator, recovering the solvents. Accurate weight, extractive value (%), colour and consistency were measured regarding air dried drug. The yield of methanolic extract was highest, so methanolic extract was used for further isolation of flavonoids [11, 12].

Isolation of PGAL from the prepared extract

Methanolic extract of the leaves of *Saraca asoca* was loaded on silica gel column (60-120 mesh) chromatography for the isolation of the phytoconstituent. The tests for flaonoid (Alkaline test, Shinoda test and ZN-HCl test) were performed on the isolated phytoconstituent having an R_f value (TLC) of 0.63 as detected by ferric chloride solution. The concentrated fraction was kept overnight in the refrigerator for crystallization [13].

Preformulation studies

Solubility studies of isolated PGAL

Solubility is an important parameter that must be studied before formulation design because solubility ultimately affects the drug dissolution and release from the formulation. The more the solubility of the drug in water, the faster its dissolution will be, and so the drug release. Thus, solubility helps in deciding the final formulation. The shake flask method was used to assess the in-house solubility of drugs. In brief, a surplus amount of PGAL was added into seven tubes containing 10 ml of water. These tubes were shaken on a platform shaker for 48 h at 37 ºC±1 ºC. Samples from each tube were then filtered through Whatman filter paper no. 41 and analyzed in triplicates after suitable dilution [14].

Compatibility studies of isolated PGAL with excipients

Physical mixtures of PGAL with all the excipients were prepared in a 1:1 ratio, ensuring uniform and intimate mixing. Their IR spectra were acquired and compared with the reference spectrum of pure PGAL for the identifying peaks. Physical mixtures were then placed in different vials and added 5% moisture to each sample; a rubber stopper was placed on each vial, and the vials were hermetically sealed with molten carnauba wax. All samples were kept for 1 w-3 w at 55 ºC. The samples were observed for discoloration, caking, liquefaction and odour. Their IR spectra were also acquired after three weeks of storage and were compared with pure for identifying peaks of PGAL [15].

Formulation of the herbal dispersible tablet of the isolated compound

Various formulae for dispersible tablets of the isolated compound PGAL were designed to directly compress the powder blend into tablets (table 1). All the constituents were passed across a screen of mesh number 120 and mixed by geometrical dilution method to maintain uniformity [16].

Table 1: Composition of herbal formulations as dispersible tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (PGAL)	46	46	46	46	46	46	46	46	46
Cross Carmellose Sodium	10	20	30	-	-	-	5	5	10
Cross Povidone	-	-	-	10	20	30	5	10	5
PVP	40	40	40	40	40	40	40	40	40
SLS	20	20	20	20	20	20	20	20	20
Talc	8	8	8	8	8	8	8	8	8
Micro Crystalline Cellulose	276	266	256	276	266	256	276	269	269
Total weight (mg)	400	400	400	400	400	400	400	400	400

Evaluation of powder blend

The powder blend, thus prepared, was evaluated for various powder micromeretic properties [17] as below-

Bulk density

A sample of 20 g of the prepared powder blend was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped twice at 2 seconds intervals using bulk density apparatus. The bulk density was then calculated by using the following formula [17]-

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Bulk volume}}$$

Tapped density

The tapped density was obtained by mechanically tapping a graduated measuring cylinder having 20 g of the prepared powder sample using bulk density apparatus till constant volume followed by calculations using the following formula [17]-

$$\text{Tapped density} = \frac{\text{Mass of powder}}{\text{Tapped volume of powder}}$$

Carr's Index (Compressibility index)

In pharmaceutics, Carr's Index (Compressibility Index) is frequently employed to measure a powder's compressibility. The difference between the bulk density and the tapped density in a free-flowing powder would be too tiny, and as a result, Carr's Index would be low. Instead, a poorly flowing powder with higher inter-particle interactions difference between the reported bulk density and tapped density would be more significant, leading to a bigger Carr's Index. Carr's Index was calculated using the following formula [17]-

$$\text{Carr}'\text{s Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

Hausner's ratio is a measure that can be employed to forecast the tendency of a given powder sample to be compressed and which is understood to reveal the significance of inter-particle interactions. Greater inter-particle interactions characterize poorer flowing materials, so a greater difference between bulk and tapped densities is observed [17].

$$\text{Hausner}'\text{s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of repose

The angle of repose (φ) can measure the frictional forces in a loose powder. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Suppose more material is added to the pile. In that case, it slides down the sides until the mutual friction of the particles, producing a surface at an angle φ, is in equilibrium with the gravitational force. The tangent of the angle of repose is equal to the coefficient of friction, μ, between the particles.

For determination of the Angle of Repose, the powder was passed through a vertically aligned funnel, and the height (h) and radius (r) of the heap formed were determined and calculated the angle of repose using the following formula [17]-

$$\text{Angle of repose } (\varphi) = \text{Tan}^{-1}\left[\frac{h}{r}\right]$$

Compression of powder blend into tablets

Powder mixtures were found to own good flow properties and compressibility, so the mixtures were compressed into tablets using hand operated tablet punching machine [9].

Evaluation of compressed tablets

Hardness

Teat for hardness (kg/cm^2) of tablets is performed to ensure that the tablets can withstand abrasion or breakage under storage conditions, transportation, and handling before use. A Monsanto Hardness Tester measured the hardness of the prepared tablets. The tablet was placed between two anvils; the force applied to the anvils and the crushing strength that caused the tablet to break was recorded [10].

Friability

The friability test was performed to ensure the prepared tablets were mechanically sound and could withstand mechanical shocks during handling and storage. The apparatus used for the purpose was Roche Friabilator. The average weight of the tablets was 0.450 g, i.e. less than 0.650 g. So, the test was performed on a sample of whole tablets corresponding to ten times the average weight of tablets, i.e. 6.5 g. The tablets were de-dusted carefully and accurately weighed. The tablets were then allowed to fall 100 times from a 6-inch height in the rotating Friability Chamber at 25 rpm. Then the tablets were removed from the friabilator chamber, de-dusted and weighed accurately. Calculate friability using the following formula [10].

$$\%\text{Friability} = \frac{\text{Weight loss of the tablet sample}}{\text{Initial weight of the tablet sample}} \times 100$$

Weight variation

This test is performed to check the drug content uniformity of the tablets provided uniform-mixing of the powder blend before compression. Randomly selected 20 tablets were individually weighed and calculated their average weights, followed by calculating the deviation of each tablet in weight from the average weight. No more than two of the individual weights differ from the average weight by more than 5% and none by more than 10% [10].

Drug content uniformity test

The drug content uniformity test was performed as per IP 2010. Determine the drug content of active ingredient(s) in each of 10 dosage units. Each tablet was crushed into powder. The crushed powder corresponding to 46 mg of the drug was exactly weighed and dissolved in 100 ml methanol for 10 min with strong shaking and centrifuged. The supernatant was collected in a separate vessel, and the residue was further extracted with fresh 100 ml methanol twice. All supernatants were mixed and evaluated for drug content after suitable dilution by UV spectrophotometric method at 655 nm. The procedure was performed on every ten tablets separately [10].

Disintegration test

The disintegration test is performed to ensure the breakdown of the tablet into smaller particles such that the drug can easily dissolve in the medium to get released from the compressed tablet, where penetration of the solvent inside the tablet becomes difficult due to compression and consolidation. From each batch, 6 tablets were arbitrarily taken to determine the disintegration time in the water as a disintegration medium at 37±0.5 °C. One tablet was introduced into each tube. The assembly was then suspended in the water-containing beaker, and the apparatus was operated and noted when all six tablets disintegrated [10].

Dispersion time

Dispersion time was measured *in vitro* by dipping the tablet in a vessel having 100 ml water. A smooth dispersion should be produced, which passes through a sieve of 710 μm aperture [10].

Antidepressant activity studies of the prepared formulation of PGAL

All the formulations, i.e. F1 to F9 have passed all the evaluation tests, and the optimized formulation has been considered based on dispersion time. Thus, the formulation having minimum dispersion time has been considered an optimized formulation. To find the antidepressant activity of the optimized formulation, a few behavioral studies (locomotion activity, tail suspension test (TST) and forced swim Test (FST)) as well as whole brain neurochemical assay (brain nitrite assay and glutamate assay) have been performed [18] on 3 mo to 4 mo old male Swiss albino mice weighing 20 g to 30 g (procured from AIIMS, New Delhi) at SGT University, Gurugram, Haryana, India after approval from Institutional Animal Ethics Committee (IAEC) vide reference number Pharma/FMHS/ SGTU/1182 Dated 20.09.2021.

Mice were kept in the central animal house at 21 ºC-23 ºC with a light-dark interval of 12 h each starting from 07:00 and 19:00 h, respectively and were provided with free access to water and food.

For TST, the mice were given oral doses as presented in table 6 and hung by tail for 6 min and Immobility duration was measured (n=6) [19].

For FST, the mice were given oral doses as presented in table 6 and kept in a cylindrical container (Height 30 cm and Diameter 20 cm) filled to the height of 15 cm with water at 25 ºC and the immobility period was measured for 6 min (n=6) [19].

A 10 %w/v brain homogenate was prepared in potassium phosphate buffer pH 7±0.1 at 4 ºC followed by deproteination using 10% trichloroacetic acid and centrifugation at 12000 rpm for 20 min at 4 ºC [20].

For brain glutamate assay, to 300 μl of the brain homogenate 100 μl of phosphate buffer pH 7.0±0.1 was added, pH of the resultant mixture was adjusted to 9.0±0.1 and allowed to stand for 10 min in an ice bath followed by measuring the absorbance at 340 nm [20]. Results have been presented in table 6.

For brain nitrite assay, 100 μl of the supernatant was added to 100 μl of the Griess Reagent and allowed to stand for 10 min at room temperature, followed by measuring the absorbance at 546 nm [21]. Results have been presented in table 6.

The data from all the tests were statistically analysed by One Way ANOVA wherever applicable.

RESULTS AND DISCUSSION

Solubility is an important parameter that needs to be studied before formulation design because solubility ultimately affects drug dissolution and release from the formulation [22]. A solubility of 0.02 g/ml indicates that PGAL has been found to be sparingly soluble in water, i.e. require 50 parts (More than 30 parts and less than 100 parts) of water for one part of the PGAL to dissolve completely. So, the solubility of PGAL needed to be improved during formulation design [22]. So, fast-dissolving dispersible tablets have been designed and evaluated.

The formulation design is shown in table 1. Before the preparation of the formulation batches, drug-excipient interaction studies were performed by FTIR, and the results of the compatibility studies are presented in tables 2-3.

All the samples show no signs of physical instability, i.e. caking, liquefaction, discolouration and odour formation. Also, the presence of entire characteristic peaks of the drug in IR spectra of the mixture at both 0 time and after 3rd week of storage proves no incompatibility between the drug and excipients (table 3) [15].

The powder blends of all the formulation batches were prepared and studied for micromeretic properties. Table 4 shows the micromeretic properties of the powder blend prepared. It has been observed that all the parameters of flow properties like Carr's Index, Hausner's Ratio and Angle of Repose were found to be within acceptable limits of 17.31% to 29.79%, 1.21 to 1.42 and 23.45º±1.01º to 31.43º±2.22º respectively [17].

Flow properties, as indicated by Hausner's Ratio, Angle of Repose and Carr's Index or Compressibility Index show that the powder blends from all the formulae can be directly compressed into tablets without granulation.

Table 2: Physical observations after 3 w of storage at 55 °C with 5% moisture

Parameters	Caking	Liquefaction	Discoloration	Odour Formation
Result	-	-	-	-

Table 3: IR data of solid-state drug-excipient compatibility study for PGAL

Wave number recorded for the physical mixture of PGAL and excipients (cm^{-1})		Absorption frequency band (cm^{-1})	Characteristic functional group/vibration
0 Time	3rd Week		
3414.85	3400.15	3200-3600	Alcoholic OH (Aromatic) Functional Group
3071.32	3140.18	3200-3600	Alcoholic OH (Aliphatic) Functional Group
3011.56	3011.65	2800-3100	CH (Aromatic) Stretching
1247.37 and 1105.42	1236.12 and 1034.54	1220 and 1025	Ar-O-C (Substituted C_5O Aliphatic Ring) bending
865.48	855.21	900-690	Aromatic C-H bending in substituted Benzene ring
742.11	821.41	815	1,2,4-trisubstituted benzene

Table 4: Micromeretic properties of the prepared powder blend for compression into tablets

Formulation	Bulk density (g/ml)*	Tapped density (g/ml)*	Carr's index (%)**	Hausner's ratio**	Angle of repose (°)*
F1	0.37±0.05	0.51±0.07	29.41	1.42	26.51±1.03
F2	0.43±0.06	0.55±0.08	21.82	1.28	25.43±1.22
F3	0.33±0.04	0.47±0.09	29.79	1.42	23.45±1.01
F4	0.39±0.05	0.51±0.10	23.53	1.30	31.43±2.22
F5	0.44±0.06	0.56±0.07	21.43	1.27	30.22±1.76
F6	0.39±0.04	0.53±0.06	26.42	1.36	27.28±1.33
F7	0.43±0.05	0.52±0.07	17.31	1.21	27.53±1.55
F8	0.44±0.03	0.57±0.05	22.81	1.30	29.25±1.41
F9	0.43±0.07	0.54±0.08	20.37	1.26	27.32±1.44

*mean±SD (Standard Deviation) for n=3 Measurements, **Calculated from mean values of bulk density and tapped density

After compression of each formula into tablets, the prepared tablets were evaluated for various official and unofficial tests of evaluation like hardness, friability, weight variation, drug content uniformity test, disintegration test, disintegration time, dispersion time, *in vitro* dissolution studies and stability studies. Results are presented in table 5 [10].

Hardness was measured by a Monsanto Hardness Tester. It was found to be 2.85±0.13 kg/cm^2 to 3.25±0.15 kg/cm^2 (table 5), indicating that the prepared tablets will reasonably withstand storage conditions, transportation, and handling and do not undergo abrasion or breakage under these circumstances. Similar is the case of the friability test. A percent weight loss of 0.35% to 0.48% (table 5), i.e. always less than 0.5% for all the batches (F1-F9), indicates that the prepared tablets from all the prepared batches were mechanically sound and could withstand the mechanical shocks during handling and storage.

As far as the test for weight variation is concerned (table 5), the tablets from all the prepared formulations were found to pass the test for weight variation as indicated by only 2.04% to 4.25% difference in weight of the tablet from the average weight of 10 Tablets (data provided only for the tablet found to have a maximum difference in weight) which is always less than the weight variation tolerance limits of 5% for tablets having an average weight of greater than 324 mg.

Table 5: Various evaluation parameters for prepared dispersible tablets

Formulation	Hardness (kg/cm^2)*	Friability (%)	Weight variation (%)**	Drug content uniformity (%)	Disintegration time (Min)	Dispersion time (Min)
F1	2.95±0.25	0.35	3.12	99.54	2.00	3.25
F2	3.00±0.16	0.38	4.13	97.35	2.50	3.75
F3	2.85±0.13	0.43	2.04	97.54	2.25	3.50
F4	3.25±0.15	0.36	3.55	98.67	2.75	3.75
F5	2.98±0.04	0.43	4.25	97.95	2.50	3.75
F6	2.96±0.06	0.45	3.37	98.13	2.25	3.50
F7	3.12±0.11	0.40	3.44	100.35	2.75	3.75
F8	2.96±0.14	0.48	2.95	97.55	2.00	3.50
F9	3.03±0.17	0.39	3.01	97.64	2.50	3.75

*mean±SD (Standard Deviation) for n=3 Measurements, **%Difference of weight of the tablet from average weight of 10 Tablets (Data provided only for the tablet found to have the maximum difference)

As the test for uniformity of mixing was not performed, it has become necessary to perform the test for drug content uniformity along with the test for weight variation. The results are presented in table 5 and were found to be 97.35% to 100.35% for all the prepared formulations, i.e. F1 to F9. These results indicate that all the prepared batches have passed the test for uniformity of drug content, as indicated by the fact that the percent drug content uniformity was always within the prescribed limits of 95% to 105%.

Disintegration time and dispersion time of 2 min to 2.75 min and 3.25 min to 3.75 min, respectively, (table 5) ensure that the drug dissolution will not be much affected by compression and consequent consolidation. A smooth dispersion produced had been passed through a sieve with a mesh aperture of 710 µm, indicating that the produced tablets have passed the criteria of tablet dispersion.

From all the formulations, i.e. F1 to F9 the optimized formulation has been considered based on minimum dispersion time, which is of F1

formulation, i.e. 3.25 min. Thus, formulation F1 (table 1) has been considered an optimized formulation, and further antidepressant activity was performed on the optimized formulation F1.

The antidepressant activity was studied via behavioural studies (i.e. locomotion activity, tail suspension test (TST) and forced swim Test (FST)) and whole brain neurochemical assay (i.e. brain nitrite assay and glutamate assay) have been performed, the results of which have been presented in table 6. Forced swim test (FST) or tail suspension test (TST) were developed as behaviour parameters to predict the antidepressant effect. These methods are simple and provide reliable results.

Table 6: Parameters for antidepressant activity

S. No.	Group (Dose)	TST (Immobility period (Sec))^	FST (Immobility period (Sec))^	Locomotion activity (Sec)^	Glutamate level (µM)^	Nitrite level (µM)^
1.	Negative Control (Stress)	218.67±37.69	60.50±12.82	50.17±16.55	1.39±0.2042	16.33±3.12
2.	Vehicle (10 ml/kg body weight)	145.67±23.24*	24.33±7.34*	34.67±10.69*	0.64±0.21*	10.28±2.69*
3.	Standard Drug Fluoxetine (10 mg/kg body weight)	146.17±71.83*	31±28.87*	38.83±21.73*	0.65±0.42*	10.46±3.45*
4.	F1 (PGAL) (50)	143±49.12*	43±16.98*	36.83±18.29*	0.58±0.28*	7.85±1.03*

^mean±Standard Deviation (n=6), *p<0.05 compared with negative control

Results show that the test drug PGAL significantly decreased (p<0.05) immobility time as did by standard control (n=6) fluoxetine when compared with a negative control group (n=6) in the TST as well as FST, which shows antidepressant-like behaviour in mice. Similarly, the significantly decreased level of brain tissue glutamate (p<0.05) as well as nitrite (p<0.05) level in PGAL-treated mice (n=6) when compared with negative control (n=6), as did by standard drug fluoxetine (n=6), indicated antidepressant-like behaviour in mice. However, no significant difference was observed in locomotion activities.

CONCLUSION

The formulation has been optimized based on dispersion time. The formulation having minimum dispersion time, i.e. F1 has been considered an optimized formulation. The prepared optimized formulation was found to comply with all physical parameters as well as antidepressant activity.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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