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Investigation of Anti-Parkinsonian Effect of Benincasa hispida Fruit Juice on Haloperidol Induced Experimental Animal Model

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ABSTRACT

The objective of the study is to investigate the anti parkinson's activity of *Benincasa hispida fresh fruit juice* on experimental animal model.In rats, catalepsy was induced using haloperidol (1 mg/kg i.p.). Treatment groups received syndopa (10 mg/kg) and BHFFJ at the dose of (100, 200, and 400 mg/kg) orally. Behavioral changes were assessed by carrying out catalepsy by bar test, muscle relaxant test by rotarod, and locomotor activity by actophotometer. Biochemical parameters were also assessed by carrying out Assay of dopamine and catalase. Syndopa and BHFFJ treated groups showed a significant difference in behavioral and biochemical parameters as compared to haloperidol control group in the experimental models***.BHFFJ*** exhibited significant antiparkinsonian activity in haloperidol rat model.

Key words: ***Benincasa hispida,*** Catalepsy, Metal bar, Haloperidol, Syndopa.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder which basically influences the motor system. It is also known as a slow progressive neurodegenerative disease in which there may be a deficiency of dopaminergic neurons projecting from Substantia nigra pars compacta toward neostriatum main to the imbalance among dopamine and acetylcholine. In addition to this, proteins known as Lewy bodies acquire in dopaminergic neurons [1,2].

The crucial pathological functions of PD are neuronal demise withinside the brain's basal ganglia (affecting as much as 70% of the dopamine secreting neurons withinside the S. nigra pars compacta via way of means of the give up of life) [3] and the incidence of Lewy bodies (gatherings of the protein alpha-synuclein) in among the last neurons. This deficiency of neurons is observed through the death of astrocytes (star-shaped glial cells) and significant increase in the number of microglia (another kind of glial cell) withinside the S. nigra [4]. Allopathic medicinal drug along With L-Dopa is the drug of preference withinside the remedy of Parkinsonism and has unfavourable outcomes inclusive of gastro intestinal facet outcomes consisting of vomiting, nausea, giddiness [5] and orthostatic hypotension bizarre movements, behavioral unfavourable effect, stop of dose deterioration or the on-off phenomenon with motor complications synonymous with the sickness itself Allopathic medicinal drug consisting of L-Dopa is the drug of preference in the in the therapy [6] . To overcome the adverse effects associated with allopathic medicine alternative medicines are preferred.

The blockade on the dopamine receptor is because of haloperidol will increase the dopamine turnover in people and rats [7, 8, 9] .It has been proposed that haloperidol induced oxidative pressure arises from the generation of free radical from catecholamine metabolism with the aid of using monoamine oxidase (MAOs). The acute and chronic administration of haloperidol in animal models which include mice resulted in the generation of notified oxidative stress in their brain regions, as was evidenced by lack of the non protein thiol anti-oxidant glutathione (GSH) and by the increase of the lipid peroxidation product[10,11].

Benincasa hipsida (Synonym: Benincasa cerifera) [12], which usually called (winter melon, ash gourd, ash guard, winter gourd, white pumpkin and wax gourd. white gourd, tallow gourd, gourd melon and Chinese watermelon) belongs to the family cucurbitaceae . It is a famous vegetable crop, specifically amongst Asian groups both for dietary and medicinal purposes [13,14]. Plant become used medicinally in diverse complains together with gastrointestinal problems, respiratory disease, cardiovascular disorders, diabetes mellitus and urinary disorders [15]. Fruits have been historically used as a laxative, diuretic, tonic, aprodisiac, cardiotonic, urinary calculi, blood sickness, insanity, epilepsy, schizophrenia and other psychologic disorders, jaundice, dyspepsia, flu, and menstrual disorders [16-18]. The active constituents of Benincasa hispida fruits are volatile oils , flavonoids, glycosides, sacchrides, proteins, carotenes, vitamins, minerals, ß-sitosterin and uronic acid [13,19-23] The pharmacological studies located that the plant has many pharmacological actions , along with primary worried effects (anxiolytic , muscle relaxant , antidepressant , withinside the remedy of Alzheimer's disorder and to limit opiates withdrawal signs), antioxidant, antiinflammatory, analgesic antiasthmatic, diuretic, nephroprotective, antidiabetic, hypolipidemic and anti microbial effects.

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MATERIALS AND METHODS:

Drugs and chemicals:

Haloperidol , Syndopa (Leavodopa + Carbidopa) ,Dragendroff 's reagent ,Mayer's reagent Wagner's reagent ,Hager 's reagent .

Plant material:

Fresh fruits of the plant *Benincasa hispida* were collected from the surroundings of the Kurnool .It was authenticated by botanist P.V.Prasanna from botanical survey of India

Preparation fruit juice of *Benincasa hispida* [24]

Before preparing the extract the seeds were removed and the pulp of the fruit were cut into pieces and weighed. After weighing , the fruit pieces were blended and filtered using muslin cloth to extract juice from the fruit , the juice were measured and filled in the bowl and kept in water bath at 60^0C till all the water content of the juice get evaporated and the fine particles get settled. Now the settled residues were been dried, collected and weighed again.

Experimental animals

36 Wistar rats weighing 150-200 g were used in the present study. They have been housed in individual polypropylene cages below preferred laboratory situations of light, temperature and relative humidity. Animals have been provided with preferred rat pellets (Pranav Argo's ltd.) and drinking water *ad libitum*. The experimental procedure was approved by the Institutional Animal Ethical Committee of Creative Educational Society College of Pharmacy (IAEC/CESCOP/2019-OCT-04).

Experimental design :

36 animals have been grouped into six, having six in each group (n=6). Group I treated as normal .Group II received haloperidol (1.0 mg/kg, i.p) suspended in 1% tween 20, and Group III received Haloperidol (1mg/kg/I.P & LDopa+ Carbidopa 100+25 mg/kg/p.o) respectively,Group IV received BHFFJ .dose/p.o+Haloperidol(1mg/kg/I.P),GroupVreceived,BHPEM.dose/P.O+Haloperidol(1mg/kg,I.P),Group VI received BHPE H.dose/P.O+Haloperidol(1mg/kg,I.P) for 20 days. After the treatment for 20 days, all six groups of animals underwent the behavioral assessment tests. Then, cervical decapitation was performed to isolate the striatum of the brains of the animals, and homogenate was prepared using ice-cold phosphate-buffered saline solution and stored.

a)Catalepsy behavioural study

Haloperidol (1.0 mg/kg i.p.) utilized in the catalepsy acceptance and the rodents were evaluated for at regular intervals as long as 120 minutes by playing out a standard bar test. Haloperidol among the antipsychotics creates a moderate cataleptic impact. Catalepsy was given in scores for the forced situation of the front appendages set on a 3 and 9 cm high wooden bar of 1 cm wide. At the point when the both front paws were taken from the bar or if the creature moves its head, this can be named as the end point. Levodopa (100 mg/kg) was taken as the standard medication, and the B.hispida remove was managed to three distinct gatherings (n=6 in each gathering) at a portion of 100,200 and 400 mg/kg p.o., separately, 1 hr before to the dosing of haloperidol.

If the animal is unable to regain its posture for about 10 seconds, it was considered to be cataleptic.

Stage I – Rat moves freely when it is placed on the table,then the score = 0.

Stage II – Rat moves when touched or pushed, score = 0.5.

Stage III – If the rat is unable to come to its original posture within 10 s when its front paws are set alternately on a 3 cm high block, the score = 0.5 for each paw with a total 1 score.

Stage IV - Rat couldn't get rid of its the front paws whilst located on a nine cm excessive block, rating = 1 with a complete rating = 2 for this stage [25] .

b) catalepsy by metal bar test

Catalepsy rating become examined for four hours at 30 min periods after haloperidol management through lightly setting each the fore paw of the rat on a metallic bar (diameter 2-5mm suspended 6cm above the tabletop .The impact of catalepsy was estimated by including the time in seconds until the rodent took both fore paws back to the tabletop, with a most extreme cut-off time of 3 minutes. At long last, scores at various time focuses were added and given as aggregate catalepsy score for correlation reason. [26]

Neurobehavioral studies

i)Locomotor activity by actophotometer meter

This test quantifies the investigation and the intentional velocity inside an encased territory. The target an incentive for the unconstrained engine action was acquired utilizing a photoactometer (INCO Ltd., India). The creature was set independently into a 30 cm × 30 cm dark metal chamber with a screen floor and a light-tight top. Six light emissions light were engaged 2 cm over the floor into photocells on the contrary side. Each bar interference was enrolled as an occasion on the outside counter. The light bar breaks were meant 5 min.[27]

ii)Rotarod Test

The rotarod equipment is a rotating rod of 70 cm duration and three cm diameter at the peak of fifty cm above the ground and has 4 divisions wherein 4 animals may be located whenever throughout the study. Before the

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assessment, all of the rats underwent 5 trials with the aid of using keeping price of rotation at 30 rpm. The control rat remains on the rod for about 5 minutes. The treated rodents were kept on the turning pole at customary interims, and the hour of the tumble off time was noted. The cutoff time for the test was 5 minutes [28]

Antioxidant parameters :

Estimation of lipid peroxidation (LPO) :

300 microns of 10% trichloroacetic acid (TCA) were added to 150 µL of each sample and centrifuged at 1000 rpm for 10 minutes at 4^0C. Around 300 µL of the supernatant was incubated with 300 µL 0.67% thiobarbituric acid at 100^0C for 25 minutes. The blend became cooled for five mins and the thiobarbituric acid reactive substances (TBARS) concentration as purple stains became measured in a spectrophotometer at 535 nm [29] .

Assay of superoxide dismutase (SOD)

SOD became quantified via way of means of the discount of look of nicotinamide adenine dinucleotide (NADH) - phenazine methosulphate nitroblue tetrazolium formazon complex. NADH became measured after ninety s of incubation and the response became stopped via way of means of the addition of glacial acetic acid. The color formed because the end point of the response became extracted into the butanol layer and measured at 520 nm [30].

Assay of catalase (CAT)

The tissue was homogenized in isotonic buffer (pH - 7.4) and centrifuged at 1000rpm for 10 minutes. 20 µl of 100-fold diluted tissue supernatant mixed to 980 µl of the assay mixture; the assay mixture contains 900 µl of 10 mmol/L of Hydrogen peroxide(H_2O_2) , 50 µl l of Tris-HCl buffer (pH - 8), and 30 30 µl of water. The degree of decomposition of H_2O_2 become measured spectrophotometrically at 240 nm [31].

Estimation of glutathione peroxidase (GPx)

A quantity of 0.1 ml of the diluted tissue stored apart at 37°C with reaction mixture such as 0.2 ml of each EDTA, sodium azide, and H2O2. To the above solution 0.5 ml of TCA was added to prevent the reaction after which the mixture become centrifuged at 2000 rpm.Then the supernatant collected to that 4 ml of disodium hydrogen phosphate and 0.5 ml 5,5'-dithiobis nitro benzoic acid (DTNB) had been added for colour formation. The colour formed become measured at 420 nm in a spectrophotometer [32].

Estimation of gluthathione reductase (GSH)

To 2ml of tissue homogenate and KCl mixture 4 ml of cold distilled water and 1 ml of 50% TCA. Were Were added and the contents are subjected for centrifuged at 3000 rpm for 15 minutes.After 15minutes 2 ml of the supernatant was collected and to that mixture added 4ml of 0.4 M Tris buffer (pH 8.9) and 0.1 ml of 0.01 M DTNB , the absorbance measured at 412 nm in opposition to the blank reagent. For blank readings, 2 ml of distilled water added used withinside the location of tissue homogenate. Total GSH become calculated the usage of the formula: Co=(A*D)/E Where, A is absorbance at 412 nm, D is dilution factor, and E is the molar extinction coefficient.
(C=13,000 M−1 CM−1); Co is the concentration of GSH. [33]

Estimation of dopamine [34].

Procedure

To the 0.2 ml of aqueous phase, 0.05 ml 0.4 M HCl and 0.1 ml of EDTA / Sodium acetate buffer ($_p$H6. 9)were added, followed by 0.1 ml iodine solution(0.1 M in ethanol) for oxidation. The reaction was stopped after 2 min by addition of 0.1 ml Na_2SO_3 solution. 0.1 ml Acetic acid is added after 1.5 min. The solution was then heated to 100°C for 6 min when the sample again reached room temperature, excitation and emission spectra were read from the spectrofluorimeter. The readings were taken at 330-375 nm for dopamine

Statistical Analysis:

The data were expressed as mean ± S.E.M from 6 animals [n=6]. The results were subjected to statistical analysis by using Unpaired t-test to calculate the significance difference if any among the groups. P<0.05 was considered as statistical significance using Graph Pad Prism Software.

RESULTS AND DISCUSSION:

Table .No.1: Preliminary photochemical screening:

S.NO	TEST NAME	RESULT
1	Alkaloids	-
2	Tannins	-
3	Glycosides	+
4	Flavanoids	+
5	Phenolics	+
6	Terpenoids	+

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Table No. 2: Effect of *BHFJ* on haloperidol induced Catalepsy by block method

Group	Drug treatment	0 min	30 min	60 min	90 min	120 min	150 min	180 min
I	**Haloperidol 1 mg/kg**	0.00±0.00	1.54±0.11##	2.74±0.17###	3.04±0.09###	3.25±0.08###	3.14±0.03###	2.98±0.05###
II	**L-Dopa+Carbidopa(100+25mg/kg) / 10 mg/kg/P.O**	0.00±0.00	0.50±0.08	1.07±0.19*	1.25±0.06**	1.12±0.05**	0.98±0.06***	0.52±0.09***
III	***BHPE* 100 mg/kg + Haloperidol 1mg/kg,I.P**	0.00±0.00	2.23±0.24	2.03±0.05	1.86±0.08	1.65±0.08	1.26±0.08*	0.85±0.04*
IV	***BHPE* 200 mg/kg + Haloperidol 1mg/kg,I.P**	0.00±0.00	1.30±0.13	1.78±0.07	1.55±0.10	1.53±0.05*	0.97±0.06**	0.59±0.04**
V	***BHPE* 400 mg/kg + Haloperidol 1mg/kg,I.P**	0.00±0.00	0.76±0.06	1.30±0.13	1.28±0.07*	1.04±0.058*	0.77±0.03***	0.28±0.04***

Values were mean ± SEM (n=6). Statistical analysis by One-way ANOVA, followed by Dunnett's multiple comparison tests. *p< 0.05. **P<0.01.

Table No.3: EFFECT OF BHFJ ON BEHAVIORAL ASSESSMENT IN HALOPERIDOL ADMINISTERED RATS BY METAL BAR TEST

Group	Drug treatment	0 min	60 min	120 min	180 min	240 min
I	**Normal**	6.46±0.08	7.50±0.13	9.65±0.14	8.51±0.10	9.33±0.18
II	**Haloperidol 1 mg/kg**	9.40±0.10	144±1.13###	183±1.92###	168±1.83###	143±1.56###
III	**L-Dopa+Carbidopa(100+25mg/kg) / 10 mg/kg/P.O**	8.56±0.08	24.1±0.87*	18.8±0.94**	15.0±0.73***	11.0±0.57***
IV	***BHPE* 100 mg/kg + Haloperidol 1mg/kg,I.P**	7.01±0.20	92.6±3.08	77.0±1.84	58.3±1.40*	17.5±0.76*

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V	***BHPE* 200 mg/kg + Haloperidol 1mg/kg,I.P**	6.20±0.24	67.6±1.33	48.1±1.24*	26.0±0.57**	13.0±0.57**
VI	***BHPE* 400 mg/kg + Haloperidol 1mg/kg,I.P**	4.72±0.17	46.5±2.55	35.0±1.52*	22.8±1.07***	9.50±0.42***

Values were mean ± SEM (n=6). Statistical analysis by One-way ANOVA, followed by Dunnett's multiple comparison tests. *p< 0.05. **P<0.01.

Table No.4: EFFECT OF BHFJ ON LPO, SOD, CAT AND GSH LEVELS IN HALOPERIDOL ADMINISTERED RAT BRAIN

Group	Drug treatment	LPO (n moles/mg protein)	SOD (µ/mg protein)	CATALASE (µ/mg protein)	GSH (µ/mg protein)	GPx (µ/mg protein)	DA (ng/mg tissue)
I	**Normal**	1.36±0.04	8.63±0.07	3.38±0.10	12.2±0.22	8.500 ± 0.4041	9.78± 0.24
II	**Haloperidol 1 mg/kg**	3.39±0.073###	4.49±0.08###	1.39±0.06###	6.29±0.20###	3.983 ±0.2211###	4.78± 0.21###
III	**L-Dopa+Carbidopa(100+25mg/kg) / 10 mg/kg/P.O**	1.42±0.07***	8.03±0.15***	3.25±0.04***	11.1±0.22***	9.133 ±0.3768***	8.90± 0.21***
IV	***BHPE* 100 mg/kg + Haloperidol 1mg/kg,I.P**	1.85±0.03*	5.45±0.11*	1.73±0.03*	8.65±0.14*	6.767 ± 0.3084*	5.79± 0.18*
V	***BHPE* 200 mg/kg + Haloperidol 1mg/kg,I.P**	1.62±0.04**	6.52±0.09**	2.50±0.07**	9.57±0.17**	7.883 ±0.2651**	6.29± 0.16**
VI	***BHPE* 400 mg/kg + Haloperidol 1mg/kg,I.P**	1.47±0.07***	7.68±0.16***	3.05±0.10***	10.4±0.09***	9.863 ±0.2973***	8.12± 0.20***

Values were expressed as mean ± SEM. Statistical significant test for comparison was done by ANOVA, followed Dunnett's't' test.

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p< 0.001 compared to Group I ,*p<0.05 compared to group II; **p<0.01 compared to group II ; ***p<0.001 compared to group II.

Table No.5: EFFECT OF BHFJ ON MUSCLE RIGIDITY BY ROTA ROD METHOD IN HALOPERIDOL ADMINISTERED RATS

Group	Drug treatment	Fall of time (Sec)						
		0 min	30 min	60 min	90 min	120 min	150 min	180 min
I	Normal	176±1.69	180±1.49	174±1.16	167±2.06	175±1.08	174±1.45	176±1.85
II	Haloperidol 1 mg/kg	162±3.42	40±0.93$^{\#\#}$	32.5±1.94$^{\#\#\#}$	37.8±2.19$^{\#\#\#}$	29±0.68$^{\#\#\#}$	24.5±0.67$^{\#\#\#}$	19.8±0.94$^{\#\#\#}$
III	L-Dopa+Carbidopa(100+25mg/kg) / 10 mg/kg/P.O	178±2.32	89.1±2.45*	107±3.93*	97.8±2.31*	124±1.80**	140±1.43***	148±2.20***
IV	*BHPE* 100 mg/kg + Haloperidol 1mg/kg,I.P	167±2.28	56.8±2.56	65±2.46	57.8±2.24	75.5±2.46*	91.5±1.91*	104±1.67*
V	*BHPE* 200 mg/kg + Haloperidol 1mg/kg,I.P	173±2.37	63.1±2	72.8±1.53	66.6±2.44	86.3±3.51*	101±2.66**	112±2.92**
VI	*BHPE* 400 mg/kg + Haloperidol 1mg/kg,I.P	178±1.82	69±1.46	80.8±1.55*	74.6±1.70*	95.5±3.97**	113±2.04***	129±2.27***

Values are expressed as Mean ± SEM (n=6). Statistical analysis was carried out by One way Anova followed by Tukey-Kramar multiple comparison test *P<0.05, **P<0.01,***P<0.00

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Table .No .6: EFFECT OF BHFJ ON LOCOMOTOR ACTIVITY AGAINST HALOPERIDOL INDUCED IN RATS USING ACTOPHOTOMETER

Group	Drug treatment	Locomoter activity Fall of time (Sec / 10min)
I	**Normal**	421.5 ± 9.746
II	**Haloperidol 1 mg/kg**	57.83 ± 7.613###
III	**L-Dopa+Carbidopa(100+25mg/kg) / 10 mg/kg/P.O**	397.8 ± 12.39***
IV	***BHPE* 100 mg/kg + Haloperidol 1mg/kg,I.P**	212.0 ± 9.000*
V	***BHPE* 200 mg/kg + Haloperidol 1mg/kg,I.P**	287.7 ± 7.911**
VI	***BHPE* 400 mg/kg + Haloperidol 1mg/kg,I.P**	374.5 ± 24.24***

Values are expressed as Mean ± SEM (n=6). Statistical analysis was carried out by One way Anova followed by Tukey-Kramar multiple comparison test *P<0.05, **P<0.01,***P<0.000

Discussion:

Free radical damage to the central nervous system (CNS) is due to its high oxygen utility, increased lipid content and inadequate antioxidant enzymes than compared to other tissue. The free radical generation in the brain influences gene expression, subsequently leading to apoptosis and neuronal death. In the brain, an array of cellular protection systems, i.e., enzymatic and non-enzymatic antioxidants exists to counterbalance the generation of reactive oxygen species. [35]

Studies show that prolonged treatment with antiparkinson drugs such as dopamine agonist, dopamine replenishment therapy, and monoamine oxidase inhibitors leads to severe side effects and decrease in the sensitivity for the therapy [36]. Further, typical neuroleptic drugs such as chlorpromazine, haloperidol, and reserpine use in schizophrenia lead to decrease in dopamine content and state of catalepsy. The cataleptic induction method through neuroleptics in rodents is the broadly popular method to check the extrapyramidal side effects of antipsychotic agents. Evidences imply that pills which produce or lessen the catalepsy in rodents may display the equal results in human beings. The conversion of levodopa to dopamine in serotonin neurons was proved as a compensatory measure in PD [37,38].

Previous research have proven that dopamine receptors withinside the striatum are concerned withinside the neuroleptic-caused catalepsy [39]. It has been established that the cataleptic consequences of haloperidol are mediated via way of means of dopamine receptors of the striatal neurons.. It was also reported that the administration of haloperidol provokes an oxidative stress in the brain tissue. An increase in SOD concentration in the present work supports the concept. Under normal conditions, decrease in the activities of SOD, GPx, and CAT enzymes in the brain leads to the accumulation of oxidative free radicals resulting in degenerative effects [40]. At normal conditions, increased concentration of these enzymes would represent the rise in antioxidant activity and exhibits a protective mechanism in neuronal tissue, therefore constituting the primary line of protection in opposition to oxidative strain in our body. Hence, any lower within side the diploma of catalepsy and upward thrust within side the SOD pastime

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with inside the drug-handled organizations shows the capacity of the drug extract to defend in opposition to the oxidative strain within side the mind tissue and decrease the severity of haloperidol-triggered catalepsy. Treatment with B.hispida fruit juice increased the activity of those enzymes with the aid of using quenching the free radicals. Researchers have proven that B.hispida possesses amazing antioxidant activity that scavenges free radicals generated after the induction of catalepsy. Lower degrees of LPO within side the brains of the drug-treated groups and expanded activities of enzymatic and non-enzymatic antioxidants suggest that the extract reduces oxidative stress. The fruit juice of B.hispida showed no signs of lethality up to 2000 mg/kg. Hence, initially, three doses, i.e., 100, 200 and 400 mg/kg of fruit juice of B.hispida were selected to study their effect on haloperidol-induced Parkinsonism in Wistar rat animal model. At a dose of 400 mg/kg, the *BHFJ* extract confirmed a tremendous reduction of the Parkinsonism impact in Wistar rats.

CONCLUSION:

The effects of the present study conclusively confirmed that *BHFFJ* has antioxidant activity and anti-parkinsonism activity at an effective dose of 400 mg/kg 100 & 200mg/kg against Haloperidol experimental model of Parkinson's disease in rats. *BHFFJ* was also found to be effective in increasing rotarod performance, locomotor activity and decreasing catatonic response. Hence the effect of *BHFFJ* on parkinson's disease may be due to presence of flavonoids. Further studies are required to understand the basic mechanism and characterization of active constitutents responsible for Parkinson's disease.

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