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Comparative Evaluation of Antidepressant Property of *Unmad Gajkesari Rasa* and Fluoxetine Hydrochloride w.s.r. to Chronic Unpredictable Mild Stress Induced Depression *(Avasad)* in Wistar Rats

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ABSTRACT

Depression (*Avasad*) is a medical disorder of the brain that affects feeling, thoughts, behaviour and physical health of person. Worldwide 450 million individuals are suffering from mental illness. Various researches have been done on development of disease, its pathophysiology, epidemiology and other aspects, but very few research works are available on its therapeutic aspect from ayurvedic view. There is a need to find a therapeutic solution for Depression (*Avasad*) and this study is aimed at the same. *Unmad Gajkesari Rasa* (UGR) a herbomineral formulation mentioned in *Yogratnakar Unmad rog* 27/1-3 is indicated for treatment of *Manas Vyadhi.*

AIM: To compare antidepressant property of *Unmad Gajkesari Rasa* & Fluoxetine Hydrochloride w.s.r. to chronic unpredictable mild stress induced Depression (*Avasad*) in wistar rats.

Materials and Methods: UGR was prepared as per reference of *Yogratnakar*. Wistar Rats were subjected to CUMS (Chronic Unpredictable Mild Stress) for induction of depression followed by oral administration of UGR & Fluoxetine Hydrochloride orally.

Observation*:* Histopathological parameters & anti-depressant property of UGR & Fluoxetine Hydrochloride in wistar rats.

Conclusion: The result of the *Unmad Gajkesari Rasa* a herbomineral formulation suggested that it had a significant antidepressant activity as compared to Fluoxetine hydrochloride in tail suspension test and weight.

Key Words: Anti-depressant activity, Depression (*Avasad*), Fluoxetine hydrochloride, *Unmad Gajkesari Rasa*, Wistar rats.

INTRODUCTION

Depression is a medical disorder of the brain that affects feeling, thoughts, behavior and physical health of person. In 2017 WHO (World Health Organization) theme was: 'Depression, let's talk.' Core of the campaign is the importance of talking about depression as a vital component of recovery. In India, the National Mental Health Survey 2015-16 discloses that nearly

15% Indian adults need active participation for one or more mental well-being issues and one in 20 Indians suffers from depression.[1] Various researches have been done on development of disease, its pathophysiology, epidemiology and other aspects, but very few research works are available on its therapeutic aspect from ayurvedic view. There is a need to find a therapeutic solution for Depression (*Avasad*). In Ayurveda, *Unmad Gajkesari Rasa* is mentioned in '*Yogratnakar'* in *Unmad rogadhikar,* which contains *Parad, Gandhaka, Manshila* and *Dhattur beeja. Bhavana dravya* of *Unmad Gajkesari Rasa* are *Vacha Kwath* and *Rasna Kwath*.[2] In Vivo and Vitro experimental study reveal Fluoxetine is a highly effective SSRI (Selective Serotonin Reuptake Inhibitors). Despite the availability of newer agents, Fluoxetine hydrochloride is used for antidepression [1]. Depression (*Avasad*) is a *Manas Roga* mentioned in Ayurvedic texts which comes under *Kaphaja Unmad*. The sign and symptoms in patient of *Kaphaja Unmad* can be co-related with Depression. As, described in Ayurveda, *Kaphaja Unmad* patients are dirty in appearance, their speech and activities are retarded and they prefer to remain in solitude and lonely places [3][4][5]. Thus, *Unmad Gajkesari Rasa* (UGR) & Fluoxetine hydrocholride was selected for the study of Depression *(Avasad).*

MATERIALS AND METHODS

Collection and Authentication of Raw Drugs

All raw drugs were procured from authenticated vendor and further authenticated from experts of *Rasashastra* and *Dravyaguna* dept. of our institute.

Pharmaceutical Study

For preparation of UGR *Shuddha Parada* (*Hydrargirum*), *Shuddha Gandhaka* (*Sulphur*), *Shuddha Manahshila* (*Realgar*), *Shuddha Dhattura beeja* (*Dattura metel*) all taken in equal parts and *kajjali* was formed. This *kajjali* was triturated for 7 times with decoction of *Vacha* (*Acorus calamus*) & *Rasna* (*Pluchea lanceolata*) respectively to obtain *Unmad Gajkesari Rasa* (UGR). The details of the procedure are as follow-

1. ***Shodhana* of *Parada*-** *Ashuddha Parada* (*Hydrargirum*) was triturated with *rasona kalka* (Allium sativum) after trituration, *Parad* get divided into small globules. The disintegrated *Parad* globules remained entrapped into the *rasona* paste. On washing the blackish paste with hot water, *Parad* globules started mixing with each other and regained its original state. After *shodhana*, *Parad* was more lustrous silver coloured and shiny. Trituration was carried out for 31 hr. [6]
2. ***Shodhana* of *Gandhaka*-** *Ashuddha gandhaka* (*Sulphur*) and *goghrita* heated in pan; *gandhaka* started melting within 2 min. This molten *Gandhak* was quenched into *godugdha* (Cow milk). This process was carried out for 3 times to have *shuddha gandhaka*.[7]
3. ***Shodhana* of *Manshila*-** *Ashuddha manshila* (*Realgar*) was triturated with *ardrak* (*Zingiber officinale*) swarasa (Juice). suitable amount of *ardrak swaras* was added and triturated till *subhavita lakshan* is observed. This process was carried out for 7 times; then we got *Shuddha manshila*.[8]
4. ***Shodhan* of *Dhattur beeja*-** *Shodhan of Dhattur beeja* (*Dattura metel*) was carried out by *Dola yantra*. *Dhattur beeja pottali* was formed and immersed into *Godugdha*(Cow milk) and heated for *1 yama* (3hr). After *swedana; dhattur seeds* were washed with luke warm water & dried and stored; thus we got *shuddha dhattur seeds*.[9]
5. **Preparation of *Rasna kwatha*-** Rhizomes of *rasna* (*Pluchea lanceolata*) were taken in *khalva yantra* and made into coarse powder. Coarse power of *rasna* 300 g was taken in a steel vessel, 2400 ml of water was added. The vessel was kept for boiling on *mandagni*. Boiled till the water reduced to 1/4th i.e., 600ml. Then the *kwatha* is filtered through the cotton cloth.[10]

6. **Preparation of *Vacha kwatha*-** Rhizomes of *vacha*(*Acorus calamus*) were taken in *khalva yantra* and made into coarse powder. Coarse power of Vacha 300 g was taken in a steel vessel, 2400 ml of water is added. The vessel was kept for boiling on *mandagni*. Boiled till the water reduced to 1/4th i.e., 600ml. Then the *kwatha* was filtered through the cotton cloth.[10]
7. **Preparation of *Unmad Gajkesari Rasa*-** *Shuddha parada* (100 g) and *Shuddha gandhaka* (100 g) taken in equal quantity in *kharal* and *mardana* was carried out till *kajjali* got formed. After that *Shuddha manshila*(100 g) and *shuddha dhattur beeja* (100 g) were added and *mardana* continued till *kajjali* got formed and finally triturated with decoction of *Rasna* & *Vacha* respectively for 7 times. The obtained mixture was dried, weighed and stored as UGR.[2]

Analytical Study

In this study, analytical evaluation of *Unamd Gajkesari Rasa* (UGR) was carried out.

(A) Organoleptic Characters: - The samples were analyzed for the characters like color, taste, touch and odor.

(B) Physico-Chemical Analysis: -
1. Estimation of pH [11]
2. Loss on Drying 105^0C [12]
3. Total ash content [13]
4. Insolubility in water [14]
5. X- Ray Diffraction (XRD) [15]

Ethical clearance

Approval for the experimental protocol was obtained from Institutional Animal Ethical Committee (IAEC) (NVE/IAEC/2019/08) as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. The proposed research work was conducted on rats of Wistar strain, which were procured from the CPCSEA recognized Laboratory.

Experimental Study

Wistar rats of either sex weighing 180g - 220g, excluding the pregnant and unhealthy, were used for the study.

Housing and feeding conditions: The temperature in the experimental animal room was 22°c (+3°c), relative humidity was 30% - 70%. Artificial lighting was given, the sequence being 12 hours light, 12 hours dark. For feeding, laboratory libitum was used with an unlimited supply of drinking water. Animals were group-caged. The animals were purposively selected and marked to permit individual identification, and kept in their cages for at least 10 days prior to dosing to allow for acclimatization to the laboratory conditions.

Experimental sketch of animal model designing

Although developing dose – response relationships in animal model requires hundreds of animals. Wistar rats model of depression induced by chronic unpredictable mild stress (CUMS) [16]. In brief, wistar rats were grouped housed and allowed to adapt to the environment for one week. Then, the wistar rats of the control group were not disturbed in their cages in a separated room throughout the following 42 days, while the rats of the other 3 groups were single housed and subjected to a variety of mild stressors for 42 days

- Food deprivation for 24 hr
- Water deprivation for 24 hr
- Overnight illumination
- Cage tilt (45^0) for 7 hr
- Soiled cage (200ml water in 100 g sawdust bedding)
- Foreign object exposure
- Light/dark perversion
- Overhang (10 min)
- Physical restraint for 3hr
- 1 min tail pinch (1 cm from the beginning of the tail)
- 5 min oscillation
- White noise

To ensure the unpredictability of the experiment, all stressors were performed randomly

Experimental parameters studied:

1. Forced swimming test (FST) [17] The immobility time were recorded as the length of time the mouse floated in the upright position without a struggle and only slight movements were made to keep its head out of the water. The duration of immobility was recorded at least 4 min of the total 6 min, which indicated the depressive state. Experiment performed for 3 times.
2. Tail suspension test (TST) [18] In tail suspension test, hang the rat 25 cm above the ground by the tip of the tail (1cm) tied up to the level. The immobility time was recorded in the test period of 6 minutes (first 1 min for adaptation and remaining 5 min were recorded). It is considered as immobile only when rat hung passively and completely suspended. Rat crawling to the tail was excluded from the experiment data analysis. Experiment was performed for 3 times.
3. Study of depressive Activity using Actophotometer [19] Locomotor activity can easily be measured by using an actophotometer which consists of a cage which is 30 cm long and 30 cm deep with a wire mesh at the bottom. A continuous beam of light from about six lights was made to fall on corresponding photoelectric cells; the photoelectric cell got activated when an animal crossed the beam of light and thereby cuts off the rays of light falling on it. An actophotometer could have circular or square arena in which the animal moves. The mobility time was recorded in the test period of 6 minutes. Experiment was performed for 3 times.
4. Pathological examination of Liver and Kidney Blood sample were collected for pathological examination of Liver and Kidney [Liver Function Test (LFT) and Kidney Function Test (KFT)]. It was carried out for 3 times.

Dose selection

According to *Yogratnakar Samhita* [2], the dose of *Unmad Gajkesari Rasa (UGR)* is *1 Masha* (1g).[20]

Dose fixation [21]

The dose was calculated by extrapolating the human dose to animal based on the body surface area ration by referring to the table of Paget and Barnes.

Conversion formula:

=human dose x 0.018 (conversion factors for rats/200 g)

Test drug *Unmad Gajkesari Rasa*

=human dose x 0.018 (conversion factors for rats)

=1000mgx 0.018

=18 mg /200 g body weight of Rat

Standard drug – Fluoxetine

=Human Dose x 0.018 (conversion factors for rats)

= 60 mg x 0.018

=1.08mg/ 200 g body weight of rat

Dose of Vehicle (Gum Acacia) – 2% in 100ml water

Route of administration: Oral

Table no. 1: Description of various intervention protocols for study groups

Group	Number of Rats	Drug	Purpose
Control group	6	2% Gum acacia	To serve as Control
Standard group	6	Fluoxetine hydrochloride	To serve as Standard
Test group	6	*Unmad Gajkesari Rasa*	To serve as Trial

Experimental parameters studied: Histopathology- The rats were sacrificed at the end of their respective study duration. The liver & kidney were isolated for histopathological alterations.

OBSERVATIONS AND RESULTS

Table no. 2: Pharmaceutical Observations and Results

Sr. No	Name of Procedure	Initial weight (g)	Final Weight (g)	Total amount of Wt. gain/ loss(g)	% Wt. gain/ loss	Observation
1.	*Shodhana* of *Parada*	200 g	187 g	13 (loss)	6.5	*Parad* became more lustrous, silver colored and shiny.
2.	*Shodhana* of *Gandhaka*	500 g	428.78 g	71.22 (loss)	14.24	*Gandhaka* gains an attractive bright yellow colour
3.	*Shodhana* of *Manshila*	300 g	312 g	12 (gain)	4	*Manashila* became reddish bright, *slakshna churna* and smell of *Aadraka* was observed
4.	*Shodhan* of *Dhattur beeja*	200 g	197 g	3 (loss)	1.5	*Dhattura beeja* was black in colour with slight shining
5.	*Preparation* of *Vacha kwatha*	300 g	600 ml	---	----	Pungent odour of *vacha* was observed
6.	*Preparation* of *Rasna kwatha*	300 g	600 ml	----	----	sweetish odour of *rasna* was observed.
7.	Preparation of *Unmad Gajkesari Rasa*	400 g	586 g	186 (gain)	46.5	UGR was changed from Black to slight black green

Table No.3: Testing Ayurvedic parameters of *Unmad Gajkesari Rasa*

Sr. No.	Ayurvedic Parameters	Results	Sr. No.	Modern Parameters-(Organoleptic characters)	Results
1.	*Shabda*	*Nishabda*	1.	Appearance	Greenish Black
2.	*Sparsha*	*Mridu*	2.	Taste	Bitter, Pungent
3.	*Rupa*	*Greenish Black.*	3.	Odour	Characteristic
4.	*Rasa*	*Tikta, Katu*	4.	Touch	Soft
5.	*Gandha*	*Mixed smell of Vacha and Dhattura*			

Table no-4. Testing results of Ayurvedic parameters of *Unmad Gajkesari Rasa*.

Sr. No.	Test Name	Results
1.	Total ash content	4.10%
2.	Loss on drying@105°C	3.61%
3.	pH	5.20
4.	Insolubility in water	77.36%

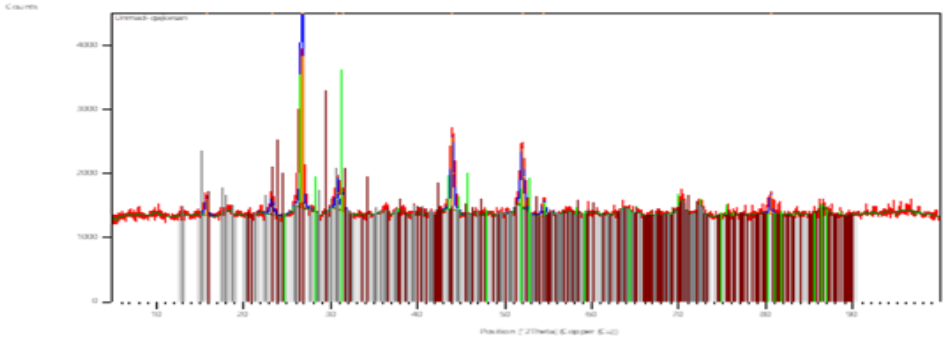

Image no. 1: - XRD study results graphics

Table no -5. Plot of Identified Phases:

Visible	Ref. Code	Score	Compound Name	Displacement [°2Th.]	Scale Factor	Chemical Formula
*	98-007-0054	13	Cinnabar	0.000	0.488	$Hg_1 S_1$
*	98-018-5785	5	Arsenic sulfide (4/4)	0.000	0.225	$As_4 S_4$
*	98-001-0436	2	Arsenic Oxide	0.000	0.422	$As_2 O_4$

Table no-6. Mean value of experimental parameter

Sr. No.	Parameter	Groups	Mean	
			AI	AM
1.	Weight (gm)	Control	232.83	314.67
		Standard	255.00	333.17
		Test	241.67	429.33
2.	Force swimming (Mobile) (sec)	Control	201.3	220.7
		Standard	192.7	231.7
		Test	191.0	258.0

Table no 6 Continued...				
3.	Force swimming (Immobile) (sec)	Control	158.7	139.3
		Standard	167.3	128.3
		Test	169.0	102.0
4.	Tail suspension (Mobile) (sec)	Control	197.0	265.8
		Standard	208.0	300.5
		Test	202.0	330.8
5.	Tail suspension (Immobile) (sec)	Control	159.7	94.2
		Standard	152.0	59.5
		Test	158.0	29.2
6.	Photo Actometer	Control	40.7	55.2
		Standard	42.8	63.2
		Test	41.3	70.0
7.	BUN	Control	22.3	20.7
		Standard	20.3	21.7
		Test	23.7	20.3
8.	Creatinine	Control	0.51	0.54
		Standard	0.58	0.52
		Test	0.57	0.57
9.	Total Bilirubin	Control	0.51	0.54
		Standard	0.58	0.52
		Test	0.57	0.57
10.	SGOT	Control	146.2	137.2
		Standard	146.3	146.0
		Test	136.7	132.5
11.	SGPT	Control	26.3	23.3
		Standard	28.2	27.3
		Test	24.8	21.7

(AI: After induction; AM: After medication)

Table no-7. Overall Effect of Therapy: Statistical analysis (Subjective)

SR NO	PARAMTETER	GROUP	MEAN	SD	F	P	POST-HOC TEST	ANOVA Test
1.	Weight	Control	81.33	32.90	25.73	<0.0001	T > C (P<0.01) T > S (P<0.01)	Significant
		Standard	78.16	26.33				
		Test	187.67	30.46				
2.	Force swimming (Mobile)	Control	19.33	23.30	4.126	0.0374	T > C (P<0.05) T ≈ S (P>0.05)	Insignificant
		Standard	39.00	34.62				
		Test	67.00	27.59				
3.	Force swimming (Immobile)	Control	19.33	23.30	4.126	0.0374	T > C (P<0.05) T ≈ S (P>0.05)	Insignificant
		Standard	39.00	34.62				
		Test	67.00	27.59				
4.	Tail suspension (Mobile)	Control	68.83	20.98	9.699	0.0020	T > C (P<0.01) T > S (P<0.05)	Significant
		Standard	92.50	19.23				
		Test	128.83	29.74				
5.	Tail suspension (Immobile)	Control	68.83	20.98	9.699	0.0020	T > C (P<0.01) T > S (P<0.05)	Significant
		Standard	92.50	19.23				
		Test	128.83	29.74				
6.	Photo Actometer	Control	14.50	5.010	5.292	0.0182	T > C (P<0.05) T ≈ S (P>0.05)	Insignificant
		Standard	20.33	5.241				
		Test	28.67	10.94				
7.	BUN	Control	1.667	3.830	2.133	0.1530	Not applicable	Insignificant
		Standard	-1.333	2.503				
		Test	3.333	5.125				
8.	Creatinine	Control	-0.031	0.064	1.885	0.1861	Not applicable	Insignificant
		Standard	0.058	0.120				
		Test	-0.003	0.037				
9.	Total Bilirubin	Control	0.113	0.193	0.754	0.4870	Not applicable	Insignificant
		Standard	0.038	0.119				
		Test	0.025	0.048				
10.	SGOT	Control	9.000	10.10	1.088	0.3620	Not applicable	Insignificant
		Standard	0.333	14.12				
		Test	4.167	3.251				
11.	SGPT	Control	3.000	4.817	0.4516	0.6450	Not applicable	Insignificant
		Standard	0.833	2.927				
		Test	3.167	5.981				

(>: Significantly effective than; ≈: No significant difference)
(C: Control; S: Standard; T: Test)

Observations of Histopathology-Liver

- Sections of liver from control group (male and female) showed normal

hepatic parenchyma with dilated central vein.

- Sections of liver from standard group male showed congested central vein, granular degenerative changes in the hepatocytes with mononuclear cell infiltration whereas sections of liver from standard group female showed cellular swelling with pyknosis nuclei and granular degenerative changes in the hepatocytes.
- Liver from test group female revealed cellular swelling with moderate sinusoidal dilatation whereas liver from male showed dilated hepatic sinusoids and granular degenerative changes in hepatocytes along with congested central vein.

Kidney

- Sections of kidneys from control group (male and female) exhibited normal histoarchitecture.
- Sections of kidney from standard group male showed moderate tubular degeneration with cast in the lumen of tubules whereas sections of kidney from standard group female showed moderate tubular degeneration.
- Sections of kidneys from test group male revealed moderate degeneration and necrosis of tubular epithelial cells whereas sections of kidneys from test group female revealed mild to moderate degeneration of tubular epithelial cells.

DISCUSSION

In the present study an attempt has been made to evaluate the anti-depressant activity of *Unmada Gajakesari Rasa* & Fluoxetine hydrochloride by studying the animal behavior activity of the drug using forced swim test, tail suspension test, pathological examination (LFT, KFT) & actophotometer and by testing chronic mild stress induced depression in Wistar rats.

Randomly selected 18 rats, weighing 150 g – 200 g, were equally divided into three groups of 6 each. The group I of control was administered 2% gum acacia suspension in rat dose of 2 ml / 200gm body weight, group II of standard group was treated with fluoxetine hydrochloride 1.08mg / 200 g body weight and lastly group III test group was treated with *Unmad gajkesari rasa* of 18 mg/ 200g body weight of rats. All the doses were given orally. Animal's depressive condition was measured from various parameters.

After induction various values obtained through experiment were noted down. It showed significant decrease in their motor activity followed by their mental state condition. After confirming depressive state of rats, medication was started. Receiving medication for duration of 30 days it showed significant results almost achieving normal motor activity where as some rats showed exceptional results in tail suspension test. During study it was observed that female wistar rats are more affected that male wistar rats. During study weight of rats was measured for specific duration. It showed that after medication, rats weight was significantly raised specially test group's rats showed better results than standard and control group's rats. Because of *katu, tikta rasa* and *Ushnavirya* of UGR *jatharaagni diapan* occurred that's why increase in weight of test group rats was observed. Pathological investigation carried out during study did not show any significant changes. After end of study, 1 male & 1 female rat were sacrificed from each group. Kidney and liver organ were collected for histopathological examination.

In histopathological study control group rats showed normal hepatic and renal structure. Test group rats showed granular degenerative changes in hepatocytes & moderate degeneration of tubular epithelial cells of kidney. Standard group rats showed cellular swelling with pyknosis nuclei and granular degenerative changes in the hepatocytes & moderate tubular degeneration in kidney.

During this study it was observed that female rats are more affected by mental stress. Histopathological examination also

revealed that degenerative changes are more in female rats as compared to male rats.

CONCLUSION

1. After induction various value obtained through experiment was noted down. It showed significant decrease in their motor's activity followed by their mental state condition. During study it was observed that female wistar rats are more affected than male wistar rats.
2. Rat's weight significantly raised, test groups rats show better results than standard and control groups rats.
3. Forced swim test duration significantly raised, test groups rats show better results than control groups but does not show better results than standard groups rats.
4. Motor activity of rats in tail suspension test showed duration significantly raised. Test groups rats show better results than standard and control groups rats.
5. Photo actometer duration significantly raised, test groups rats shows better results than control groups but does not show better results than standard groups rats.
6. Hepato-toxic effect and Nephrotoxicity seen promiently in standard group rats as comapared to test group and control group. Degenerative changes are more in female rats as comapred to male rats.
7. The result of the *Unmad gajkesari rasa* suggested that it had a significant antidepressant activity as compared to Fluoxetine hydrochloride.

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