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EVALUATION OF MULTITARGETED ANTIPSYCHOTIC ACTIVITY OF UNMADGAJAKESARI - A HERBOMINERAL FORMULATION - AN ANIMAL EXPERIMENTAL STUDY

Rajeeta Joseph [*1], V. Pandit [2], A. Wele [3], G. Deshmane [1] and M. Pawar [3]

Department of Pharmacology [1], Bharati Vidyapeeth Dental College and Hospital, Katraj, Pune - 411043, Maharashtra, India.
Department of Pharmacology [2], Bharati Vidyapeeth Medical College, Katraj, Pune - 411043, Maharashtra India.
Department of Rasashastra [3], Bharati Vidyapeeth College of Ayurveda Katraj, Pune - 411043, Maharashtra India.

Keywords:

Unmadgajakesari, Antipsychotic, Antidopaminergic, Antiserotonergic, NMDA

Correspondence to Author:
Rajeeta Joseph

Department of Pharmacology, Bharati Vidyapeeth Dental College and Hospital, Katraj, Pune - 411043, Maharashtra, India.

E-mail: rajeetajoseph@gmail.com

ABSTRACT: Schizophrenia is a chronic and complex mental disorder characterized by hallucinations and delusions that significantly affect emotions, behavior, and mental processes. Currently used antipsychotics are characterized by the multireceptor mode of action (antagonism of dopamine D_2 and serotonin receptors), there is no consensus regarding an "ideal" target engagement. Moreover, they are associated with adverse effects. Presently the focus is on the search for safe and efficacious drugs from the traditional system of medicine. In the present study, an attempt has been made to evaluate the multitarget antipsychotic activity of Unmadgajakesari - A herbomineral formulation in animal models. *Unmadgajakesari* (*UGK*) was evaluated for its effect on dopaminergic, serotonergic and NMDA activity in the following animal models: Inhibition of apomorphine-induced climbing in mice (dopamine), Inhibition of 5-HTP induced head twitches in mice (serotonin), Antagonism of MK-801induced hyperlocomotion (NMDA) in mice. For studying each neurotransmitter, animals were divided into 6 groups, each group comprising of 6 animals. Group I - Normal control, Group II - Vehicle control (ghrita), Group III - Drug control (positive control). In test groups (IV-VI), UGK was administered in doses 100 mg/kg, 200 mg/kg and 400 mg/kg in mice. All the drugs were given orally for 8 days. Readings were taken on day 1 and 8. On day 1, UGK exhibited significant antidopaminergic, antiserotonergic, and NMDA enhancing activity. However, on day 8 antidopaminergic and NMDA activity was reduced, whereas antiserotonergic activity continued. The activity profile of UGK changes from day 1 to day 8. UGK was found to be most effective in low dose.

INTRODUCTION: Schizophrenia is a chronic and complex mental disorder characterized by symptoms including delusions, hallucinations, disorganized speech or behavior, and impaired cognitive ability [1].

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Though the exact etiology of schizophrenia is unknown, experts believe it to be resulting from a complicated interplay of environmental, biologic, psychological, cultural and genetic factors [2] with multiple biochemical abnormalities involving the dopaminergic, serotonergic, glutamate, γ-amino-butyric acid (GABA), cholinergic, adrenergic systems and neuropeptides [3].

Antipsychotic medications are the mainstay for the treatment of schizophrenia. “Typical” anti-psychotics, antagonize dopamine at D_2 receptors and are effective in treating positive symptoms but

are ineffective in treating negative or cognitive symptoms associated with schizophrenia [4]. Adverse effects associated with them include debilitating extrapyramidal symptoms (tardive dyskinesia), hyperprolactinemia, and cognitive deficits, thus reducing their therapeutic benefits [5]. The antipsychotic effects of atypical neuroleptics are attributed to a combination of 5-HT_2 and D_2 receptor blockade [6]. Although they have a lower risk of extrapyramidal symptoms, they provide a broad range of efficacy of relieving both positive and negative symptoms, but do not improve cognitive dysfunctions.

Moreover, their use is associated with weight gain, metabolic syndrome (glucose dysregulation and dyslipidemia) and cardiovascular adverse effects [5]. Both typical and atypical antipsychotic drugs can lower the seizure threshold, thus increasing the chances of seizure induction [7]. A new generation of atypical antipsychotics (''dopamine stabilizers'') such as aripiprazole, acts on different receptors (partial agonist at D2 and 5-HT1A, but antagonist at 5-HT2A) and offers an advantage in treating negative symptoms with decreased incidence and severity of central and peripheral side effects [8].

Currently used antipsychotics are characterized by multireceptor mode of action (antagonism of dopamine D_2 and serotonin receptors), there is no consensus regarding an "ideal" target engagement. These medications are largely addressed towards the treatment of positive symptoms; the challenge lies in identifying compounds showing clinically significant improvements in the treatment of negative symptoms and cognitive dysfunction. Also, a major issue with many of the antipsychotic drugs remains side-effect liabilities. Hence, to improve these liabilities, novel drug treatment targets beyond the dopamine hypothesis, which includes serotonin, glutamate, acetylcholine, GABA neurotransmitters [9, 10]. Although GABAergic drugs (gabapentin, oxcarbazepine, valproate, topiramate, vigabatrin) present a promise in the treatment of schizophrenia, they are used as adjuncts to antipsychotic drugs [11]. This has provoked the interest in the search for drugs, especially those belonging to the traditional system of medicine like Ayurveda. Ancient Ayurveda text gives a detailed description of mental disorders known as 'unmada,' and schizophrenia can be correlated to it [12]. *Unmadgajakesari* (*UGK)* is a herbo-mineral formulation especially recommended in the treatment of 'schizophrenia (*Unmad*) and epilepsy (*Apasmar*) [13]. It is commonly used in Indian Ayurvedic practice for the treatment of psychosis, mania, schizophrenia, MDP and epilepsy, and administered along with ghee/ghrita (clarified butter) [14]. In modern medicine, there is no single drug addressing to both, *i.e.* psychosis and epilepsy effectively together. It is interesting to note that UGK as a single formulation can be used for treating both, *i.e.* psychosis and epilepsy [13]. Rajeeta *et al.,* have reported the antiepileptic activity of UGK in PTZ and MES animal models [15]. Scientific evidence as regards to the antipsychotic activity of UGK is lacking; hence, the present study was designed to evaluate the same and to understand the rational basis for its formulation contributing towards its effects. Amongst the 8 different methods of preparation of UGK mentioned in Ayurvedic literature [16], the commonly used UGK preparation from the text "Rasa Chandanshu (Unmad chikitsa /180-182)" was selected for our study.

MATERIALS AND METHODS:

Drugs: Apomorphine hydrochloride, 5-HTP, MK-801(Dizocilpine maleate) and PTZ were purchased from Sigma- Aldrich, USA. Haloperidol injection (Serenace, RPG Life Sciences, India), Olanzapine (OPINEX-10, Psychoremedies, Ludhiana) Sodium valproate (Sun Pharma Laboratories Ltd, Mumbai) and Water for injection (WFI) were purchased from a local pharmacy. All drugs were dissolved in WFI.

Preparation of UGK: UGK was prepared using the following ingredients:

Minerals: *Mercury (parad), sulfur (gandha)* and r*ealgar* (*manahshila*)

Herbs: *Dhatura.innoxia (Dhatura), Acorus calamus (Vacha), Sesbania grandiflora (Agasti)* and *Bacopa monnieri (Brahmi)*

Mercury (Merck, USA), sulfur and realgar were identified and authenticated from the Department of Geology, University of Pune, Pune, India. For all the herbs, voucher specimen was deposited for authentication at Agharkar Research Institute, Pune, India and voucher number allowed, *i.e. Dhatura innoxia* (voucher no. S-138), *Acorus*

calamus (voucher no. R-140), *Sesbania. grandiflora* (voucher no. L-056) and *Bacopa monnieri* (voucher no. WP-92). They were further standardized and passed for quality control criteria following the standard procedures of Ayurvedic Pharmacopoeia of India (API) [17], by the department of Rasabhajshajya Kalpana, Bharati Vidyapeeth College of Ayurveda, Pune, India.

UGK was prepared according to the Ayurveda text reference *Rasa Chandanshu* - chapter 13 titled *Unmad Chikitsa* [13] using wet trituration method and tested with physicochemical and organoleptic tests for quality control by the department of Rasabhajshajya Kalpana, Bharati Vidyapeeth College of Ayurveda, Pune, India. It was administered orally along with ghrita (vehicle) to the animals [18].

Animals: Experimental protocols and procedures were approved by the Institutional Animal Ethics Committee, and were by guidelines of the Committee for Control and Supervision of Experimental Animals (CPCSEA), New Delhi, India (ref no. BVDUMC/1084/2011-12). Swiss Albino mice of either sex from our breeding stock were used in this study. They were in the house at the institute animal house in groups of six animals per cage at standard laboratory conditions at a temperature of 24 ºC ± 1 ºC, the relative humidity of 45-55% and 12:12 h dark and light cycle. Animals were given standard pelleted laboratory animal diet and water *ad libitum*. The experiments were conducted between 10.00 to 17.30 h in a semi-soundproof laboratory.

Acute Toxicity Studies: Acute toxicity study was carried out according to the Organization of Economic Co-operative and Development (OECD) guideline 423. 15 healthy female Wistar albino rats of 10-12 weeks old, weighing 150 gm ± 20 gm were divided into 5 groups, each group comprising of 3 rats. All the animals were fasted overnight but allowed water *ad libitum* before administration of the test drug (UGK). Before dosing the animals, their weight was noted. UGK was administered orally along with 0.1 ml of ghrita (vehicle) with the help of a spatula. Dosing was started with a single dose of 100 mg/kg in group I. 48 h later, when no mortality of animals was noted in this group, the dose was increased to single dose of 300 mg/kg in group II, 1000 mg/kg in group III and 2000 mg/kg in group IV with 48 h interval in between dosing in different groups. Group V served as the vehicle control group and was administered ghrita (0.1 ml). After dosing food was withheld for 3 h in all the groups. Animals were observed individually after dosing at least once during the first 30 min, periodically during the first 24 h, with special attention given during the first 4 h, and daily after that for a total of 14 days for any signs of toxicity [19]. The therapeutic dose of UGK in humans is 750 mg [13]. This dose was extrapolated to animal dose [20] and considered as X-dose. Following doses were then selected for the study: X dose = 100 mg/kg, 2X dose = 200 mg/kg and 4X dose = 400 mg/kg body weight. Since antipsychotic drugs have been reported to take up to three weeks to achieve their maximal therapeutic effects [21], UGK was administered daily for 8 days and assessed for its immediate activity on day 1 and delayed activity on day 8.

Methods:

Apomorphine-Induced Climbing Behavior in Mice: This model is widely used for selecting compounds interacting with dopaminergic neurotransmission *in-vivo* [22]. The method of Chung et al. was followed with minor modifications. Each mouse was placed in a cylindrical wire mesh cage (height 13 cm, diameter 14 cm and mesh size 3 mm) 1 h before experimentation to adjust to the new environment. Animals (36) were divided into six groups (n=6).

Group-I received DW (0.1 ml, p.o.); Group-II received ghrita (0.1 ml, p.o.); Group III received haloperidol (1.5mg/kg, p.o.) while Group IV-VI received UGK (100 mg/kg, 200 mg/kg and 400 mg/kg) respectively along with ghrita (0.1ml, p.o.) as vehicle, 1 h prior to administration of apomorphine (1.5 mg/kg, s.c.). After 10 min of apomorphine injection, climbing behavior was assessed visually at 10 min intervals for a period of 3 min (3 times). The scoring system was as follows: 0 = no paws on the cage, 1 = two paws on the cage, 2 = four paws on the cage. The score recorded for each animal was based on the position of the animal at the moment it was first observed [23]. The observations were recorded as mean of the total climbing score.

5-HTP Induced Head Twitches in Mice: This model was selected to assess the antiserotonergic activity of UGK. Animals (36) were divided into six groups (n=6). Group-I received DW(0.1 ml, p.o.); Group-II received ghrita (0.1 ml, p.o.); Group-III received olanzapine (1 mg/kg, p.o.) while Group IV-VI received UGK (100 mg/kg, 200 mg/kg and 400 mg/kg) respectively along with ghrita (0.1 ml, p.o.) as vehicle, 1 h prior to administration of 5-HTP (100 mg/kg, i.p.). Animals were placed in a transparent plastic cage for observing head twitches. 5 min after administration of 5-HTP, the number of head twitches was counted for 15 min. The observations were recorded as the mean of the total head twitches [24].

MK-801 Induced Hyperlocomotion in Mice: Locomotor activity (ambulations) was measured by using computerized actophotometer. An array of 16 infrared emitter/detector pairs measured the animal activity along the single axis of motion, the digital data being displayed on the front panel meters as ambulatory movements. Mice were allowed to acclimatize for 5 min. Basal locomotor activity score was obtained after which the animals were administered respective drugs as per groups. Animals (36) were divided into six groups (n=6). Group-I received DW (0.1 ml, p.o.); Group-II received ghrita (0.1 ml, p.o.); Group-III received haloperidol (1.5 mg/kg, p.o.) while Group IV-VI received UGK (100 mg/kg, 200 mg/kg and 400 mg/kg) respectively, along with ghrita (0.1 ml, p.o.) as vehicle. 1 h later, animals were injected with MK-801 (0.5 mg/kg, i.p.) and placed again in the actophotometer for recording the locomotor activity score. The activity was measured at every 30, 60 and 90 min for 10 min. The locomotion was expressed in terms of total photobeam interruption counts per 10 min. The observations were recorded as mean change in the locomotor activity [23, 25].

Statistical Analysis: The data were analyzed by one-way analysis of variance (ANOVA) followed by Dunnet's test and presented as mean ± SEM. The significance was set at $p<0.05$. Statistical analysis was done with Graph Pad Prism 5 software.

RESULTS:

Acute Toxicity Studies: UGK was found to be safe up to up to 2000 mg/kg dose. However, reduced locomotory activity was observed in all the animals at all the doses for a few hours, which disappeared completely within 24 h of administration of UGK. No other behavioral signs of toxicity were exhibited by the animals. There was no significant change in body weight of the animals when compared to control during 14 days of observation. Gross and pathological examinations revealed no pathological abnormalities in organs such as liver, spleen, kidneys, heart, lungs, brain, and sex organs. The dose that was selected for the study in animals was 100 mg/kg, 200 mg/kg, and 400 mg/kg body weight.

Apomorphine Induced Climbing in Mice: Haloperidol (positive control) significantly ($p<0.001$) inhibited apomorphine-induced climbing behavior on day 1 and day 8 when compared to control, ghrita (vehicle) and all the test groups. UGK (100 mg/kg, 200 mg/kg and 400 mg/kg) showed significant ($p<0.05$) reduction in average time spent in climbing when compared with control and ghrita (vehicle) group on day 1. However, no significant effect was observed at any of the test doses on day 8 **Fig. 1**.

5-HTP Induced Head Twitches in Mice: Olanzapine (positive control) significantly decreased ($p<0.001$) the number of head twitches on day 1 and 8 when compared to control and ghrita (vehicle) group. On day 1 observation, the number of head twitches was significantly decreased ($p<0.001$) by UGK at doses 100 mg/kg and 200 mg/kg when compared to control and ghrita (vehicle) group. On day 8, UGK 100 mg/kg reduced head twitches significantly whereas 200 and 400 mg/kg dose produced non-significant effects **Fig. 2**.

MK-801 Induced Hyperlocomotion in Mice: Haloperidol (positive control) inhibited the stimulatory locomotor effects induced by MK-801 significantly ($p<0.001$) on day 1 and day 8 when compared to all the groups. On day 1, *UGK* in doses 100 mg/kg and 200 mg/kg inhibited stimulatory locomotor effects significantly ($p<0.001$) when compared to control and ghrita (vehicle) group. However, UGK in all doses was ineffective in reducing these hyperlocomotor effects on day 8 **Fig. 3**.

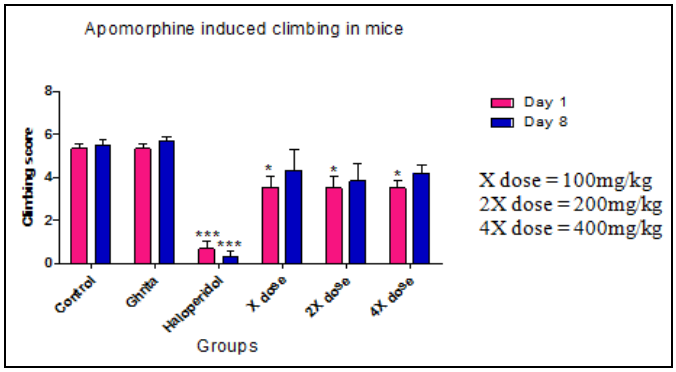

FIG. 1: INHIBITION OF APOMORPHINE INDUCED CLIMBING IN MICE. Effect of UGK in apomorphine induced climbing behavior in mice. Each column represents mean ± SEM of total climbing score (*n*=6). At *p<0.05, ***p<0.001 when compared to control and ghrita (vehicle control).

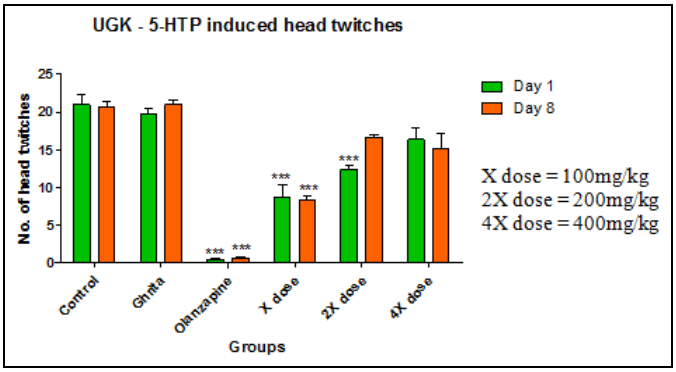

FIG. 2: INHIBITION OF 5-HTP INDUCED HEAD TWITCHES IN MICE. Effect of UGK in 5-HTP induced head twitches in mice. Each column represents mean ± SEM of number of head twitches (*n*=6). At ***P<0.001 when compared to control and ghrita (vehicle control).

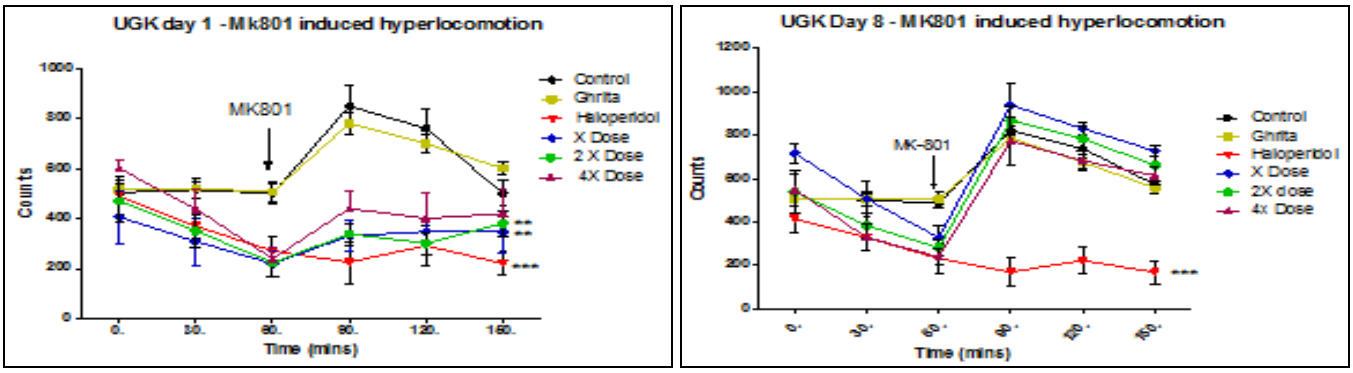

FIG. 3: INHIBITION OF MK-801 INDUCED HYPERLOCOMOTION IN MICE

X dose = 100 mg/kg, 2X dose = 200 mg/kg, 4X dose = 400 mg/kg

Effect of UGK in MK-801 induced hyperlocomotion in mice. Each point represents the mean ± SEM of number of light beam interruption (*n*=6). At ***p<0.001, **p<0.01 when compared with control and ghrita (vehicle control).

DISCUSSION: Current drug treatments for schizophrenia are limited by poor efficacy and tolerability. Combining antipsychotics / adding adjuncts to antipsychotics have also yielded in disappointing results [26]. Hence, the need for search into drugs belonging to the traditional system of medicine like Ayurveda, which has a well defined conceptual framework and considered as ancient forms of system-biology-based medicine [27]. Medicinal plants contain mixtures of different chemical compounds that may act immediately, additively or in synergy to produce certain therapeutic action and eliminate/reduce unwanted side effects [28]. Addition of minerals to herbs produces improvement in efficacy by synergistic action and targeted delivery of the formulation [29, 30]. *Unmadgajakesari (*UGK*)*, herbs-mineral formulation, which is recommended in the treatment of psychosis and epilepsy in Ayurveda [13], was selected for our study. The mechanism of every effective antipsychotic medication in schizophrenia involves dopamine and its interaction with other neurochemical pathways such as those of serotonin, glutamate, GABA, and other neuropeptides [31]. Hence, UGK was evaluated for its antipsychotic activities based on the neurotransmitters which are known/hypothesized to have relation to psychosis in animal models.

The dopamine hypothesis of schizophrenia proposes hyperactive dopamine transmission in the mesolimbic areas to be the underlying cause of psychotic disorder [31]. Apomorphine is a mixed D_1/D_2 agonist. Administration of apomorphine to mice results in a peculiar climbing behavior characterized initially by rearing and then spontaneous climbing activity. Mice injected with low doses of apomorphine tend to adopt a vertical position and try to climb walls of cylindrical wire mesh, [13] which were observed in our study. Antagonism of apomorphine-induced climbing behavior in the mouse has been correlated with antipsychotic activity [32], suggestive of either/both the D_1 and D_2 receptor blockade [33].

In our present study, *UGK* exhibited significant antidopaminergic activity on day 1 and non-significantly on day 8. The ability of UGK to antagonize apomorphine-induced climbing behavior supports the hypotheses of central activity related to anti-dopaminergic actions on the limbic system [34]. Acute administration of antipsychotics exerts their therapeutic benefit by blocking dopamine receptors and increase in the number of dopamine neurons firing which is consistent with the dopaminergic nature of psychosis suggesting the rapid response of schizophrenia.

However, after 3+ weeks of treatment, dopamine neurons undergo depolarization block and decrease the number of firing spontaneously thus explaining its delayed appearance of maximal effects [35]. UGK by exhibiting antidopaminergic activity on day 1 may thus be useful in acute psychosis, but its effect on prolonged administration further needs to be studied to observe for its maximal antipsychotic activity. Hollerman *et al*., have demonstrated the reversal of depolarization block produced following 21 days of antipsychotic administration in rats, by administering apomorphine [36]. Similar was our observation on day 8, as UGK did not exhibit antidopaminergic activity on the administration of apomorphine.

Evidence suggests 5-HT2 blockade contributing to the therapeutic efficacy of atypical antipsychotics [2]. Hence the antiserotonergic activity of UGK was assessed in 5-HTP induced head twitches in mice model. 5-Hydroxytryptamine (5-HT) receptor agonists induce a characteristic head-twitch response. This effect provides a model for the study of central 5-HT receptor activation due to activation of 5-HT2 receptors [37]. Injection of 5-HTP in mice induces head twitches, which were observed in our study. Antagonism of 5-HTP induced head twitches in mice indicates anti-serotonergic activity. In our study UGK at lower doses (100 mg/kg and 200 mg/kg) significantly reduced the number of head twitches on day 1, however, on day 8, this effect was observed at dose 100 mg/kg. Thus a low dose of UGK produced sustained antiserotonergic activity *i.e.* on day 1 and day 8, suggesting its central 5-HT2 antagonistic activity. Antagonism of 5-HT2A receptors have also been associated with efficiency against negative symptoms of psychotic disorders and decreased frequency to cause extrapyramidal symptoms [38]. In our study, EPS was not observed even at a higher dose. UGK not only exhibited its antipsychotic potential, but it may prove to be useful in addressing negative symptoms as well. Further studies need to be taken up for exploring the same.

The NMDA receptor hypofunction hypothesis of schizophrenia has recently been suggested as an alternative/additional neurochemical model of schizophrenia [39]. NMDA receptor antagonists produce behavioral effects *via* disinhibition of glutamate, mesolimbic dopamine release, and reduced GABAergic inhibition, thus supporting positive, negative, and cognitive symptoms of schizophrenia [40]. Drugs targeting glutamatergic transmission might help to normalize these deficits. Hence UGK was assessed for its NMDA activity in MK-801 induced hyperlocomotion in mice model. MK-801 (dizocilpine) is a non-competitive antagonist of the NMDA receptor in the glutamate and has been designated a PCP-type drug. Administration of MK-801 in mice induces hyperlocomotion related to interactions between glutamatergic and dopaminergic neurotransmission also suggesting serotonin involvement. Antipsychotic agents antagonize this MK-801 induced hyperlocomotion [41, 42].

In our study, MK-801 exerted stimulatory locomotion in mice. Haloperidol inhibited these effects suggesting the role of dopamine in hyperlocomotor behavior. UGK in low (doses 100 mg/kg and 200 mg/kg) inhibited stimulatory locomotor effects on day 1, but not on day 8 at any of the doses. UGK thus exhibited antipsychotic activity by enhancing NMDA receptor function and reducing dopaminergic hyperactivity. But its activity could also be attributed to its direct antidopaminergic and antiserotonergic activity as seen in the above results. The activity of UGK as an NMDA agonist remains questionable as it may act indirectly affecting glutamatergic neurotransmission.

Data from animal and postmortem studies suggest that schizophrenia is associated with brain GABAergic dysfunction, as gamma-aminobutyric acid (GABA) signaling interacts very closely with glutamatergic and dopaminergic neurons. Post-

mortem studies have found differences in GABA receptor subunit expression and reduced GABAergic cell types in the brains of patients of schizophrenia [43]. A novel positive allosteric modulator of the alpha-5 subunit of GABA-A receptors has shown to reduce hyperactive locomotor response and spontaneously active VTA dopamine neurons, suggesting that normalization of hippocampal GABAergic function to be a valid approach to antipsychotic drug development [39]. There is no drug-induced animal model *via* the application of GABA antagonists to induce psychosis [44]. To assess GABAergic activity of UGK it is reasonable that GABA receptor antagonist be tested. Our previous study has reported the antiepileptic activity of UGK attributing to its GABAergic mechanism. UGK antagonized the effects of PTZ, but the maximum effect was observed on day 8, at a low dose (70 mg/kg in rats). Thus UGK possesses GABAergic potential but requires prolonged administration (8 days) to produce significant effects [15].

The above findings from our studies suggest that UGK possesses a multitude of actions by modulating various neurotransmitters but at different period **Fig. 4**.

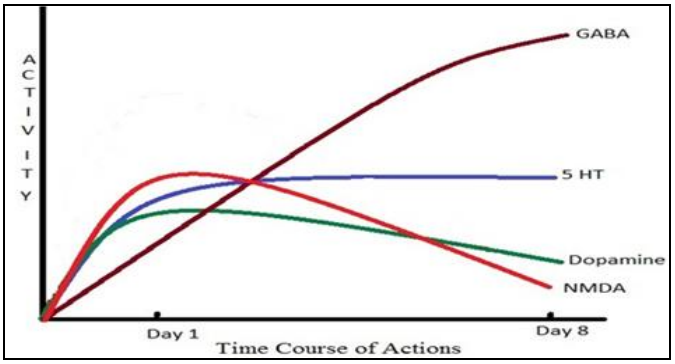

FIG. 4: TIME COURSE OF ACTIONS OF UGK

As seen in the above figure activity profile of UGK changes from day 1 to day 8. Antidopaminergic and antiserotonergic activity are maximum initially on day 1, and GABA activity is seen to develop on day 8. NMDA enhancing and antidopaminergic activity is reduced by the 8th day, whereas antiserotonergic activity is maintained throughout. All these effects occur at a low dose, which is used clinically. Dopamine and serotonin are the main neurotransmitters involved in the acute manifestation of psychosis; apparently it is observed that UGK can maintain significant antidopaminergic and antiserotonergic activity initially and GABAergic activity later. UGK by its GABAergic action probably may regulate glutamatergic transmission and effectively control psychosis. It is rational to presume that UGK may contribute to its anti-psychotic action by enhancing the GABAergic system. Further studies are required to assess the delayed activities of UGK on dopamine and to establish the relevance of GABA-based pharmaco-logical models of schizophrenia.

Major neurotransmitters such as dopamine, serotonin, acetylcholine and noradrenaline are all known to regulate seizure activity [45]. GABAergic activity of UGK may also help to reduce the epileptogenic effect of these neurotransmitters. Rather UGK possesses antiepileptic actions [15] and is used clinically as an antiepileptic agent [13, 14]. Thus, the above activity profile elucidates us the reason why UGK against all available antipsychotic drugs, is useful not only in psychosis but also in epilepsy.

Ayurvedic formulations often complex with several herbal-mineral ingredients are governed by well-described pharmacological principles of preparation, compatibility, and administration Ayurvedic formulations often complex with several herbal-mineral ingredients are governed by well-described pharmacological principles of preparation, compatibility and administration [46]. Drug combinations are envisaged to serve synergistic actions, combined actions, toxicity neutralization actions, and specific actions [47]. Looking at the above results, the designing of UGK formulation for the treatment of psychosis as given in Ayurveda seems to be rational and effective. *Kajjali* (mercuric sulfide) owns properties as catalyst (*yogavahi*) which helps in carrying other drugs to CNS and enhance the efficacy and potency of the formulation [48], *Realgar* (*manashila*) acts as CNS depressant by potentiating the activity of GABA [49], *Datura innoxia* contains atropine and scopolamine which is anticholinergic besides scopolamine being sedative [50], *A. calamus* is reported to exert neuromodulatory effects on nigro-striatal dopaminergic system [51]. *Acorus, Sesbania*, and *Brahmi* are all reported to have GABAergic actions along with antioxidant and neuroprotective activity [52-54]. The choice of vehicle for administering UGK is justified as ghrita being

lipoidal helps to assimilate the properties of drugs and reach it to the brain. Its antioxidant property offers neuro-protection and normalizes the chemical changes in the brain by balancing the neurotransmitters [55].

Drugs targeting enhancement of NMDA receptor [56] and GABA [39] are now a novel approach to the treatment of schizophrenia. Current evidence supports their use as adjunctive agents in individuals failing to respond to antipsychotic drugs. UGK thus appears to be a novel single formulation exhibiting a combination of anti-dopaminergic, antiserotonergic, NMDA enhancing, and GABAergic activity. These activities may not only contribute to its antipsychotic actions but may likely address negative and cognitive domains as well. Further studies need to be carried out to assess its potential for the same. Selection of minerals and herbs with the method of processing in traditionally validated method attribute to increasing in bioavailability, improving therapeutic properties of each other and balancing the excitatory and inhibitory neurotransmitters in CNS. The combination of mineral with herbs seems rational. Antioxidant effects of herbs further add to its effects. This formulation acts best in clinically prescribed dose, *i.e*. low dose.

CONCLUSION: Multi-receptor agents appear to be more promising as antipsychotic agents because of interactions between neural circuits employing multiple neurotransmitters. *Unmadgajakesari* appears to be a novel drug exhibiting multireceptor profile by modulating various neurotransmitters at different period. Considering the gaps in the understanding of schizophrenia and the complexity of its neurochemical basis, this study explores the value of traditional medicinal systems in unveiling the actions of UGK. This study also supports the claim in Ayurveda of UGK being useful in the treatment of psychosis at the clinically mentioned dose as mentioned in *Unmad chikitsa*.

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CONFLICT OF INTEREST: No

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