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Comparison of the antidepressant like activity of homeopathic remedies (*Argentum nitricum, Staphysagria* and *Ignatia amara)* and their effect on the behavior of rodents

Humaira Anser[1]*, Rahila Ikram[2], Humera Khatoon[4], Sadaf Naeem[1], Saira Saeed Khan[2], Urooj Nazim[3], Shahlla Imam[1], Yusra Shafiq[1] and Sumaira Ishaque[1]

[1]Institute of Pharmaceutical Sciences, Jinnah Sindh Medical University, Karachi, Pakistan
[2]Department of Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan
[3]Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi
[4]Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan

Abstract: The majority of the world population suffers from mental and behavioral disorder. It is the need of the time to find an alternate of presently available medicines in order to decrease the medical expense. Homeopathic remedies are available and prescribed by homeopaths for treatment of anxiety and depression. Unfortunately, no data are available that proves its potential to relieve mental illness. The current study is designed to assess neuro behavioral and antidepressant like effects of homeopathic remedies *Staphysagria, Argentum nitricum and Ignatia amara* in comparison with standard drug (escitalopram). Different neuro behavioral activities were analyzed. The animals were administered the doses of all homeopathic remedied (60 µl to the rats) and escitalopram (0.042 mg to rats) through the oral route. The activities were observed on day 30th and day 60th. Our result suggests that the swimming time in *Staphysagria* treated group were significantly improved ($p<0.001$) after day 60th and significance rise was observed ($p<0.01$) in *Ignatia amara* treated animals, whereas significant decline ($p<0.05$) in struggling time was observed in *Argentum nitricum* administered animals after the 60th day as compared to 30th day. The central square crossings were improved highly significantly ($p<0.001$) after the 30th day dosing, by all three remedies and peripheral squares crossing were found highly significantly increased ($p<0.001$) after chronic dosing in *Staphysagria* and *Ignatia amara* treated groups. It is concluded from the results that all three homeopathic remedies produce comparable effects like standard drug while among all three remedies *Staphysagria* possess a potent antidepressant activity. To the best of our knowledge the current study reports first time the anti-depressant potential of homeopathic remedies in rodents.

Keywords: *Argentum nitricum, Staphysagria, Ignatia amara,* antidepressant, homeopathic remedy.

INTRODUCTION

The majority of the world population suffers from mental and behavioral disorders (such as depression and anxiety). Although allopathic medicines are available in the market, but still doesn't produce complete cure. Many people who are diagnosed with anxiety, will develop depression later in their life, and considered as a two sides of a single coin. Depression is one of the most common psychotic disorders and is life threatening also. Normal daily living activities are also affected in individuals with depression. It is considered the fourth most commonly occurring disease in the world. (Lotfaliany *et al*., 2018) A depressed person experiences sadness, decreased interest, loneliness and poor quality of life with comorbid sufferings like cardiovascular, neuropsychiatric illnesses (Levinson, 2006; Murray, 1997). The majority of the population affected by depression are women. The major anatomical site for anxiety and depression is hippocampus, which was confirmed by imaging studies. Images showed size reduction in hippocampus and amygdala in patients with depression and anxiety (McEwen, 1998; Irle *et al*., 2010). Sheline *et al* (1996) reported that this hypotrophy reveals the time duration of major depression. Depression may be caused by use of drugs for example, alcohol, anxiolytics, antiviral drugs, etc. It may occur due to gene mutation, stress, hormonal imbalances, and due to deficiency of vitamin B_{12}, B_6 and other dietary deficiencies (Ford *et al*., 2008).

Several conventional medicines are available for the treatment of depression, for example Selective Serotonin Reuptake Inhibitor's, Selective Norepinephrine Reuptake Inhibitor's, MonoAmine Oxidase Inhibitor's, Tricyclic Antidepressant's, etc., but these drugs are not capable of providing a complete relief from depression. A large number of population in the world is using homeopathic remedies as an alternative medicine, which have potential for the treating depression. However, in order to get long-term constant results it is strongly recommended to individualize these remedies to each patient and prescribe accordingly. Adler *et al* (2011) found a homeopathic remedy safer and equally effective as fluoxetine when prescribed as personalized treatment in patients with moderate to major affective disorder. Gelabert, (2017) discovered that 60 % of patients diagnosed with panic

**Corresponding author:* e-mail: humera124@gmail.com

disorder, phobias and major depression showed improvement in behavior with such homeopathic remedies. *Staphysagria*, *Argentum nitricum and Ignatia amara* are used as classical remedies in complementary medicine for treatment of depression and anxiety-like symptoms among patients (Pilkington *et al*., 2006).

Staphysagria is isolated from *the Delphinium staphysagria plant*, belongs to family Renunculaceae and specie delphinium (larkspur). The plant possesses potent emetic and cathartic properties and also stated as a vermifuge (Maud grieve, 1931). Staphysagroine, staphysagrine, delphinine, delphisine and delphinoidine are the key alkaloids found as its chief constituent. *Staphysagria* is used as a homeopathic remedy for treatments of various disorders and classified as an anti-parasitic, anti-psoriatic, effective against syphilis, anti-cancer, anti epileptic, anti-eczematic, anxiolytic, anti-psychotic and also beneficial for dental caries (Anshutz, 1910; Jurj, 2002, Cialdella *et al*., 2001)

The source of *Argentum nitricum* is a mineral (Silver nitrate, $AgNO_3$). It showed its therapeutic activity in conditions like apprehensions, neuralgic pain, vertigo with trembling that ends up with vomiting. It is reported to possess anti-nociceptive activity in abdominal ache, trigeminal pain, hemicrania or pain in the chest because of cardiac ischemia (Anser and Najam, 2015). *Argentum nitricum* is an imperative therapy for generalized anxiety disorders, agoraphobia, panic attacks, and social fear (Pilkington *et al*., 2006).

Ignatia amara is obtained from *Strychnos Ignatii*, belongs to the family Loganiaceae. Brucine, bassorin and strychnine are major alkaloids found along with fixed oil, gum and resin as major constituents (Maud Grieve, 1931) it is used as an energizer and a stimulant. In homeopathy, it is used in the treatment of problems linked with stress (Marzotto *et al*., 2012)

Based on a literature search, since no comparative study has been carried out to compare the antidepressant like activity of these homeopathic remedies this study was designed at 30 C potencies in animal experimental model.

MATERIALS AND METHODS

Drugs and chemicals

All three homeopathic remedies were purchased from the local homeopathic drug store. Escitalopram was purchased from a local pharmacy.

Animal selection and housing

Fifty albino rats of either sex were selected for the study. The mean weight of animals was ranging from 0.15 to 0.18 kg for rats. Animals were kept two per cage under standard conditions (22-26^{o} C) with 12 hour day / 12 hour night cycle and the relative humidity was 25%$\pm$5%. The animals have easy access to food and water all the time.

For animal handling Helsinki Resolution 1964 were followed. The study was approved by BASR of University of Karachi [vides Resolution No.10 (50)].

Animal grouping

All rats were assigned into 5 groups separately. Every group contains 10 animals with either sex distribution.

The first group of animals served as a control group,

Group two served as the treated group for *Argentum nitricum,*
Group three served as the treated group *for Staphysagria,*
Group four served as the treated group for *Ignatia amara*.
Group five served as the standard group for Escitalopram.

Escitalopram was selected as standard drug in order to compare the antidepressant effects of homeopathic remedies with it.

Rats were used for FST, OFT and cage crossings.

Dosing

We selected 30 C potency of *Argentum nitricum, Staphysagria, Ignatia amara*, because the remedies range from 30-200 C potency are considered as prime potency and better for the treatment of psychic diseases (Manish Bhatia, 2009; Hart *et al.*, 1997). It is advised 30 C as starting treatment (Rawat, 2011).

The recommended daily dose of all three homeopathic remedies for adults is 2-3 drops of 30C potency in 30ml of water. So taking 70 kg as an average adult body weight, the dose calculated for rats was 60 microliter.

The recommended adult dose of Escitalopram is 20 mg daily, therefore it was calculated as 0.042 mg for rats. All the doses were administered orally with the help of feeding tubes for two months. The animals were deprived of food overnight prior to perform the test.

General Behavioral Activities

Despair swimming test: an animal depression model

The apparatus used was made of a clear plexiglass cylinder (30cm in height, 20 cm in diameters) filled with water to the level that the animal tail doesn't touch the floor of the cylinder. Albino rats were chosen for this activity. The effects of drugs were observed after day 30 and 60 of dosing. On experiment day, each individual rat of all treatment groups was placed gently in the cylinder and allowed to swim for 5 minutes (Drugan *et al*., 2010).The animal was gently taken out from the water, dried and returned to their home cages. After each swimming session the apparatus was washed and filled

with fresh, clean water to avoid any contamination (Crawley, 2007).

Cage crossing activity

The home cage apparatus includes a transparent cage made of plexiglass (26 × 26 × 26 cm) (Najam and Anser, 2011). The home-cage activity was observed after day 30 and 60 of dosing. On test day, the rats were kept in home cage individually in the apparatus for ten minutes and cage crossings were noted. Increase in cage-crossing activity reflects an increased exploratory activity in rodents.

Open field activity (OFT)

The specification of apparatus was as per Anser *et al* (2014) and Brown *et al* (1999). The test is performed after 30th and 60th day of dosing. On the day of activity, albino rats of all groups were placed in the corner of the apparatus separately for 10 minutes and numbers of peripheral and central squares crossed by the animals were counted.

STATISTICAL ANALYSIS

All the data were given as Mean± SD, statistically analyzed through one way analysis of variance, and to determine the difference in significance Turkey's multiple comparison test is used. For all this procedure Statistical Packages for the Social Sciences version 20 (SPSS, Inc., Chicago, IL, USA) was used. The paired t test is used to analyze the differences within the groups after day 60th as compared to day 30th.

RESULTS

Forced swim test

Results of forced swimming test are displayed in fig. 1. The animals of all the groups produced significant results on the 30th and 60th day among groups and in the groups ($F=30.22$, $p<0.001$), ($F=65.39$, $p<0.001$) respectively.

Post hoc multiple comparison test confirms non significantly improved swimming time in *Argentum nitricum* treated rats in comparison with control and

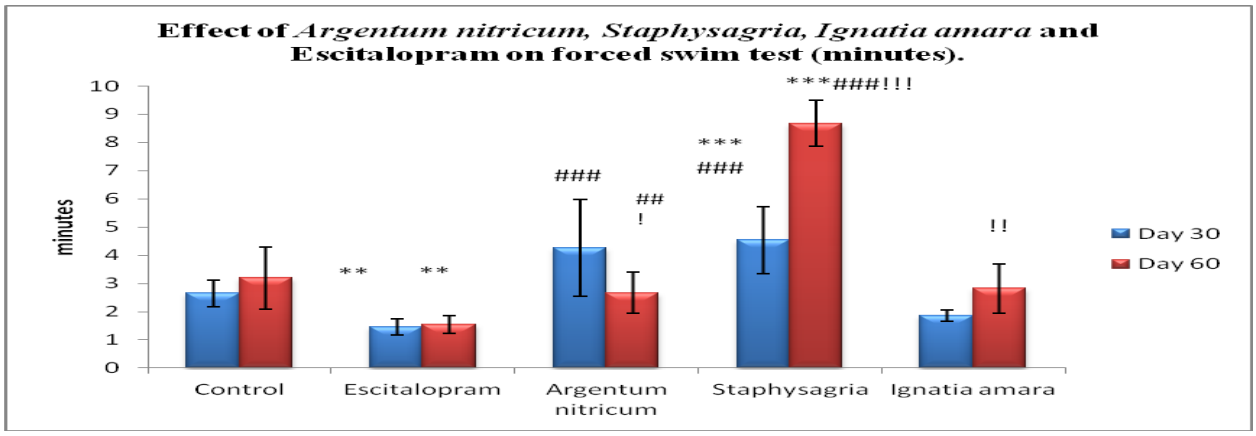

Fig. 1: Effect of homeopathic remedies and Escitalopram on swimming time in rats (minutes).

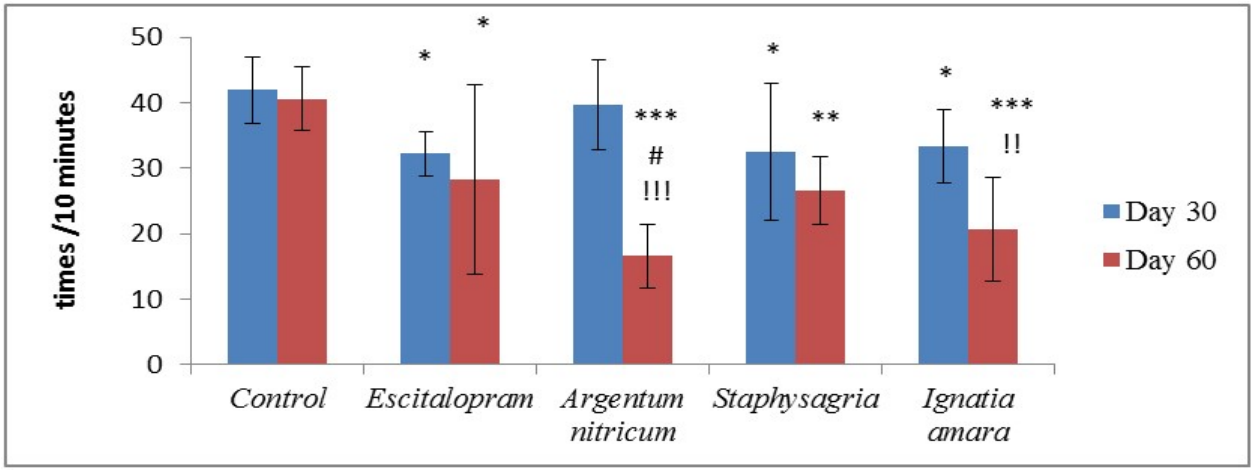

Fig. 2: Effect of homeopathic remedies and Escitalopram on home cage activity.

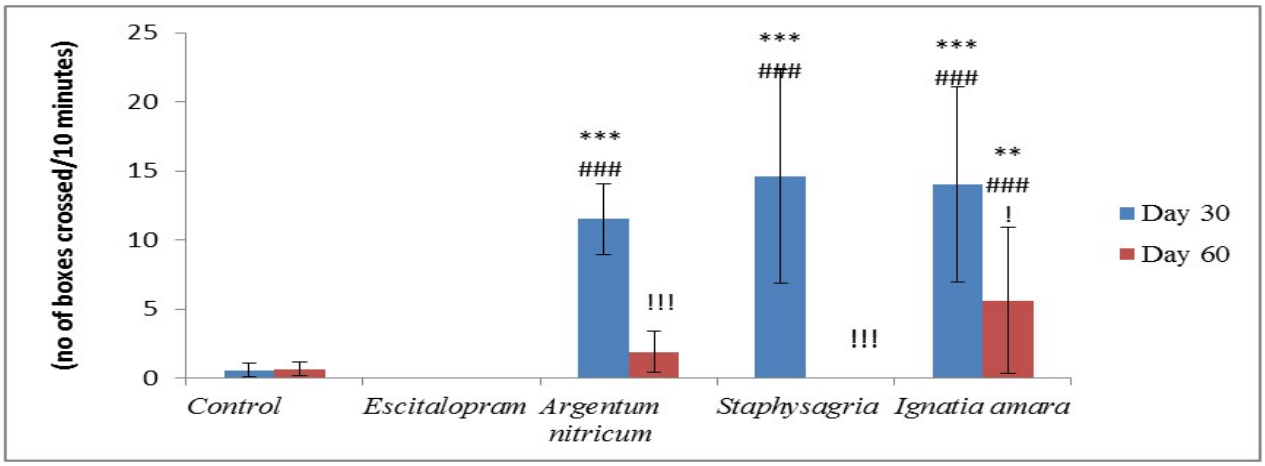

Fig. 3: Effect of homeopathic remedies and Escitalopram on open field (Number of square crossed in central area)
Mean values ± SD. Comparison between control v/s all the other groups. Statistical test done by one-way ANOVA followed by Post-hoc Tukey's multiple comparison test, *p<0.05, **p<0.01; *** p<0.001 when compared with control and #p<0.05, ##p<0.01; ###p<0.001 when compared with escitalopram. !p ≤ 0.05,!!p ≤ 0.01,!!! p ≤ 0.001 when compared to one month (30 days) values.

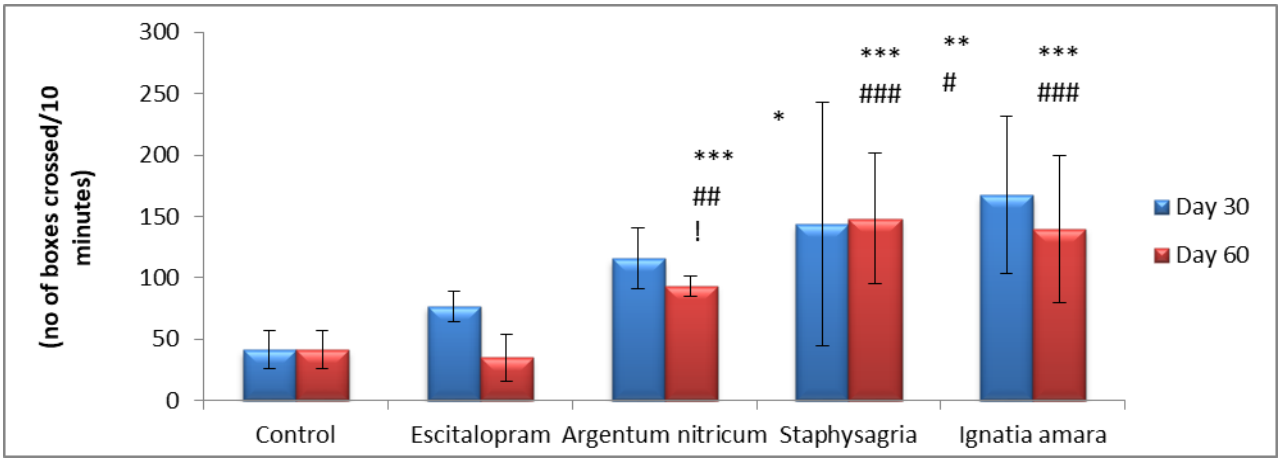

Fig. 4: Effect of homeopathic remedies and Escitalopram on open field (Numbers of square crossed in peripheral area)

highly significant elevation in struggling time in comparison with escitalopram (p<0.001) after the one month of dosing, while insignificantly reduced struggling time in comparison with control after the two months of dosing. Further *Argentum nitricum* treated group showed a moderately significant elevation in struggling time after day 60 in contrast with escitalopram (p<0.01). Analysis by paired sample test, the results showed that *Argentum nitricum* treated group significantly decreased struggling time after two months of dosing when compared with struggling time after one month of dosing.

Post hoc multiple comparison test confirmed that *Staphysagria* treated group showed highly significantly increased swimming time when compared with both control as well as with escitalopram (p<0.001) after one month and two months of daily dosing. The pair t test analysis showed that *Staphysagria* had significantly increased the struggling time after two months comparative to after one month of dosing.

Further, *Ignatia amara* treated group represent non significantly decline in struggling time after a month and after two months in contrast with control, however, insignificantly improved struggling time after 30th and 60th day of drug administration when compared with standard (escitalopram). As per pair t test analysis, *Ignatia amara* treated group showed moderate significant increase in struggling time after two month when compared with one month of dosing.

Home cage activity

Results of home cage activity test are shown in fig. 2. The test animals of groups exhibited significant results, between groups and within groups (F=4.493, p<0.01), that further improved on the 60th day among groups and in groups (F=12.06, p<0.001).

Post hoc Tukey's multiple comparison test showed that animals in *Argentum nitricum* group showed insignificantly reduced home cage activity on the 30th

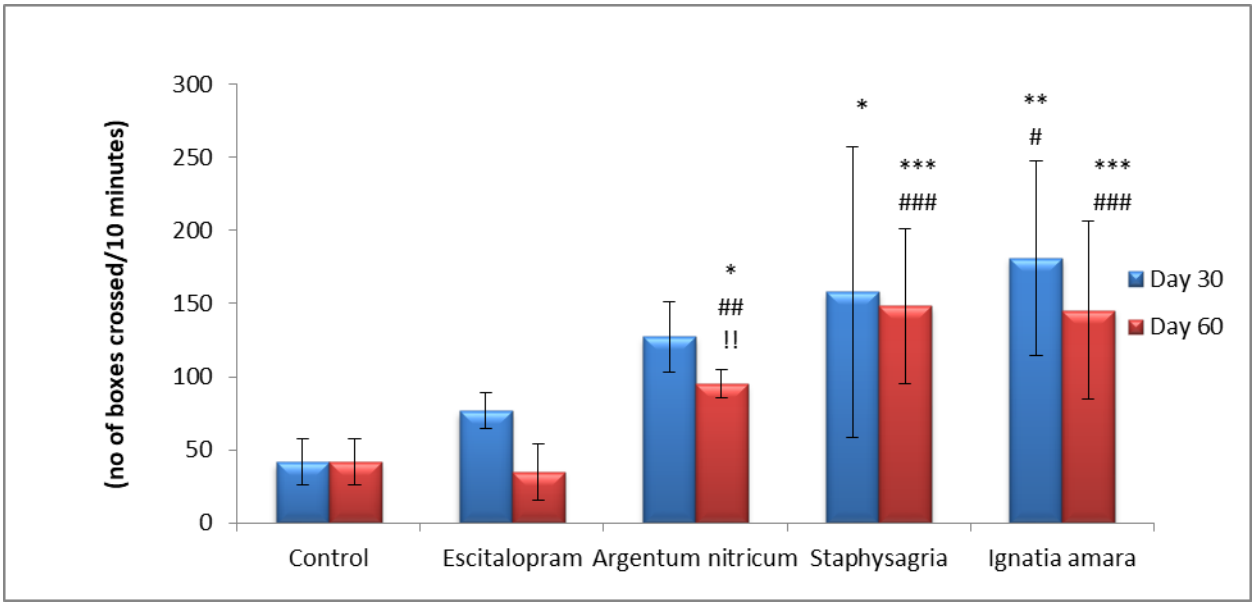

Fig. 5: Effect of homeopathic remedies and Escitalopram on open field (Total number of square crossed in 10 min).Mean values ± SD. Comparison between control v/s all the other groups. Statistical test done by one-way ANOVA followed by Post-hoc Tukey's multiple comparison test, *p<0.05, **p<0.01; *** p<0.001 when compared with control and #p<0.05, ##p<0.01; ###p<0.001 when compared with escitalopram. !p ≤ 0.05,!!p ≤ 0.01,!!! p ≤ 0.001 when compared to one month (30 days) values.

day and highly significant decrease (p<0.001) in home cage crossings on the 60th day respectively in contrast to control. *Argentum nitricum* showed significant decrease in cage crossings in comparison with standard at day 60th (p<0.05). The pair t test analysis showed a highly significant decrease in cage crossings after two months than as compared to 30th days of dosing in *Argentum nitricum* treated group (p≤ 0.001).

Staphysagria treated animals displayed significant reduction in cage crossing activity (p≤0.05) on the 30th day and moderate significant reduction was seen on the 60th day (p<0.01) in contrast with control.

Ignatia amara treated group showed significant immobility with reduced movements in the cage on the 30th day (p≤0.05) while highly significant decline were seen in cage crossings on the 60th day when compared with control (p≤ 0.001). Data analysis by pair t test showed a moderate significant decrease in the cage crossings after 60th day than as compared to after day 30th of dosing.

Open field activity (OFT-central square crossing)

Results of central square crossing in the open field apparatus are shown in fig. 3. In the open-field test, highly significant results were seen in the central squares crossing in an open field on the 30th day (F=22.407, p<0.001) and on the 60th day among groups and in groups (F=6.734, p<0.001).

Post hoc Tukey's multiple comparison test showed that *Argentum nitricum* treated animals showed a highly significant rise in crossings in the central region of the apparatus (p≤0.001) after 30 days of treatment when compared with control as well as standard, however no significant differences were seen after day 60th in comparison with control. The pair t test showed a highly significant decrease in central squares crossings after 60th day when compared with 30yh day of dosing in *Argentum nitricum* treated group.

Animals in *Staphysagria* showed a highly significant rise (p≤0.001) in the number of crossings in Central Square after 30days of treatment in comparison with control as well as the standard, while insignificant reduction was seen after day 60th in comparison with control. The pair t test showed highly significant decline in the locomotion in the central region after 60th days comparative to 30th days of dosing (p≤ 0.001).

Animals in *Ignatia amara group* present highly significant rise in crossing (p≤0.001) after the 30th day, however moderate significant elevation in number of central crossings (p<0.01) after the day 60th in contrast to control. *Ignatia amara* highly significantly increased central square crossings on day 30th and 60th in comparison to standard (p<0.001). The pair t test analysis showed significant decrease in the central squares crossings after 60th day in comparison with after 30th day of dosing (p≤ 0.05) in *Ignatia amara* treated group.

Open field activity (peripheral squares)

Fig # 4 showed the results of peripheral square crossing in open field apparatus. Significant results in the peripheral region on the 30th day were seen among groups and in groups ($F=4.412$, $p<0.01$) and highly significant outcomes were obtained after the 60^{th} day among groups and in groups ($F=24.812$, $p<0.001$).

Post hoc Tukey's multiple comparison test exhibited that animal in *Argentum nitricum* group showed an insignificant rise in peripheral square crossing on the 30^{th} day, while highly significant rise were seen after the day 60th ($p\leq0.001$) in comparison to control. It moderately significantly increased peripheral squares crossings after 60^{th} day of dosing when compared with standard. Paired t test showed significant decrease in peripheral squares crossings after 60^{th} day in comparison with 30^{th} day of dosing.

Staphysagria also showed a significant rise ($p\leq0.05$) on the 30th day, which was further risen on the 60th day ($p\leq0.001$) in comparison with control. *Staphysagria* showed highly signicant elevation on day 60^{th} ($p<0.001$) in comparison with standard.

After treatment of animals with *Ignatia amara* significant rise in the crossings in peripheral squares on 30^{th} day ($p<0.01$), was observed which was further elevated on 60^{th} day ($p<0.001$) in comparison to control. *Ignatia amara* treated rats showed significant rise ($p<0.05$) on day 30^{th} and highly significant rise ($p<0.001$) in the crossing after 60^{th} day of dosing when compared with standard group.

Open field (total crossings)

Fig # 5 showed the results of total square crossings in open field apparatus. In the open-field test, all treated groups showed significant result in the total squares crossed after the 30^{th} day among groups and in groups ($F=5.607$, $p<0.001$), and highly significantly rise in total squares crossing on the 60^{th} day between groups and within groups ($F=20.557$, $p<0.001$).

Post hoc Tukey's multiple comparison test reflects that animals in *Argentum nitricum group* there was insignificant rise in the number of total squares crossing on the 30^{th} day and showed significant rise in total square crossing activity after 60^{th} day ($p\leq0.05$) in comparison with control. *Argentum nitricum* showed significance and improved total crossings after day 60^{th} when compared with standard group ($p<0.01$). The pair t test showed a moderate signifant decrease after 60^{th} days in contrast to 30^{th} days of dosing.

Similarly in *Staphysagria* group of animals, significant rise after the 30th day ($p<0.05$) and highly significantly rise ($p<0.001$) in comparison with control after the 60^{th} day, in total number of square crossing. *Staphysagria* showed significant rise in total crossings on day 60^{th} when compared with standard drug group ($p<0.001$).

Ignatia amara treated rats also caused significant rise in total number of squares crossing ($p<0.01$) on the 30th day and further increased ($p<0.001$) after the 60th day in contrast to control. *Ignatia amara* group significantly raised the total crossings after day 30^{th} ($p\leq0.05$) and highly significant improved in comparison to escitalopram ($p<0.001$).

DISCUSSION

For the treatment of depression various antidepressants are available in the market, but due to their adverse effects and delayed onset of action, the population is using alternative medicine also. As per a study by Pannek *et al*. (2015) the alternative treatments specially the homeopathic treatments are proven effective.

The behavioral despair test is widely used tool for the evaluation of compounds and drugs having antidepressant like effect and could be efficacious to prevent or revert the depressive symptoms. The rat actively swam and tried to escape from the cylinder, but after a few minutes it started floating on the surface of the water that reflects its hopelessness state. Various parameters can be determined for example immobility time, struggling time or swimming time. The determination of each parameter can help in interpreting the neuro-chemical mechanisms (Estrada-Camarena *et al.*, 2003; Chaki *et al*., 2004). Our study confirmed that *Argentum nitricum* after 30 days of dosing, increased the swimming time reflecting its antidepressant activity, the antidepressant effect of *Argentum nitricum* could be due to modulation of the catecholamine levels, which is confirmed by Gerber (2013) and Antsiferova *et al.* (2018). However, after chronic dosing of *Argntum nitricum* we found decreased struggling time in FST showing hypoactivity and fearless behavior in the animal, which is supported by Zhang *et al* (2013) who suggested that chronic dosing of nano particles of silver (Ag) resulted in a decrease in locomotion. This hypolocomotion caused a decrease in cage crossings in treated animal showing an anxiolytic activity (Zhang *et al*., 2013; Strużyńska, 2017). Open field test paradigm is used widely for the determination of exploration and locomotion in the rodents. The effect of *Argentum nitricum* on locomotion is supported by our finding that it causes an increase in open field activity which was found more pronounced after 30 days of dosing. Possibly due to the modulation of neurotransmitter release, especially norepinephrine and dopamine After 30 days of dosing the total crossings were increased which is supported by Krugers *et al.* (2012) and Antsiferova *et al.* (2018) who confirmed that silver particles are capable of increasing corticosterone levels in rodents which in turn increases norepinephrine release.

However the total crossings were decreased on the 60th day of dosing than as compared to 30th days dosing which is supported by Zhang *et al* (2013).

Staphysagria had increased the swimming time, that could be attributed to its flavonoidal contents that are responsible for the elevation of the catecholamines (Graziani and Chayoth, 1979). *Staphysagria* contain flavonoids like quercetin and kaempferol which inhibits Monoamine oxidase- A enzyme, that results in an increase in 5HT and norepinephrine (NE) levels thus producing its antidepressant activity. As per Kehr *et al.* (2012) these flavonoids also increase the levels of acetylcholine and dopamine in prefrontal cortex and mid brain that leads to an improvement in locomotory and coordinated muscular movements reflecting its antidepressant profile.

The decrease in cage crossing activity in S*taphysagria* treated group was due to the presence of diterpenoid alkaloids (chasmamine, delphinine, neoline, isoazitine) and flavonoids (quercetin, kaempferol) in *Staphysagria* seed that are nervine, neurotropic, and induces narcosis and are responsible for the anxiolytic activity (Wang *et al.*, 2009, Diaz *et al.*, 2008, Rabanal *et al.*, 2005, Verma *et al*., 2010, Goutman and Calvo, 2004; Jung and Lee, 2014). The study done by Verma *et al* (2010) confirms benzodiazepines-like activity by flavonoids that produces calmness (Goutman and Calvo, 2004; Jung and Lee, 2014). It doesn't affects locomotion, but the decrease in central zone of open field is because of this mechanism. Although the cage crossings in comparison with standard drug was found improved or equal reflecting less effect on locomotion as compared to escitalopram.

The flavonoids potentiate the GABAergic effect when administered in low concentration but cause inhibition of it or opposed action, when given in high concentration (Hanrahan *et al.*, 2011). This supports the hypothesis that the administration of 30 C potency of *Staphysagria* (high dilution) produces anxiolytic action. However the increase in total squares crossings can be due to presence of glycosidal content of *Staphysagria* seeds (quercetin and kaempferol) which increases adrenaline availability (Kumar and Pandey, 2013). As per our finding *Staphysagria* had increased the locomotion in peripheral area and total number of crossings in open field showing its tendency to increase the levels of serotonin and norepinephrine via monoamine oxidase and catechol-O – methyl transferase enzyme inhibition and increased dopamine and acetylcholine levels (Bandaruk *et al.*, 2012; Singh *et al.*, 2003;.Kehr *et al.*, 2012).

Ignatia amara decreased the swimming time in animals which could be due to fearless, reflecting the anti anxiety effect which is also supported by the decrease in cage crossings by the treated animals in our study. As per studies conducted by Xu *et al*. (2009) and Thambi & Cherian (2015), the presence of various alkaloids (strychnine, brucine, isobrucine, novacine, vomicine, loganin etc) in *Strychnoss ignatii* beans could produce this effect. After chronic administration of *ignatia amara* there was decrease in exploration which could be attributed to alkaloidal content (that resembles with structure of strychnine) of *Ignatia amara* which increased the formation of neurosteroid allopregnanelone in neuroglia of spinal cord. This neurosteroid bind with $GABA_A$ receptor at its allosteric site or on glycine receptor (strychnine- sensitive) (Maksay *et al.*, 2001) this effect will increase the movement of chloride ion inside the cell producing the depressive behaviour (Belliviate *et al.,* 2009).

An increase in the central region in an open field in *Ignatia amara* treated group reflects anxiolytic activity which is supported by Venard *et al*., (2008) who also confirms increase in allopregnanelone synthesis through the process of hormesis (i.e. low doses produces positive effect rather than toxic effects), although it is known that strychnine is an antagonist of strychnine sensitive glycine receptors, but glycine boost the allopregnanelone synthesis. Thus, through the above mentioned mechanism the highly diluted doses of strychnine stimulates glycine receptors leading to anxiolytic activity. However increase in peripheral squares and total numbers of crossings in open field shows an improvement in locomotion which could be attributed to the mechanism which is reported by Rougé-Pont *et al*. (2002) that increased allopregnanelone synthesis, increases the dopamine release from the nucleus accumbens.

CONCLUSION

This study is a novel work as it reported the comparative neuropharmacological profile of three different homeopathic medicines for the first time. We found that among all three homeopathic remedies *Staphysagria* possess a potent antidepressant activity. *Argentum nitricum* produces antidepressant effects after 30 days of dosing but chronic dosing resulted in depressive response. While *Ignatia amara* also showed comparatively low antidepressant activity as compared to *Staphysagria.* In conclusion all three homeopathic remedies showed a comparable antidepressant like activity to standard drug.

Still, the determination of brain biogenic amine is recommended so that we could correlate them with their pharmacological effects.

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