# Journal of Pharmacology and Toxicology

ISSN 1816-496X

Academic Journals Inc.

www.academicjournals.com

Journal of Pharmacology and Toxicology 7 (1): 29-37, 2012
ISSN 1816-496X / DOI: 10.3923/jpt.2012.29.37
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# Modulation in Pharmacokinetic Properties of Mirtazapine and Citalopram During Contemporaneous Therapy with Ritonavir

[1]B.N. Thakar, [2]K. Shah, [2]U. Desai, [1]D.K. Suresh, [2]R. Rawal and [1]S. Khalid
[1]Department of Pharmacology, Luqman College of Pharmacy, Gulbarga, India
[2]Department of Medicinal Chemistry And Pharmacogenomics, Gujarat Cancer Research Institute, Ahmadabad, Gujarat, India

*Corresponding Author: B.N. Thakar, A/41, Shayamal Park Society, Opp. Shaktinagar Society, Nicol-Naroda Road, Nava Naroda, Ahmedabad-382325, Gujarat, India Tel: +91 8460767835, 9510886300*

## ABSTRACT

The present study was carried out to evaluate the drug-drug interaction between antidepressant and antiretroviral drugs. Interaction of Mirtazapine, the known antidepressant drug and citalopram, the known SSRI class antidepressant drug with Ritonavir, the known protease Inhibitor antiretroviral drug was evaluated in Mice. *In silico* (Molecular modeling) studies on interaction of Ritonavir with the mirtazapine and citalopram was done by biosuite version 3.0 (TATA consultancy service limited), where as *in vivo* studies were done by following forced swim test and compulsive gnawing test. *In silico* study (Molecular modeling study) shows that ritonavir is having more binding affinity towards CYP2D6 compare to mirtazapine and citalopram, which indicate that Ritonavir may inhibit the metabolism of mirtazapine and citalopram. *In vivo* study result indicate that Ritonavir (100 mg $kg^{-1}$, p.o.) pretreatment has not significantly altered the onset of antidepressant effect of Mirtazapine (10 mg $kg^{-1}$, p.o.) but significantly increased the peak antidepressant effect in mice (19.97±0.4906% antidepressant activity before treatment to 23.99±0.4162% antidepressant activity after treatment), while duration of antidepressant effect was increased from 18 h to more than 20 h in both groups. Similarly pretreatment with Ritonavir (100 mg $kg^{-1}$, p.o.) has significantly no effect on the onset of antidepressant effect of Citalopram (5 mg $kg^{-1}$, p.o.) but it significantly increased the peak antidepressant effect in mice (34.16±1.348% reduction before treatment to 36.66±0.9426% reduction after treatment), while duration of antidepressant effect was increased significantly to the more than 24 h. This study indicates that Therapeutic Drug Monitoring (TDM) has to be required to readjust the therapeutic doses of Ritonavir and antidepressant drugs like Mirtazapine and Citalopram when they used concomitantly.

**Key words:** Influence of ritonavir, antidepressant effect of mirtazapine, citalopram, drug interaction, *in silico* study

## INTRODUCTION

To obtain a desired therapeutic aspiration or to treat co-existing diseases many a times it becomes indispensable to use several drugs contemporaneously, leads to the drug-drug interactions. A drug interaction is a state of affairs where one drug will either restrain or persuade the effect of the other drug. This kind of reaction may prove some time favorable or sometime perilous to our body, in general the hazardous effect will results in poor possibility outcome of therapeutic activity of either drug (Hansten and Horn, 2003).

In multidrug therapy, the monitoring of the incidence and frequency of occurrence of drug interactions is needed, to prevent the serious perilous effect of the drug interaction. We also need to identify an agent accountable to produce the perilous effect (Sunilkumar *et al.*, 1998). Study shows when 5 or fewer drugs were administered concomitantly the incidence of drug reaction were rise to 4.2% and when 20 or more drugs are administered concomitantly the incidence of drug reaction were rise to 45%. According to the report in general hospitalized patient the 3.7% has experienced the drug interaction where as in 1.8% of patient the drug interaction has proved fatal (Anitha *et al.*, 2008; Uppal *et al.*, 2000).

Acquired immune deficiency syndrome or Acquired Immunodeficiency Syndrome (AIDS) is caused by the Human Immunodeficiency Virus (HIV) which will reduces the immunity of the body. (Sepkowitz, 2001; Weiss, 1993; Cecil, 1998). The reduction in the immunity because of the AIDS infection will increase the individuals susceptible to opportunistic infections and tumors. Now a days AIDS is widely emerging diseases, according to UNAIDS (2010), there are 33.3 million people suffering with HIV, from that 2.5 million were children. In 2009 around 2.6 million new cases of HIV infection has been noted and an estimated 1.8 million peoples were died because of the AIDS (UNAIDS, 2010).

It can be understood that complicated disease like AIDS may change patient life style and normal behavior. There are probabilities to develop depression in the patient of AIDS. The depressive patient may also raise the chances of the transmission of the HIV to the other and vice versa depression may also cause the obscure HIV virus infection to become active. Overall, it can be conclude that depression can make HIV disease to progress faster. So there are many chances to develop depression along with the AIDS (Kelly *et al.*, 2009; WHO, 2008).

Depression is a state of low mood and loathing to activity characterized by low self esteem or loss of interest or pleasure (Salmans, 1997). Study shows 17% of people suffering from the HIV/AIDS have not informed to them family about their health condition, even though more than 96% have disclosed their health status to at least one person. Study of the 2000 HIV infected patient in the US has shown around 42% of people was feeling isolated and depressed (Hendrick, 2010).

In such cases multiple drug therapy is needed to prescribe to treat the AIDS along with depression. Study has shown that concomitant therapy of Anti depressant has increased patient adherence towards the AIDS therapy (Yun *et al.*, 2005). So, antidepressant agents like Mirtazapine, Citalopram, Venlafexin etc. and Antiretroviral agents like Ritonavir, Indinavir, Nelfinavir, Saquinavir etc are administered concomitantly.

According to previous study Mirtazapine, Citalopram is known to get metabolized through Cytochrome P-450 2D6 enzyme system (Brockmoller *et al.*, 2007), hence there are possibilities of occurrence of pharmacokinetic type of drug interactions with concomitantly used drugs which can either induce or inhibit the CYP450 2D6 enzyme system. Ritonavir has been proved one of the well known inhibitor of many CYP 450 systems like CYP2D6, CYP3A4, CYP1A2, CYP2C9 and CYP2E1 (Eagling *et al.*, 1997; Oesterheld *et al.*, 2004). Therefore, the present study was carried out on mice to assess the influence of antiretroviral drug pretreatment on the antidepressant effects of mirtazapine and citalopram.

*In silico* study is the study which is performed by computer or computer simulation. *In silico* study is helpful to reduce the trial in the laboratory. It is convenient to check the protein-ligand interaction by molecular docking. X-ray crystallography structure of the protein and bound ligand complex gives valuable information about its binding mode and their functional analysis. We can predict the active site and binding mode of the Cyp450 from their three dimensional structure with inhibitory drug. If there is any modification in structural conformation or changes in ligand and/or

enzyme will directly affect their binding affinity, which will leads to the chance for the Cyp450 to bind with another drug. All of these details help in predicting a new compound with good potentiality (Anzenbacher and Anzenbacherova, 2001; Kirton *et al.*, 2005; Lussenburg *et al.*, 2005).

Information from the complex structure of CYP-2D6 with their bound drug, it becomes very easier to indentify and predict their putative binding site and to find out how drug will metabolize and inhibit these enzymes. Structural data indicate that a peculiar heme group and five amino acids are involved in CYP-2D6 binding site, may impact their binding mode. There are mainly five amino acids are involved in binding site. Amino acids Glutamate 216 and Aspartate 301 are resides in F-G helix and I- helix, respectively and remaining are Phenylalanine 102, 481 and 483. The heme group present in the binding site is responsible for the hydroxylation of the substrate, whenever the substrate is close enough to the heme group and it will fit in to the binding cavity, it will be get hydroxylated. When the substrate is fit into the binding cavity but not close enough to the heme group it will be result in the interaction. (Kirton *et al.*, 2005; Lussenburg *et al.*, 2005; Marechal *et al.*, 2008; Chowdry *et al.*, 2002). The objective of the study is to evalute the drug-drug interaction belween antidepressant and antiretroviral drugs.

## MATERIALS AND METHODS

***In silico* study:** Cytochrom P450 isoenzyme CYP2D6, a protein structure was downloaded from PDB. (http://www.pdb.org/pdb/home/home.do) (PDB id: 2F9Q). Three Drug molecules Mirtazapine, Citalopram and Ritonavir were downloaded from Drug Bank. (http://www.drugbank.ca/) structure refinement and energy minimization of protein structure was done in Biosuite Version 3.0 (TATA consultancy service limited). Binding site was predicted using till date published literature data. Following amino acids are involved in binding sites: Phe102, Phe120, Leu213, Glu216, Glu222, Phe219, Asp 301, Ser304, Phe481, Phe483 (Kirton *et al.*, 2005; Lussenburg *et al.*, 2005; Marechal *et al.*, 2008; Chowdry *et al.*, 2002).

The molecular docking operations in our studies were performed by the Biosuite Version 3.0 (TATA consultancy service limited) to investigate the interactions between CYP2D6 and three aforementioned drug molecules. During the whole docking process, drug molecules were flexible, while the protein molecule kept rigid. And after docking, poses with energy levels for each compound was noted which shows the binding affinity of particular drug interaction with protein. Binding energy of particular drug with CYP2D6.

### *In vivo* study

**Animals:** The present study was conducted on healthy mice of either sex, weight range 25-30 g. The animals were procured from Sri Mahavir Enterprises, hyderabad. They were housed under standard conditions (temperature of 25±2°C and 50±2% relative humidity with 12 h light/dark cycle) and provided with water ad libitum. Prior approval by institutional ethics committee (reg. No: 346/CPCSEA) was obtained for conduction of experiments. Groups of six animals were organized and, in order to reduce the influence of day variation, all assays were conducted from 8 to 13 h, in a special noise-free room with controlled illumination.

**Drugs:** Ritonavir was obtained from Jai Radhe Sales, ahmadabad, Gujarat. Mirtazapine was obtained from TAJ pharmaceutical Ltd., mumbai and citalopram was obtained from torrent pharmaceutical Ltd., ahmadabad; Gujarat. Ritonavir (100 mg $kg^{-1}$, p.o.), Mirtazapine (10 mg $kg^{-1}$, p.o.) and Citalopram (5 mg $kg^{-1}$, p.o.) suspensions were prepared using 2% w/v gum acacia as suspending agent.

**Experimental procedure**

**By forced swim test:** The healthy mice were marked conveniently and distributed randomly into three groups of 6 animals each. The animals in group 1 received Ritonavir (100 mg $kg^{-1}$, p.o.), the animals in the group 2 received Mirtazapine (10 mg $kg^{-1}$, p.o.) and animals in group 3 received Citalopram (5 mg $kg^{-1}$, p.o.) in 2% w/v acacia suspension. Antidepressant activity was evaluated by following the forced swim test method.

Here it consists of direct immersion of animals after injecting drugs; the mice were subjected to pre test session for 15 min. In a glass cylinder (21×12×12 cm) containing water up to a height of 9 cm maintained at 25°C twenty four hours later, the animals were treated orally either with drug and each animal was against forced to swim in similar environment for a period of 5 min in a test session and immobility time was recorded. The mouse was judged immobile if it ceased struggling and remained floating motionless in water making only those movements necessary to keep its head above water (Kasture, 2006).

In the next phase of the experiment, after the washing period of 10 days, the same animals of group 2 and 3 received Ritonavir 100 mg $kg^{-1}$, p.o. for eight days. On the 8th day, Ritonavir was given as usual to the animals of both groups. One hour after the treatment, animals of group 2 received mirtazapine 10 mg $kg^{-1}$, p.o. and animals of group 3 received citalopram 5 mg $kg^{-1}$, p.o. The anti depressant activity were measured at various time intervals by following above mentioned procedure.

**By compulsive gnawing method:** The healthy mice were marked conveniently and distributed randomly into five groups of 6 animals each. The animals in group 1 received no drug , the animals in the group 2 received Apomorphine (10 mg $kg^{-1}$, s.c.), animals in group 3 received Apomorphine (10 mg $kg^{-1}$ s.c.) and Ritonavir (100 mg $kg^{-1}$ p.o.), animals in group 4 received Apomorphine (10 mg $kg^{-1}$ s.c.) and Mirtazapine(10mg $kg^{-1}$ p.o.) and animal in group 5 received Apomorphine (10 mg $kg^{-1}$ s.c.) and citalopram (5 mg $kg^{-1}$ p.o.) in 2% w/v acacia suspension. Antidepressant activity was evaluated by following the compulsive gnawing method.

Mice are injected s.c. with 10 mg $kg^{-1}$ Apomorphine. Prior to 30 min of Apomorphine treatment they treated orally with respected drug. Immediately after Apomorphine injection 6 mice are placed into a cage 45×45×20 cm with a wired lid. The bottom of the cage is covered with corrugated paper, the corrugation facing upwards. The mice start to bite into the paper causing fine holes or tear the paper. The mice remain 1 h in the cage. The number of bites into the corrugated paper is evaluated by placing a template upon the paper. The template has 10 rectangle windows divided into 10 areas of the same size. In a total of 100 areas the number of bites is checked. In this way percentage of damaged paper in calculated. Percentage gnawing is compared (Vogel, 2002).

In the next phase of the experiment, after the washing period of 10 days, the same animals of group 4 and 5 received Ritonavir 100 mg $kg^{-1}$, p.o. for eight days. On the 8th day, Ritonavir was given as usual to the animals of both groups. One hour after the treatment, animals of group 4 received Apomorphine (10 mg $kg^{-1}$ s.c.)+mirtazapine(10 mg $kg^{-1}$ p.o.) and animals of group 5 received Apomorphine (10 mg $kg^{-1}$ s.c.)+citalopram (5 mg $kg^{-1}$ p.o.). The oral treatment will be given prior to 30 min of Apomorphine injection. The anti depressant activity was measured by following above mentioned procedure.

**Statistical analysis:** The data were analyzed by Student't' test. p-values lower than 0.05 were considered as statistically significant.

## RESULTS

***In silico***: Interactions of the three drug molecules have been assessed by docking studies showed differential binding affinity to the binding pocket of CYP2D6. The characteristics of the binding pocket play a central role for the ligand binding of CYP2D6. The output of docking results depicted in terms of binding free energy suggestive of highest binding efficiency with lowest free energy change for the binding site. In this case, It is evident from Table 1 and Fig. 1-3 that ritonavir having lowest binding free energy (-26.7714) as compared to Mirtazapine (-16.0798) and Citalopram (-14.1439) which is suggestive of a stronger binding affinity of Ritonavir towards CYP2D6 binding site. Earlier studies have reported pivotal role of glutamate 216 and Phenylalanine 481 in binding with CYP2D6. Present results have confirmed the above interactions.

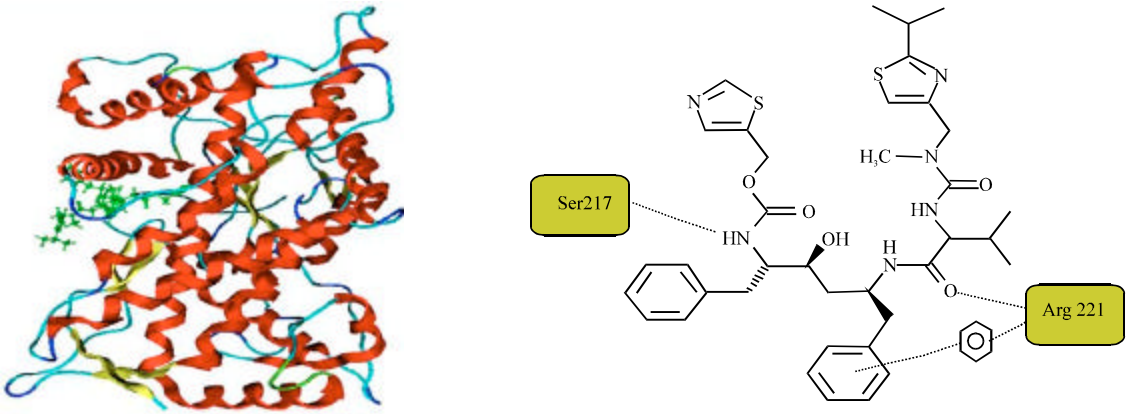


Fig. 1: Molecular docking of ritonavir with CYP2D6. Here form docking results we can see that the ritonavir will bind with the receptor interacting mainly 2 amino acid namely Ser 217 and Aeg 221. The binding energy for CYP2D6 and ritonavir binding is -26.7714 kcal $mol^{-1}$

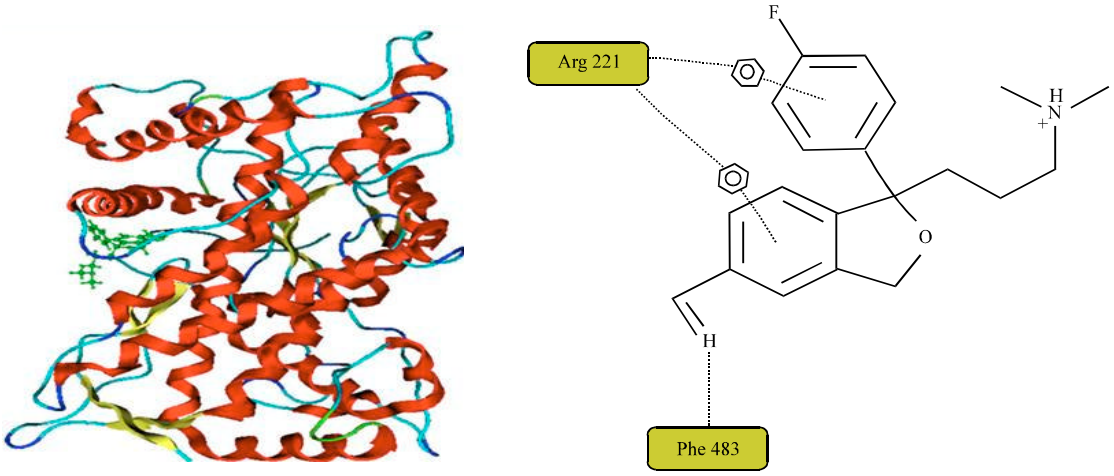


Fig. 2: Molecular docking of citalopram with CYP2D6. Here form docking results we can see that the citalopram will bind with the receptor interacting mainly 2 amino acid namely Phe 483 and Aeg 221. The binding energy for CYP2D6 and citalopram binding is -16.0798 kcal $mol^{-1}$

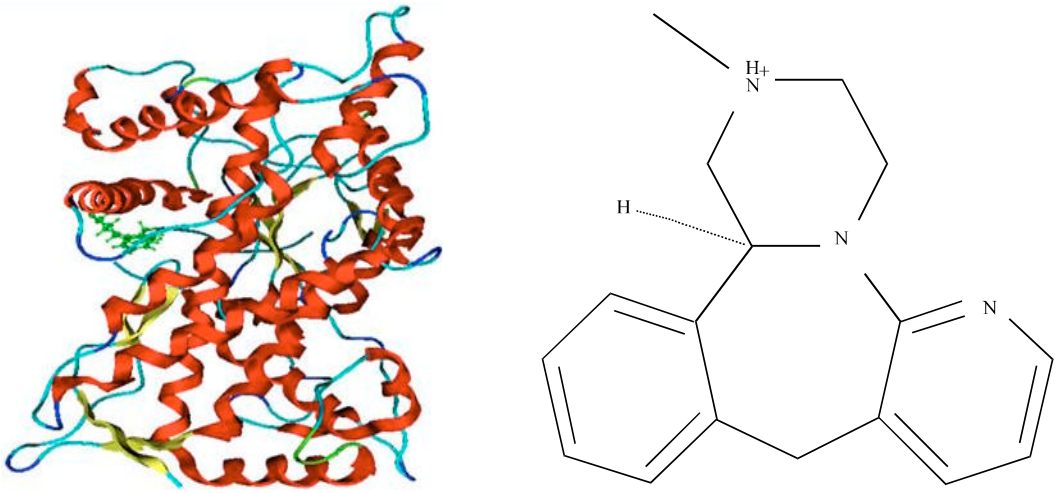


Fig. 3: Molecular docking of mirtazapine with CYP2D6. Interaction of mirtazapine with CYP2D6 has been shown in above images. The binding energy for CYP2D6 and mirtazapine bindind is -14.1439 kcal $mol^{-1}$

Table 1: Binding energy with CYP2D6

| Drug | Binding energy (kcal $mol^{-1}$) |
|---|---|
| Ritonavir | -26.7714 |
| Citalpram | -16.0798 |
| Mirtazapine | -14.1439 |

Table 2: Anti depressant activity by forced swim test

| | Percentage of antidepressant activity (Mean±SEM) | | | | |
|---|---|---|---|---|---|
| Time (h) | Ritonavir (100 mg $kg^{-1}$. p.o.) | Mirtazapine (10 mg $kg^{-1}$. p.o.) | Citalopram (5 mg $kg^{-1}$, p.o.) | Ritonavir (100 mg $kg^{-1}$. p.o.) +Mirtazapine (10 mg $kg^{-1}$. p.o.) | Ritonavir (100 mg $kg^{-1}$. p.o.) +Citalopram (5 mg $kg^{-1}$. p.o.) |
| 0.5 | -0.004223±0.2373 | 0.3579±0.1821 | 11.24±0.6385 | 5.011±0.5049*** | 15.04±1.093*** |
| 1.0 | 3.275±0.3784 | 13.01±0.4469 | 18.34±0.9151 | 13.78±0.7132 | 21.14±1.145** |
| 2.0 | 1.751±1.175 | 19.97±0.4906 | 28.51±0.6471 | 20.95±0.6738** | 31.18±1.183* |
| 4.0 | 1.564±1.077 | 15.27±0.5126 | 34.16±1.348 | 23.99±0.4162*** | 36.66±0.9426** |
| 6.0 | 0.9658±0.5777 | 10.30±0.6873 | 29.85±1.143 | 18.26±0.7764*** | 32.45±0.9134 |
| 8.0 | 3.262±0.5479 | 6.501±0.3286 | 23.91±1.102 | 12.80±0.8046*** | 28.23±0.8740*** |
| 12. | 0.08970±0.5673 | 3.252±0.1411 | 19.96±0.6984 | 8.499±0.7626*** | 22.85±0.9597*** |
| 18. | 0.1707±0.4274 | 0.3520±0.4993 | 14.39±0.5105 | 5.010±0.8125*** | 15.94±1.080 |
| 24. | -0.004223±0.2373 | 0.3579±0.1821 | 11.24±0.6385 | 5.011±0.5049*** | 15.04±1.093*** |

*Significant at $p<0.05$, **highly significant at $p<0.01$, ***very highly significant, $p<0.001$

However, we have reported a novel interaction between Arg 221 residue with Ritonavir and citalopram, which might be important for binding.

***In vivo*:** It is evident from Table 2 that treatment with ritonavir alone did not alter the behavior of mice. However, Ritonavir pretreatment (100 mg $kg^{-1}$, p.o.) has no significant effect on the onset

Table 3: Antidepressant activity by compulsive gnawing test

| Group | Percentage of gnawing by mice (Mean±SEM) |
|---|---|
| Control (No drug treatment) | 36.50±1.607 |
| Apomorphine (10 mg $kg^{-1}$ s.c.) | 41.00±1.155 |
| Apomorphine (10 mg $kg^{-1}$ s.c.)+Ritonavir (100 mg $kg^{-1}$ p.o.) | 40.50±0.7638 |
| Apomorphine (10 mg $kg^{-1}$ s.c.)+Mirtazapine (10 mg $kg^{-1}$ p.o.) | 49.17±0.7923 |
| Apomorphine (10 mg $kg^{-1}$ s.c.)+Citalopram (5 mg $kg^{-1}$ p.o.) | 48.00±1.033 |
| Apomorphine (10 mg $kg^{-1}$ s.c.)+Mirtazapine (10 mg $kg^{-1}$ p.o.)+Ritonavir (5 mg $kg^{-1}$ p.o.) | 52.33±0.8819*** |
| Apomorphine (10 mg $kg^{-1}$ s.c.)+Citalopram (5 mg $kg^{-1}$ p.o.)+Ritonavir (5 mg $kg^{-1}$ p.o) | 51.50±0.9916*** |

n = 6, *Significant at $p<0.05$, **highly significant at $p<0.01$, ***very highly significant at $p<0.01$

of antidepressant effect of Mirtazapine (10 mg $kg^{-1}$ p.o.) and citalopram (5 mg $kg^{-1}$ p.o.) but it significantly increased peak antidepressant effect of mirtazapine (10 mg $kg^{-1}$ p.o.) from 19.97±0.4906% before treatment to 23.99±0.4162% after treatment at 4th h and of citalopram (5 mg $kg^{-1}$ p.o.) from 34.16±1.348% before treatment to 36.66±0.9426% after treatment at 4th h. Duration of antidepressant effect of mirtazapine was increased from 18 h to more than 20 h. Duration of antidepressant effect of citalopram was increased to more than 24 h.

It is evident from Table 3 that treatment with ritonavir alone did not alter the gnawing behavior of mice. However, Ritonavir pretreatment (100 mg $kg^{-1}$ p.o.) has increased gnawing behavior of Mirtazapine (10 mg $kg^{-1}$ p.o.) from 49.17±0.7923 to 52.33±0.8819% and of citalopram (5 mg $kg^{-1}$ p.o.) from 48.00±1.033 to 51.50±0.9916%.

## DISCUSSION

Over the completion of near about 40 years of a world of HIV and AIDS, it has been clear that impact of this virus has been deteriorating globally. And it has been estimated that near around 33.3 million peoples are suffering with the HIV infection (UNAIDS, 2010). Now a days HIV has been recognized as a one of the major civilized crisis and biggest challenge towards the socio-economic development. According to the report of the World Health Organization (WHO), AIDS is the one of the leading cause of death and disability which can be linked closely to mental disorder. (WHO, 2008).

Among the many number of psychiatric syndromes depressed mood is one of the main symptom. Mood disorders are a group of disorders from which major depressive disorder is one of the worsen diseases which is also known as major depression or clinical depression, is this condition in which the person remain in the depressed mood for at least two weeks or a loss their interest or pleasure in nearly all daily activities (APA, 2000). Clinical depression is the most commonly observed mental health disorder among 22% of the HIV-infected patients (Komiti *et al*., 2003). Study has shown that concomitant therapy of Anti depressant has increased patient adherence towards the AIDS therapy (Yun *et al*., 2005). All such condition emphases physician towards preferring concomitant therapy of Anti Retroviral drug like Ritonavir, Indinavir, Saquinavir, etc. and Anti depressant drug like Mirtazapine, Citalopram, Duloxetine, Venlafexin etc.

In such instances, there are possibilities of occurrence of drug interactions. Our pilot study has indicated that drug interactions occur when Ritonavir and Mirtazapine or Ritonavir and Citalopram are administered concomitantly at therapeutic doses. However, the therapeutic dose was found to influence the antidepressant effect significantly. For the assessment of the potentiation of antidepressant effect, onset of action, (time taken to reduce minimum of 15-20% reduction in depression levels), peak effect, duration of anti depressant effect (duration in which minimum of 15-20% reduction in depression levels are maintained) were considered.

Since ritonavir (100 mg $kg^{-1}$) alone did not having anti depressant activity and thus the possibility of occurrence of pharmacokinetic interaction can be ruled out. In our study, pretreatment with ritonavir (100 mg $kg^{-1}$) has not significant effect on the onset of action of mirtazapine (10 mg $kg^{-1}$) and citalopram(5 mg $kg^{-1}$), whereas peak effect and duration of antidepressant effect were significantly increased as compared to mirtazapine (10 mg $kg^{-1}$. p.o.) and citalopram (5 mg $kg^{-1}$,. p.o.) plain treatment. This suggests that Ritonavir diminish the metabolism of these antidepressant drugs by inhibiting the enzymes responsible for their metabolism. There are reports that mirtazapine and citalopram are mainly metabolized by 2D6 enzyme system. Brockmoller *et al.* (2007) reports also indicate that Ritonavir is an inhibitor of CYP2D6, CYP3A4, CYP2B6 and CYP2C19 (Eagling *et al.*, 1997; Oesterheld *et al.*, 2004). It is evident from the results that the therapeutic dose of ritonavir induced the antidepressant effect of mirtazapine and Citalopram. This may be due to inhibition effect of Ritonavir on CYP2D6 (Oesterheld *et al.*, 2004).

Our studies by *in silico* method and *in vivo* method by forced swim test and by compulsive gnawing test suggested that drug interaction occurs between ritonavir and mirtazapine and ritonavir and citalopram when they used concomitantly in pathophysiological co-existence of AIDS and depression.

In this present study, it indicates clearly that during the concomitant administration of ritonavir with mirtazapine and citalopram at therapeutic doses, the dose and frequency of administration of mirtazapine and citalopram need to be readjusted.

## CONCLUSION

The present study concluded that, during simultaneous treatment of AIDS with Depression, ritonavir do interact with mirtazapine and citalopram at therapeutic doses. Therefore, it is necessary to adopt therapeutic drug monitoring so as to readjust dose and frequency of administration of these drugs, when they are used concomitantly to avoid the patients from adverse effect of overdosing of mirtazapine and citalopram.

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