PHARMACOKINETIC AND PHARMACODYNAMIC DRUG INTERACTION OF SIMVASTAIN WITH TRIGONELLINE

Raghuram Reddy Adidala*, Mounika Arrabelli1, Jayanth Regula2, Goverdhan Puchakayala2, Srinivasa Reddy Karka2

*1Department of Pharmaceutical Analysis, Synapse Life Sciences, Nakkalagutta, Hanamkonda, Warangal, Telangana, India.
2Department of Pharmacology, Vaagdevi College of Pharmacy, Hanamkonda, Warangal, Telangana, India.

ABSTRACT
Hyperlipidemia is a heterogeneous disorder characterized by an elevated lipid profile, itself it usually causes no symptoms but it can lead to symptomatic vascular diseases, including coronary artery disease (CAD) and peripheral arterial disease. Simvastatin is a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor, it is widely used in the treatment of hypercholesterolaemia. In the present study we planned to do the pharmacokinetic and pharmacodynamic drug interactions between Simvastatin and the lipid lowering drug Trigonelline. From the results it may be inferred that drug-drug interaction of Simvastain with Trigonelline is pharmacokinetic and pharmacodynamic type.

KEY WORDS
Simvastain, Trigonelline, Pharmacokinetic and Pharmacodynamic.

INTRODUCTION
Cardiovascular diseases have remained one of the leading causes of death all over the world. The development of these diseases has been linked to several factors such as high calorie diet intake, lack of exercise, smoking, age, alcohol consumption and genetic disposition. These factors ultimately result in disorders of lipid and lipoprotein metabolism including lipoprotein overproduction and deficiency. Drug interaction is an interaction said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or by some environmental chemical agent. The outcome
can be harmful if the interaction causes an increase in the toxicity of the drug. For example, there is a considerable increase in risk of severe muscle damage if patients on statins start taking azole antifungal.

The more drugs a patient takes, the greater the likelihood that an adverse reaction will occur. One study had found that the rate of drug interaction was 7% in those taking 6 to 10 drugs but 40% in those taking 16 to 20 drugs, which represents a disproportionate increase.

Pharmacokinetic interactions are those that can affect the drugs absorption, distribution, metabolism and excretion (the so-called ADME interactions). Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action.

Hyperlipidemia is a heterogeneous disorder characterized by an elevated lipid profile itself. It usually causes no symptoms but it can lead to symptomatic vascular diseases, including coronary artery disease (CAD) and peripheral arterial disease. Various approaches have been employed in the treatment of hyperlipidemia. These include lifestyle modification and pharmacotherapy. Among the drugs that are often prescribed are bile acid resins, nicotinic acid, fibrates and the HMG-CoA reductase inhibitors. Statins are the first line of drug treatment for the hyperlipidemia which acts by inhibiting HMG-CoA reductase, an enzyme which plays a major role in the biosynthesis of cholesterol.

Simvastatin is a methylated analogue of lovastatin synthesized from a fermentation product of Aspergillus terreus. Simvastatin is an 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor it is widely used in the treatment of hypercholesterolaemia. Its chemical name is (1S, 3R, 7S, 8S, 8aR) - 8- [2- [(2R, 4R) – 4 – hydroxy-6-oxooxan-2-yl]ethyl]-3,di methyl 1, 2, 3, 7, 8, 8a-hexahydonaphthalen-1-yl 2,2-dimethylbutanoate It is obtained by the replacement of the 2-methylbutyryl side chain of lovastatin with a 2, 2-dimethyl-butyl group.

The 6-membered lactone ring of simvastatin is hydrolyzed in vivo to generate the beta, delta-dihydroxy acid, an active metabolite structurally similar to HMG-CoA (hydroxymethylglutaryl CoA). Once hydrolyzed, simvastatin competes with HMG-CoA for HMG-CoA reductase, a hepatic microsomal enzyme. Interference with the activity of this enzyme reduces the quantity of mevalonic acid, a precursor of cholesterol.

The oxidative biotransformation of simvastatin is mediated primarily by CYP3A4. Because of the extensive CYP3A4-mediated metabolism, simvastatin has a low mean oral bioavailability of about 5%. Simvastatin is usually well tolerated. However, high plasma concentrations increase the risk of musculoskeletal adverse effects (Figure No. 1).

Fenugreek (Trigonella foenum-graecum L. Fabaceae) is one of the oldest medicinal plants, originating in India and Northern Africa. Trigonelline is the active ingredient of the Trigonelline foenum. Fenugreek is also a part of the ayurvedic pharmacopoeia used in arthritis, spondylosis, adjunct in diabetes mellitus, hyperlipidaemia, carminative, tonic and aphrodisiac. Several confections made with this are recommended for use in dyspepsia with loss of appetite, in the diarrhea of puerperal women and in rheumatism.

The possible hypoglycaemic and antihyperlipidemic properties of oral fenugreek seed powder have been suggested by the results of preliminary animal and human trials. Investigations were conducted on the ability of fenugreek seed to lower blood lipids levels.

Hence the present study is designed to study the effect of Trigonelline on the Pharmacokinetic and Pharmacodynamics of the Simvastatin.

**EXPERIMENTAL METHODS**

**Chemicals and Reagents**

Simvastatin, Lovastatin and Trigonelline were obtained from Aurobindo pharma ltd, Hyderabad, Lupin ltd, Hyderabad, Natural Remedies Pvt ltd, Bangalore respectively. All solvents and reagents were of analytical and HPLC grade. Acetonitrile, Water and Glacial acetic acid, Sodium citrate,
Diethyl ether were purchased from Finar chemicals (Ahmedabad) India and all the remaining ingredients were procured from Tarsons products Pvt. Ltd Kolkata. Glucose estimation kit was obtained from Excel diagnostics.

**Instruments and Chromatographic Conditions**

Shimadzu SPD 10 UV Detector and LC 10AD Pump detector. The column and HPLC instrument was maintained at room temperature. The reverse phase chromatography was performed with an analytical inspire C18 column. Acetonitrile: 0.1% Glacial acetic acid in Water: (80:20 % v/v). was used as the mobile phase. The flow rate was set at 1 ml/min and the injection volume was 20 µL. The HPLC detector was set at a wavelength of 240nm.

**Preparation of Standard Solutions**

Primary stock solutions of Simvastatin and Lovastatin (Internal standard) were prepared in methanol at a concentration of 1 mg/ml and stored at -20°C.

**Animals**

Male Sprague Dawley rats (250 - 300 g) were purchased from Teena Bio Labs (Reg no.177/99 CPCSEA) Hyderabad, Andhra Pradesh and housed four to a cage in CPCSEA Approved (Reg.no.1047/ac/07 CPCSEA) animal house at Vaagdevi college of pharmacy, Ramnagar. The animals were maintained on a 12 h light–dark cycle (light on from 8:00 to 20:00 h) at ambient temperature of 25 ± 2 °C and 50 ± 15% relative humidity. Rats were fed with a commercial pellet (Hindustan lever Pvt. Ltd. Bombay, India.) diet and water ad libitum. They were fasted overnight prior to the experiment, and during the experiment, the food is withdrawn but not the water. The animal experiments were performed after prior approval of the study protocol by the Institutional Animal Ethics Committee (IAEC 03/2011) of Vaagdevi college of Pharmacy, Warangal, Andhra Pradesh, India.

**Grouping of animals (n=4)**

Hyperlipidimic rats and Normal rats were grouped as follows:

- **Group-I**: Control (5% Gum Accacia 10ml/kg p.o).
- **Group-II**: Disease Control (5% Gum Accacia 10ml/kg p.o).
- **Group- III**: Simvastatin (10mg/kg p.o for a single day).
- **Group- IV**: Trigonelline (5mg/kg i.p for a single day).
- **Group V**: Trigonelline and simvastatin (Trigonelline 5mg/kg i.p and simvastatin 10mg/kg p.o for a single day).
- **Group VI**: Trigonelline (5mg/kg i.p for 8 days)
- **Group- VI**: Trigonelline (Trigonelline 5 mg/kg i.p for 8 days and on 8th day simvastatin 10mg/kg p.o).

**PHARMACOKINETIC STUDY OF SIMVASTATIN**

Hyperlipidimic and normal rats were administered with drugs as mentioned above. Blood samples (0.3 ml) were collected through retro-orbital plexus under mild ether anesthesia at a time period of 0, 1, 2, 4, 6, 12 and 24 h following drug administration using Sodium citrate (3.8%) as an anticoagulant. Plasma was separated immediately by centrifugation at 4000 rpm for 10 min and stored at -20°C until analysis. At the time of analysis the stored plasma was used for extraction as described below.

**Extraction Procedure**

To 100 µL of plasma samples, 20 µL of internal standard (from 100 µg/ml of working solution) and 400 µL of methanol was added, the resultant solution was centrifuged at 4000 rpm for 10 min and the Supernant was separated, which is called Supernatant I and 400 µL of methanol was added to residue and the resultant solution was mixed again for 2 minutes on cyclomixer at room temperature and centrifuged at 4000 rpm for 10 min and then Supernant was added to the Supernatant I. Now the total volume of the Supernant is evaporated to dryness on water bath, the residue was dissolved in 200 µL of mobile phase and after filtration through 0.2 µm syringe filter, 20 µL of the solution was used for the HPLC analysis.

After determining the concentration of Simvastatin in extracted plasma, the graph was plotted by taking Time (hr) on X- axis and corresponding average concentration values of Simvastatin in plasma samples on Y-axis. Various pharmacokinetic parameters like Cₘₐₓ, Tₘₓ, AUC, MRT, t₁/₂ and Kₑ.
V_d and Cl was calculated by applying Non-Compartment model by using Kinetica 5.0 software.

**PHARMACODYNAMIC STUDY**

**Induction of hyperlipidimia**

Male Sprague Dawley rats (250-300 g) were selected and housed in polypropylene cages in a room where the temperature was 25 ± 2 °C and 12 hrs light and dark cycles were maintained. The animals were allowed to acclimatize to the environment for 7 days and supplied with a standard pellet diet and water ad libitum. Before induction of hyperlipidemia, the lipid profiles of the animals were estimated. The High fat diet was prepared and was given to the rats about 35 days (5 weeks) for the induction of the Hyperlipidimia. On the 35th day the blood was withdrawn from retro-orbital to analyze for lipid profiles (TC, TG, LDL-C and HDLC levels) to confirm the induction of hyperlipidemia and it is confirmed with an increase of more than 80% of cholesterol levels of the Initial values.

**Estimation of Lipid Profile**

There are several methods for the estimation of lipid profile. Present study we used the enzymatic, CHOD/PAP, GPO/PAP method.

**Estimation of Total Cholesterol by CHOD/PAP method**

**Principle**

Cholesterol esterase hydrolyses esterified cholesterol to free cholesterol. The free cholesterol is oxidized to form hydrogen peroxide which further reacts with phenol and 4- aminoantipyrene by the catalytic action of peroxidase to form a red coloured quinoneimine dye complex. Intensity of the colour formed is directly proportional to the amount of cholesterol present in the sample.

**Procedure**

Total Cholesterol Procedure Pipette in a clean dry test tube labeled as Blank (B), Standard(S) and Test (T) (Table No.1).

Mix well and read the optical density (OD) at 500nm against Blank after five minute incubation (37°C). The final color is stable for at least 1 hour.

**Estimation of High density lipoprotein-cholesterol (HDL)**

**Procedure**

**Step I: Precipitation**

Serum - 0.2 ml, HDL PPT reagent - 0.3 ml

**Step II: Colour development**

Mix well incubate for 5 min at 37°C read the measure the absorbance 500 nm (Table No.2).

**Estimation of Low density lipoprotein-cholesterol (LDL)**

\[ \text{LDL} = \text{TC} - (\text{HDL} + \text{TG}/5) \]

**Estimation of Triglycerides by GPO/PAP method**

**Principle**

Triglycerides are hydrolyzed by lipase to glycerol and free fatty acids. Glycerol is phosphorylated by ATP in the presence of glycero kinase (GK) to Glycerol-3-phosphate (G-3-P) which is oxidized by the enzyme Glycerol-3-phosphate oxidase (G-P-O) producing hydrogen peroxide. Hydrogen peroxide so formed reacts with 4-aminoantipyrine and ESPAS in the presence of enzyme peroxidase (POD) to produce a brown colour complex. The intensity of the color developed is proportional to the triglycerides concentration.

**Procedure**

Pippete in a clean dry test tube labeled as Blank (B), Standard(S) and Test (T).

Mix well and incubate for 10 minutes at 37°C. Read absorbance of Standard and Test against Blank on photocolorimeter at 546nm/green filter (Table No.3).

**RESULTS AND DISCUSSION**

**Pharmacokinetic Data**

The concentration of Simvastatin in extracted plasma was determined; the graph was plotted by taking Time (hr) on X-axis and corresponding average concentration (ng/ml) values of drug in plasma samples on Y-axis. Trigonelline has influenced significantly the pk parameters of simvastatin by concomitant administration, C_max, AUC, MRT and t_1/2 has increased by 89.38, 98.23, 5.92 and 8.69 % respectively where as Cl and V_d has decreased by 50 and 45.32 % respectively. Furthermore upon continuous administration of trigonelline for 8 days it has minor effect on the pk
parameters of simvastatin. The combination of trigonelline and simvastatin has significant effect on the lipid profile when compared to disease control and trigonelline alone treated rats. Results were shown in Table No.4 and 5 and Figure No.2-8.

**Pharmacodynamic Data**
The lipid profile of the hyperlipidemic rats were estimated after the administration of Simvastatin and Trigonelline on the first and eighth day. Our study showed that the trigonelline alone has a significant effect on lipid profile of hyperlipidemic rats. But the combination of trigonelline and simvastatin has a significant effect on the lipid profile when compared to disease control and trigonelline alone treated rats. Results were shown in Table No.6 and Figure No.9-12 on day1, Table No.7 and Figure No.13-16 on 8th day.

**Table No.1: Total Cholesterol Procedure Pipette in a clean dry test tube labeled as Blank (B), Standard (S) and Test (T)**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Addition Sequence</th>
<th>B (ml)</th>
<th>S (ml)</th>
<th>T(ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Enzyme reagent</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>Deionized water</td>
<td>0.01</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>Cholesterol standard(s)</td>
<td>---</td>
<td>0.01</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>Serum</td>
<td>---</td>
<td>---</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Table No.2: Estimation of High density lipoprotein-cholesterol (HDL)**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Addition Sequence</th>
<th>B (ml)</th>
<th>S (ml)</th>
<th>T(ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HDL ppt reagent</td>
<td>1.0 ml</td>
<td>1.0 ml</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>2</td>
<td>Cholesterol std</td>
<td>---</td>
<td>0.01 ml</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>Supernant step from I</td>
<td>---</td>
<td>---</td>
<td>0.1 ml</td>
</tr>
<tr>
<td>4</td>
<td>Distilled water</td>
<td>0.1 ml</td>
<td>0.1 ml</td>
<td>---</td>
</tr>
</tbody>
</table>

**Table No.3: Estimation of Triglycerides by GPO/PAP method**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Addition Sequence</th>
<th>B (ml)</th>
<th>S (ml)</th>
<th>T(ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Enzyme reagent</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>Standard (s)</td>
<td>---</td>
<td>0.01</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>Serum</td>
<td>---</td>
<td>---</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Table No.4: Concentration and Time profile of Simvastatin

<table>
<thead>
<tr>
<th>S.No</th>
<th>Time (hr)</th>
<th>Simvastatin</th>
<th>Simvastatin + Trigonelline 1st day</th>
<th>Simvastatin + Trigonelline 8th day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>270.61</td>
<td>17.71</td>
<td>510.11</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>390.35</td>
<td>33.62</td>
<td>753.89</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>666.17</td>
<td>43.88</td>
<td>1261.63</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>461.70</td>
<td>43.90</td>
<td>881.97</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>241.12</td>
<td>8.28</td>
<td>462.49</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>132.80</td>
<td>7.29</td>
<td>264.29</td>
</tr>
</tbody>
</table>

Table No.5: Pharmacokinetic Data of Simvastatin, Simvastatin + trigonelline after Single Day and simvastatin + trigonelline on 8th day administration

<table>
<thead>
<tr>
<th>S.No</th>
<th>Pharmacokinetic Data</th>
<th>Animal</th>
<th>C_{max} (ng/ml)</th>
<th>T_{max} (hr)</th>
<th>AUC (ng.hr/ml)</th>
<th>t_{1/2} (hr )</th>
<th>MRT (hr)</th>
<th>Cl (lit/hr)</th>
<th>V_d (lit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Simvastatin</td>
<td>Mean</td>
<td>666.17</td>
<td>4</td>
<td>8510.01</td>
<td>9.55</td>
<td>15.19</td>
<td>0.94</td>
<td>13.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>43.88</td>
<td>0</td>
<td>365.48</td>
<td>1.04</td>
<td>0.86</td>
<td>0.04</td>
<td>1.18</td>
</tr>
<tr>
<td>2</td>
<td>Simvastatin+Trigonelline 1st day</td>
<td>Mean</td>
<td>1261.63</td>
<td>4</td>
<td>16870.4</td>
<td>10.38</td>
<td>16.09</td>
<td>0.47</td>
<td>7.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>115.94</td>
<td>0</td>
<td>1023.62</td>
<td>1.35</td>
<td>1.42</td>
<td>0.02</td>
<td>0.55</td>
</tr>
<tr>
<td>3</td>
<td>Simvastatin + Trigonelline 8th day</td>
<td>Mean</td>
<td>581.22</td>
<td>4</td>
<td>7833.43</td>
<td>11.48</td>
<td>17.75</td>
<td>1.03</td>
<td>16.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>21.0</td>
<td>0</td>
<td>526.95</td>
<td>1.73</td>
<td>2.79</td>
<td>0.06</td>
<td>1.44</td>
</tr>
</tbody>
</table>

Table No.6: Lipid profile of different groups after treatment with Simvastatin alone and in combination with Trigonelline on day 1

<table>
<thead>
<tr>
<th>S. No</th>
<th>Groups</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal control</td>
<td>44.16±2.24</td>
<td>79.1±4.3</td>
<td>16.95±0.85</td>
<td>11.38±0.57</td>
</tr>
<tr>
<td>2</td>
<td>Disease control</td>
<td>88.62±5.37</td>
<td>166.09±7.82</td>
<td>10.59±0.5</td>
<td>44.56±3.71</td>
</tr>
<tr>
<td>3</td>
<td>Simvastatin</td>
<td>84.26±3.91</td>
<td>159.75±9.80</td>
<td>11.09±0.35</td>
<td>40.98±3.75</td>
</tr>
<tr>
<td>4</td>
<td>Trigonelline</td>
<td>82.52±4</td>
<td>152.25±9.21</td>
<td>11.85±0.36</td>
<td>39.71±4.60</td>
</tr>
<tr>
<td>5</td>
<td>Simvastatin+trigonelline</td>
<td>79.53±4.15*</td>
<td>136.68±6.30***</td>
<td>13.48±0.27**</td>
<td>36.72±3.1***</td>
</tr>
</tbody>
</table>

Available online: www.uptodateresearchpublication.com July - September 111
Table No.7: Lipid profile of different groups after treatment with Simvastatin alone and in combination with Trigonelline on day 8

<table>
<thead>
<tr>
<th>S. No</th>
<th>GROUPS</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal control</td>
<td>44.16±2.24</td>
<td>79.1±4.3</td>
<td>16.95±0.85</td>
<td>11.38±0.57</td>
</tr>
<tr>
<td>2</td>
<td>Disease control</td>
<td>88.62±5.37</td>
<td>166.09±7.82</td>
<td>10.59±0.5</td>
<td>44.56±3.71</td>
</tr>
<tr>
<td>3</td>
<td>Trigonelline</td>
<td>71.23±3.76 ***</td>
<td>117.63±1.82 ***</td>
<td>15.49±0.58 ***</td>
<td>31.96±3.95 ***</td>
</tr>
<tr>
<td>4</td>
<td>Simvastatin + Trigonelline</td>
<td>69.72±4.32 ***</td>
<td>119.76±5.67 ***</td>
<td>15.36±0.85 ***</td>
<td>31.91±1.48 ***</td>
</tr>
</tbody>
</table>

Figure No.1: Structure of Simvastatin

Figure No.2: Graph Showing Conc vs Time profile of simva on day 1 and simva + trigo on day 1 and day 8
Figure No.3: AUC of Simvastatin with and without continuous administration of Trigonelline for 1st day and 8 days (***P<0.001)

Figure No.4: C_{max} of Simvastatin with and without continuous administration of Trigonelline for 1st day and 8 days (***P<0.001)

Figure No.5: T_{1/2} of Simvastatin with and without continuous administration of Trigonelline for 1st day and 8 days
Figure No.6: MRT of Simvastatin with and without continuous administration of Trigonelline for 1st day and 8 days

Figure No.7: Clearance of Simvastatin with and without continuous administration of Trigonelline for 1st day and 8 days (**P<0.001)

Figure No.8: Volume of Distribution of Simvastatin with and without continuous administration of Trigonelline for 1st day and 8 days (**P<0.001)

(*P<0.05, **P<0.01; ***P<0.001) When compared with the Disease control by using One Way ANNOVA followed by Dunnets test.
Figure No.9: Cholesterol concentration of various groups after administration of simvastatin with and without trigonelline in hyperlipidimic rats

Figure No.10: Triglycerides concentration of various groups after administration of simvastatin with and without trigonelline in hyperlipidimic rats

Figure No.11: HDL concentration of various groups after administration of simvastatin with and without trigonelline in hyperlipidimic rats
Figure No.12: LDL concentration of various groups after administration of simvastatin with and without trigonelline in hyperlipidemic rats (*P<0.05, **P<0.01; ***P<0.001) When compared with the Disease control by using One Way ANNOVA followed by Dunnets test.

Figure No.13: Cholesterol concentration of various groups after administration of simvastatin with and without trigonelline in hyperlipidemic rats (***P<0.001)

Figure No.14: Triglycerides concentration of various groups after administration of simvastatin with and without trigonelline in hyperlipidemic rats (***P<0.001)
CONCLUSION
The present study showed a significant effect of trigonelline on the pharmacokinetics of simvastatin on 1st day, but on 8th day the concentration of simvastatin has decreased but not to significant level. Furthermore the trigonelline had significant effect on pharmacodynamic parameters of simvastatin. But an extensive research is needed to prove the effect of trigonelline upon chronic treatment because there is a slight decrease in concentration and AUC of simvastatin.

ACKNOWLEDGEMENT
All authors would like to acknowledge Synapse Life Sciences, Nakkalagutta, Hanamkonda, Warangal, Telangana, India for the preparation of the research work.

BIBLIOGRAPHY


