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Effect of Pomelo Extract on Behavioral Activity of Rats

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Abstract:- Food drug interactions are again one of the most emphasized sectors of drug interactions. The effect of drug alters when ingested with food, beverages and dietary supplements which interact in person. Diet and lifestyles sometimes play a significant role on the metabolism of drugs. In this experiment the effects Citrus maxima fruit are studied with respect to a Benzodiazepine moiety diazepam which includes the Locomotory, Muscle tone and the Anti-anxiety activity tests. Synergistic effect of C. maxima with diazepam is being achieved that gives an idea about the usage of diazepam in low dosing units with minimum adverse drug reactions.

Keywords:- *Food-Drug interactions, Diazepam, Pomelo, Stress, Depression.*

I. INTRODUCTION

Drug interaction is defined as a cross reaction between a drug with a certain entity viz. food, another drug etc. which prevents the drug from working to its full potential. This type of interaction either increases or decreases the therapeutic efficacy and the side effects of the drug or sometimes leads to a newer unknown effect [1]. Consequences of Drug interactions leads to elevation or reduction in the desired effects of a drug, increase or decrease in the adverse effects of the drug, sometimes results in unnecessary pain and suffering.

Drug interactions can be pharmacokinetic (pk) or pharmacodynamic (pd). Pharmacokinetic interaction results from alterations in absorption, distribution, metabolism or excretion mechanisms of a drug. On the other-hand pharmacodynamic interactions results from the influence of combined treatment at a site of biological activity and yield altered pharmacological actions at standard plasma concentrations. Drug interactions affect absorption in many ways mechanisms of absorption include passive diffusion, convective transport, active transport, facilitated transport, ion-pair transport and endocytosis [2].

The rate of drug absorption by passive diffusion depends upon the solubility or dissolution of a compound in gastric fluid. Basic drugs are very much soluble in acidic fluids and vice versa. Therefore, the compounds that create an environment with a specific pH may result in decrement in the in the solubility of compounds needing an opposing pH for absorption. However, absorption is not completely ensured by drug solubility since it occurs only in case of unionized molecules. In spite of acidic drugs being soluble in basic fluids, decrement in the proportion of solubilized unionized acidic molecules can take place in basic environments. For an example if ketoconazole, itraconazole and dapsone which requires acidic environment shows reduced absorption when induced concomitantly [3].

Drugs may result in the formation of insoluble complexes by chelation in the gastrointestinal tract. Chelation results in the formation of insoluble compound which do not permeates the intestinal mucosa due to the lack of drug dissolution. For an example the quinolone antibiotics if administered with magnesium and aluminum containing antacids results in chelation [15].

High fat containing meals can result in a significant increase in the extent of absorption of fat-soluble compounds such as griseofulvin, cefpodoxime, and cefuroxime proxetil. Prolonged stomach retention may result in excessive degradation of acid labile compounds viz. penicillin and erythromycin. Modulation of intestinal blood flow can be done by vasoactive agents and theoretically absorption of lipophilic compounds can be affected. However, till date there exists no evidence of clinical data regarding these drug interactions. Multiple intestinal transporters located on the brush border and basolateral membrane of the enterocyte are potential absorption and the inhibition of these transporters interferes in drug effect. In fact, gastrointestinal CYP iso-enzymes, responsible for Phase I oxidative metabolism are most highly concentrated in the proximal two thirds of the small intestine [15].

Interactions with foods are again one of the most emphasized sectors of drug interactions. The effect of drug alters when ingested with food, beverages and dietary supplements which interact in person. Diet and lifestyles sometimes play a significant role on the metabolism of drugs. Major side effects in some diet on drugs include alteration in absorption by fatty, high protein and fiber diets. The most important interactions include the high risk of treatment failure that arises from reduction in the bioavailability during the fed state. Gastric acid secretion sometimes affects the bioavailability of certain drugs due to the physiological response to food intake [2,6]. In this experiment grape fruit or pomelo (*Citrus maxima*) is used to study its effect

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regarding the antidepressant activity of the benzodiazepine (BZD) moiety.

Citrus maxima or pomelo or shaddock or grape fruit is a citrus fruit native to Southeast Asia belonging to the family of *Rutaceae* [14]. Grape fruit and grape fruit juice generally interact with number of drugs causing adverse effects [4,5,6]. Generally, it contains vast quantities of furanocoumarins [7]. Organic compounds containing furanocoumarins derivatives cause alterations in the hepatic and intestinal CYP 450 especially CYP3A4 and are believed to be responsible for *C.maxima*. In general drugs falling under class benzodiazepines (triazolam, midazolam, nitrazepam, dextroamphetamine, levoamphetamine, diazepam, alprazolam and quazepam [8]), antihyperlipidemic drugs (atorvastatin, lovastatin, simvastatin [10]), antiarrhythmics (amiodarone, dronedarone, quinidine, disopyramide, propafenone and carvedilol [9]) and others like calcium channel antagonists, HMG Co-A reductase inhibitors are mostly affected [13].

If spoken about the mechanism of interaction of the pomelo results in the elevation of the drug bioavailability and significant alterations in the pk-pd factors of the drug. Generally, it inhibits the CYP450 3A4 in the small intestine consequences in the reduction of the drug pre-systemic metabolism and P-glycoprotein. The CYP450 3A4 enzyme is responsible for the first pass metabolism in liver. The chemical constituents that are present in pomelo mainly furanocoumarins tend to inhibit this drug metabolism by the cytochrome enzymes [11]. If consumed in small amount it inhibits the intestinal enzymes. Generally, the duration of action of pomelo stands for 72 hours and the onset of action starts from 4 hours of ingestion before the drug [12]. In 2007 ***Taguchi*** reported purpurea in a 79-year individual due to the combined ingestion of cilostazol, aspirin and pomelo which disappeared on the cessation of pomelo intake.

In this experiment the BZD moiety which is used in diazepam which falls under the antidepressant category of sedative and hypnotic class of drugs. Generally, its site of action is in the midbrain ascending reticular formation and limbic system. It acts by inhibiting the pre/post synaptic inhibition through the BZD receptor of $GABA_A$ receptor chlorine ion channel complex by increasing the frequency of the chlorine ion channels [15].

II. MATERIALS AND METHODS

Citrus maxima were collected from the Durgapur region of Bardhhaman district, West Bengal, India. Diazepam (10mg/ 2ml) under the trade name 'PAXUM inj.' was procured from East India Pharmaceuticals Pvt. Ltd. Wister Albino rats (100-180g) of either sex were used in this experiment. Favorable laboratory environment is provided with standard laboratory conditions combined with access to food and water ad libitum. The whole experimental work was done obeying CPCSEA guidelines. Here 12 animals were grouped in 4 batches containing 3 individuals each.

A. Extraction of Pomelo Juice

The pomelo juiced was extracted after separation of the pulp with the help of a mixer grinder. After extraction the leftover remnants were eliminated using a sieve and the freshly prepared juices were placed in a cleaned vessel.

B. Conduction of Locomotory Activity Test

The Locomotory activity can be easily carried out with using Ajanta actophotometer Model AEI-AP-SH-03. Then Wister Albino rats weighing between 100-180 g were collected and separated into 4 groups with 3 individuals each. The basal activity score of all the individuals were recorded after 30, 60, 120 and 240 minutes of the rats after treated with drug individually (4mg/kg intraperitoneal), pomelo extract individually and with combined effect of drug and pomelo extract [16].

C. Conduction of Muscle tone Activity Test

It is basically carried out using Ajanta Rota rod Model AEI-RR-SH-04. Then the respective batches of mice were put into the Rota rod and their riding time or endurance is being checked at 25 rpm for 30, 60, 120 and 240 minutes of the rats after before and after treated with drug individually (4mg/kg intraperitoneal), pomelo extract individually and with combined effect of drug and pomelo extract [16].

D. Conduction of Anti-anxiety Test

The antianxiety test was carried out with the help of an elevated plus maze for the measurement of anxiety level based on the principle of exposure of an individual to open arms of the plus maze to be stronger than that of the enclosed one. [7] The open arms were measured to 50x10 cm and the enclosed arms were 50x10x40 cm. The device was elevated from the floor at a height of 50 cm. of the rats after before and after treated with drug individually (4mg/kg intraperitoneal), pomelo extract individually and with combined effect of drug and pomelo extract [17].

III. RESULTS AND DISCUSSIONS

A. Locomotory Activity Test

In Table.1, the locomotion with diazepam was seen to be reduced to 7.5±4.5 and 17±3.5 after 30 minutes and 60 minutes of drug administration which were at a high significance as compared to the control group. Reduction of the locomotion to 40±7.50 and 60±5.50 at 120 and 240 minutes after the drug administration when compared to the control was seen. This is occurring due to the CNS inhibitory effect of diazepam at that dose. After 4 hours of drug administration a significant recovery was observed. In case of the pomelo fed groups a reduced locomotion up to 4 hours was found again due to the CNS inhibitory effect of the pomelo. In the group of diazepam administered with pomelo group at 30 minutes of interval a significant reduction in the ambulatory activity were found.

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B. Muscle tone Activity Test

In Table.2, the muscle tone was found to reduce to 4.02±2.5 and 5.5±2.5 after 30 and 60 minutes of the diazepam administration because of the muscle relaxant property of diazepam. In case of the pomelo fed groups no muscle tone activity was observed signifying the lack of muscle tone activity of the pomelo. But when administered with diazepam a significant drop in muscle tone was witnessed signifying the synergistic property of pomelo on diazepam.

C. Anti-anxiety Test

In Table.3, the data of antianxiety tests in elevated plus maze were depicted. Here at all the time intervals a latency period was observed indicating the entry of animals in the closed arm of the plus maze. This phenomenon resulted due to the anxiety of the animals which resisted them to proceed towards the open ends. Though diazepam falls under antianxiety category but in case of mouse a dose of 4mg/kg proved to be sedative that resisted the open arm visit at different time intervals for all the groups.

IV. CONCLUSION

This study was conducted to find the effect of pomelo extract on the BZD moiety and the behavioral changes of the organisms. Pomelo itself proved to be a CNS depressant which ameliorates the CNS depressant activity of diazepam and moreover pomelo prolongs the duration of action of BZD in the body limiting its elimination from the body. So, through this study it can be concluded that with the intake of pomelo with BZD favorable therapeutic effects to be experienced by the patient at low doses of BZD as compared to the marketed dosing amounts thus resulting in the reduction of intake and subsequently the adverse effects of BZD.

V. FUTURE PROSPECT OF THE EXPERIMENT

Here in this experiment, the results have been concluded on the basis of laboratory results. For further establishment of the concluded study clinical trials are to be carried out and through subsequent preclinical and clinical trails the bedrock of this study is to be more solidified.

VI. TABLES

Table 1 Locomotary Activity Test Results in an Actophotometer

Groups	**Duration**			
	30 minutes	***60 minutes***	***120 minutes***	***240 minutes***
Control	102.33±18.14	-	-	-
Diazepam (4mg/kg)	7.33±3.51 [a]	16.33±3.51 [a]	42.33±7.50 [b]	59±5.56 [b]
Diazepam (4mg/kg) + Pomelo	34.33±5.033 [b]	7±3.60 [a]	15±6.08 [a]	28±5 [b]
Pomelo	24.33±6.50 [b]	40.66±9.60 [b]	44.33±6.11 [b]	38.33±13.42 [b]

[a]P<0.001, [b] p<0.01, n=3

Table 2 Rota Rod Data to Measure Change Iin Muscle Tone

Groups	**Duration**			
	30 minutes	***60 minutes***	***120 minutes***	***240 minutes***
Control	25.68±5.92	-	-	-
Diazepam	3.86±1.76 [b]	5.42±3.95 [b]	22.03±6.81	24.86±21.19
Diazepam (4mg/kg) + Pomelo	1.39±0.49 [b]	3.07±1.06 [b]	4.75±1.81 [b]	16.51±4.52
Pomelo	36.79±14.33	38.3±14.68	33.53±11.86	46.85±11.51

[b] p<0.01, n=3

Table 3 Antianxiety Test Data in a Plus Maze

Groups	**Closed arm statistics**											
	30 minutes			***60 minutes***			***120 minutes***			***240 minutes***		
	Latency	Entries	Spent time	Latency	Entries	Spent time	Latency	Entries	Spent time	Latency	Entries	Spent time
Pomelo	3.89± 3.49	1±0	296.09±3 .52	2.46± 1.65	1.66± 1.15	296.18 ±1.78	1.77±0. 92	5±4.85	294.24 ±2.80	6.41±8. 34	2±1.73	292.08± 7.31
Diazepam	2.28 ± 0.87	1.33 ±1.5 2	174.99±1 51.99	2.74± 2.99	1±0	201.94 ±162. 97	1.53±1. 22	0.66±0. 57	199.45 ±172.7 2	1.50±0. 81	1±0	298.29± 1.51
Diazepam (4mg/kg) + Pomelo	4.61 ± 5.92	1.66 ±1.1 5	2.67.60± 4460	2.87± 0.28	2±1	281.97 ±19.3 8	1.57±0. 40	1.33±0. 57	297.85 ±0.84	3.32±2. 58	1.33±0. 57	291.12± 10.16
Control	3.33 ±	1.33	248±83.1	-	-	-	-	-	-	-	-	-

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Groups	Closed arm statistics											
	30 minutes			*60 minutes*			*120 minutes*			*240 minutes*		
	1.15[a]	±0.57[a]	3[a]									

[a] The Control Data was Taken Once After Dosing with Normal Saline

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