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Study on the effect of Shallaki (*Boswellia serrata* Roxb.) on the Pharmacokinetics of Pioglitazone in Rat Plasma

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Abstract
The study is designed to test the pharmacokinetic interaction of pioglitazone with shallaki in rats. Group I received pioglitazone 10mg/kg p.o and group II received 415mg/kg of extract equivalent to 250mg/kg of boswellic acid p.o and given 30min. before the administration of pioglitazone once daily for 8 days. Blood samples were collected on day 0 and day 8 of treatment. Pioglitazone was extracted and plasma concentration estimated using HPLC. With single dose treatment C_{max} (p<0.001) and $AUC_{0\text{-}24hr}$ (p<0.01) of pioglitazone were significantly increased whereas it had no significant effect on the T_{max}, K_{el} and $t_{1/2}$ (p>0.05). But with one week repeated administration, C_{max} (p<0.001), T_{max} (p<0.001), $AUC_{0\text{-}24hr}$ (p<0.001) and $t_{1/2}$ (p<0.001) were significantly increased and K_{el} (p<0.001) is significantly decreased. The study reveals that shallaki increases the bioavailability of pioglitazone when given concurrently, which could be due to increased absorption or decreased metabolism and elimination or a combination of both.

Keywords: pharmacokinetic interaction, pioglitazone, shallaki, herb drug interaction

1. Introduction
The popularity of herbal medicinal products (HMPs) makes it important to understand potential interactions between herbs and prescribed drugs, since the interaction of herbal drugs with other drugs cannot be entirely ruled out. Previous reports have suggested that arthritis affects about 50% of individuals with diabetes [1]. Pioglitazone (PGZ) is a thiazolidinedione antidiabetic agent with an oral bioavailability of 80% and metabolized by Cytochrome P450 isoforms such as CYP2C9 and CYP3A4 [2-3]. Historically, *Boswellia serrata* is recommended for a variety of conditions including osteoarthritis and rheumatoid arthritis with non-selective inhibitory effects on drug metabolizing CYP enzymes 1A2/2C8/2C9/2C19/2D6and 3A4 [4].
The purpose of this study is to evaluate the effect of shallaki on the pharmacokinetics of pioglitazone in rat plasma.

2. Materials and method
2.1 Procurement of drug samples and chemicals
Standard PGZ was obtained from Ranbaxy Laboratories Dewas, M.P., India and shallaki was obtained from Himalaya outlet, sapna-sangeeta road, Indore (M.P.) and manufactured by The Himalaya Drug Company, Banglore, India. Each capsule contains shallaki 125mg (*Boswellia serrata* Roxb.) which is standardized to contain 60% boswellic acid. All the chemical and reagents used were of HPLC grade and purchased from Spectrochem, Mumbai, India.

2.2 Experimental animals
Male Wistar rats (150–200 g) were used and obtained from New Sai Fish Center, Indore and housed in individual cages feded with a standard pellet diet supplied by Godrej Agrowet Ltd, Indore and water *ad libitum.*

2.3 Shimadzu LC 10 ATVP HPLC system
The LC system consists of pump (Shimadzu LC-10ATVP) with universal loop injector of injection capacity 20 µL. The equipment was controlled by a PC work station equipped with software CLASS M 10-VP software (Shimadzu, Kyoto, Japan). The volume capacity of the reservoir was greater than 500ml.

2.4 Study Protocol

2.4.1 Dosing of PGZ and shallaki

Twelve male wistar rats weighing between 150-200 g were divided into two groups of six each. The rats were fasted overnight and allowed to have free access to water. Animals of Group I (control) were treated with PGZ 10 mg/kg p.o [5]. (The PGZ solution for oral administration was prepared by suspending 10 mg of PGZ in 10 ml of 0.1% solution of potassium citrate) and animals of group II received 250 mg/kg of boswellic acid in shallaki p.o (prepared as suspension in 0.05% CMC) 30 min. before the administration of PGZ once daily for 8 days [6].

2.4.2 Blood Collection and sampling

Using a #22 surgical blade, tail was gently nicked around the midline. Blood samples (approximately 0.1ml) were collected in heparinized Eppendorf tubes (1.5ml) from the lateral tail veins after overnight fasting on day 0 and day 8 of treatment at 1, 2, 4, 6, 8 and 24 hr of PGZ administration. Collected blood samples were stored at -4 ºC until assayed.

2.4.3 Extraction of PGZ from Blood

The stored samples were centrifuged at 5000 rpm for 10 minutes at room temperature and 0.1 ml of plasma was transferred to plastic centrifugation tube (1.5 ml) then 0.5 ml of acetonitrile was added, after vortex mixing for 30 seconds, the mixture was centrifuged at 5000 rpm for 5 min. The upper layer was filtered through 0.22µm and 20 µl of sample was injected into HPLC apparatus.

2.4.4 Assay of PGZ in plasma

The HPLC conditions for analysis were as follows:

- Column -C_{18} column
- Detector- Photodiode array detector
- Mobile Phase- Methanol: Water (90:10)
- Column temperature- Room temperature
- Flow rate- 1 ml/min
- Detection wavelength- 225 nm

2.4.5 Data analysis

2.4.5.1 Pharmacokinetic analysis

Plasma concentration – time curve was plotted, and the peak plasma concentration (C_{max}) and time needed to reach the peak plasma concentration (T_{max}) were noted directly from the generated data. The area under the plasma level – time curve ($AUC_{0\text{-}24hr}$) was calculated using Trapezoidal rule The elimination rate constant (K_{el}) was calculated from the semi-log plot of the data using slope of the terminal elimination phase; and half-life ($t_{1/2}$) was calculated by $0.693/K_{el}$ [7].

2.4.5.2 Statistical analysis

All the means are presented with their standard deviation (mean ± S.D.) and one-way ANOVA is used to determine the significant difference in the pharmacokinetic parameters of PGZ between control and test group.

3. Results

3.1 Linearity of pioglitazone

The retention time of PGZ in the given HPLC conditions was found to be 4.22 min. The method was linear over 1-50µg/ml with r^2 = 0.999. The linear equation obtained is y=33669x-6426 where x = concentration and y = area. On day 0, as compared to control group C_{max} (p<0.001) and $AUC_{0\text{-}24hr}$ (p<0.01) of test group were significantly increased whereas it had no significant effect on the T_{max}, K_{el} and $t_{1/2}$ (p>0.05). But on day 8, as compared to control group C_{max} (p<0.001), T_{max} (p<0.001), $AUC_{0\text{-}24hr}$ (p<0.001) and $t_{1/2}$ (p<0.001) were significantly increased and K_{el} (p<0.001) is significantly decreased.

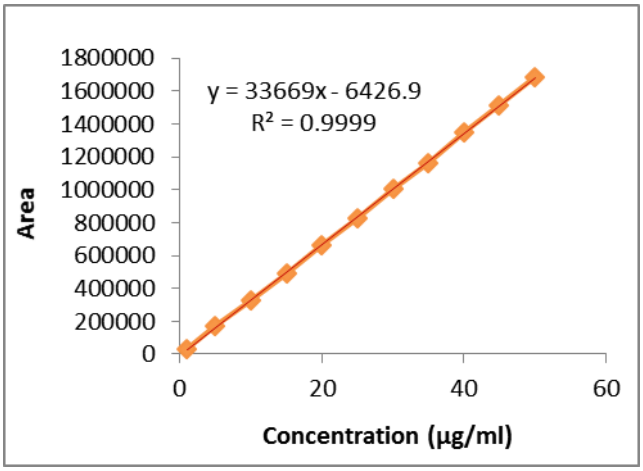

Fig 1: Linearity curve of PGZ

3.2 Pharmacokinetic calculations

The various pharmacokinetic parameters calculated for PGZ in control and test group are C_{max}, T_{max}, $AUC_{0\text{-}24hr}$, K_{el} and $t_{1/2}$. The concentration of extracted PGZ in the plasma samples were calculated from the HPLC area using the linear equation. Since the C_{max} of pioglitazone when co administered with shallaki occurred at about 2 hrs later that that of pioglitazone alone, it's an indication that shallaki may have caused delay in the rate absorption of pioglitazone. Also with repeated administration, $AUC_{0\text{-}24hr}$ of test group is increased by 33% as compared to control. As the co administration of shallaki and pioglitazone reduced the elimination rate constant, it invariably caused prolongation of half-life further suggesting the inhibition of pioglitazone metabolism by shallaki.

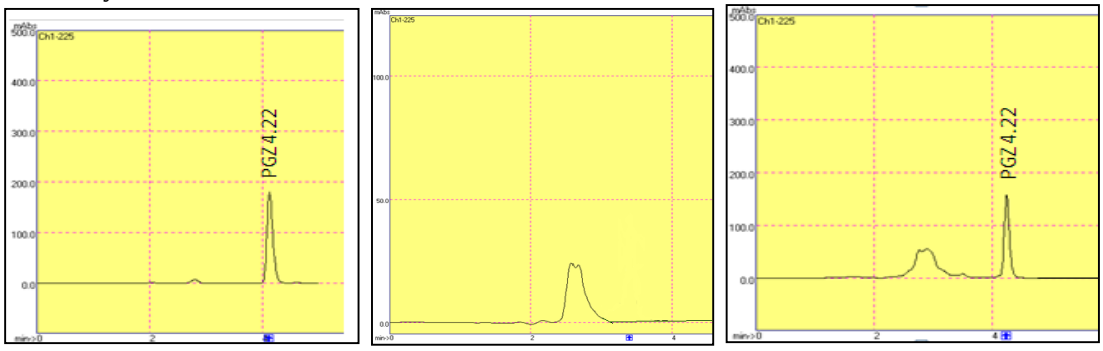

Fig 2: Chromatogram of (a) PGZ (b) blank rat plasma (c) PGZ in rat plasma

Table 1: Mean value of pharmacokinetic parameters of PGZ in control and test group on day 0 and day 8

Parameters	On 0th day		On 8th day	
	Control	Test	Control	Test
C_{max} (µg/ml)	23.92±0.601	29.71±1.802***	23.64±1.172	33.56±1.537***
T_{max} (h)	2	2 NS	2	4***
AUC_{0-24hr} (µg h/ml)	257.87±23.947	296.60±14.332**	259.16±0.657	344.39±6.543***
K_{el} (h^{-1})	0.0914±0.007	0.0871±0.007NS	0.0890±0.002	0.0818±0.001***
$t_{1/2}$ (h)	7.62±0.565	8.00±0.661NS	7.79±0.149	8.47±0.112***

Each value is expressed as mean ± standard deviation (n=6), NS-Not Significant, *p<0.05, **p<0.01, ***p<0.001 as compared to control group

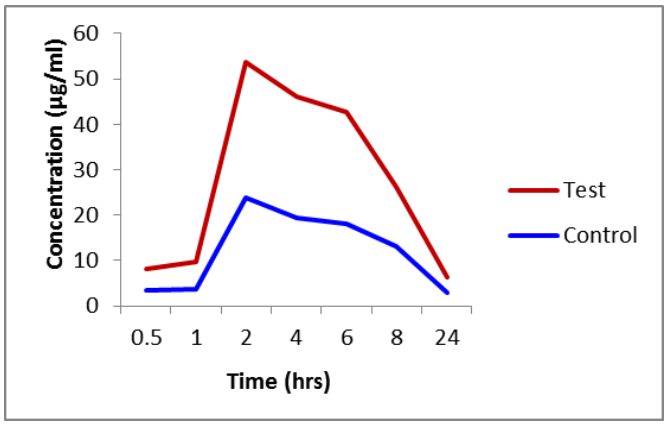

Fig 3: Comparison of concentration-time profile of PGZ between control and test on day 0

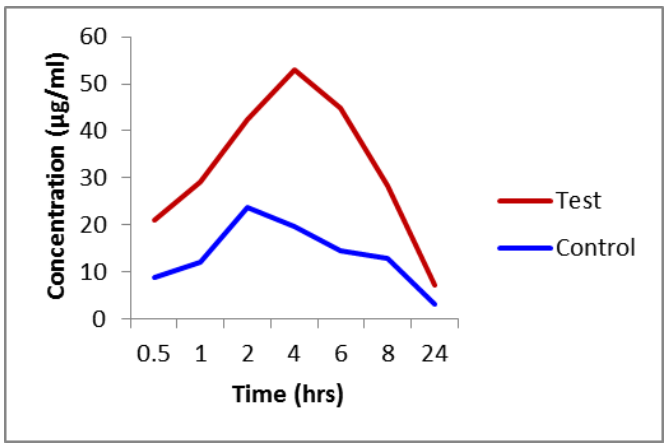

Fig 4: Comparison of concentration-time profile of PGZ between control and test on day 8

4. Discussion

The present study revealed that with single dose treatment, C_{max} of PGZ co administered with shallaki is significantly increased by 24% as compared to control indicating that shallaki have increased the absorption of PGZ. Also 15% increase in the AUC_{0-24hr} of test group as compared to control group indicates that shallaki have enhanced the extend of absorption of PGZ by inhibiting its metabolism. However, there is no significant effect on T_{max}, K_{el} and $t_{1/2}$. But with one week repeated administration, C_{max} is increased by 42% in test as compared to control.

These effects of shallaki must be cautiously considered if pioglitazone is used by a patient who consumes shallaki concurrently, to avoid complications due to increased bioavailability of pioglitazone.

5. References

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