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Resveratrol's Effect on Naproxen's Pharmacokinetics and Pharmacodynamics: Role of CYP1A2 Inhibition

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Introduction

Naproxen (NAP) (6-methoxy-α-methyl-2-napthalene acetic acid) is a non-steriodal anti-inflammatory medication that works well as an analgesic (Ruedy and Mcullongh 1973) and for rheumatoid arthritis (Bowers et al. 1975). The plasma concentrations of naproxen are correlated with its effectiveness (Day et al., 1982). Due to its strong binding to plasma albumin, naproxen is mostly concentrated in plasma (Runkel et al. 1972) and is well absorbed orally at dosages up to 900 mg (Runkel et al. 1974). (Brogden et al. 1984) Naproxen belongs to the 2-arylpropionic acid class of nonsteroidal anti-inflammatory drugs and is stereochemically pure. When used orally, naproxen is quickly and completely absorbed. Only a little portion of naproxen is removed unaltered after biotransformation into glucuroconjugated and sulphate metabolites, which are eliminated in urine. Since buildup happens in end-stage renal illness, the excretion of the 6-0-desmethylnaproxen metabolite conjugate may be related to renal function. Cytochrome P450 (CYP) dealkylates naproxen in phase I to produce the O-demethylated metabolite, which is then followed by phase II acylglucuronidation. Naproxen is thus converted to naproxen acyl glucuronide and 6-0-desmethylnaproxen acylglucuronide (6-DMNG) after being oxidized to 6-0-desmethylnaproxen (6-DMN). According to a preliminary investigation, the CYP2C9-specific inhibitor Sulfaphenazole reduced the human liver microsomal O-demethylation of S-naproxen. The majority of human liver demethylation of naproxen is likely caused by CYP2C9 and lA2 working together, as evidenced by a subsequent study that found that sulfaphenazole decreased microsomal demethylation of S-naproxen by 47% and the CYPIA2 inhibitor furafylline decreased O-demethylation of S-naproxen by 28%.

A naturally occurring polyphenolic phytoalexin, resveratrol (RSV) (3, 4′, 5-trihydroxystilbene) is found in fruits, vegetables, grape skins, and red wine in particular. RSV has a variety of physiological and biochemical characteristics, such as immune-modulatory and anti-inflammatory effects, and it offers a host of health advantages, from cardioprotection to chemoprevention (Kalantari and Das, 2010; Brisdelli et al., 2009). In many tumoral cell lines, RSV has recently been demonstrated to exhibit genoprotective, cytotoxic, antiproliferative, and proapoptotic effects (Romano et al., 2013). By altering the enzymes and pathways that generate inflammatory mediators, RSV demonstrates anti-inflammatory action. RSV shows promise as an alternative or supplemental treatment for inflammatory conditions (Das and Das, 2007; Udenigwe et al., 2008). Furthermore, it has been demonstrated that RSV has a low profile of adverse effects (Cottart et al., 2010). Therefore, using NAP and RSV together may be a different approach to treating inflammatory illnesses.

NAP is a commonly used anti-inflammatory medication that may be administered in conjunction with long-term treatment that includes herbal remedies or dietary supplements including RSV. A thorough review of the literature turned up no evidence of a relationship between RSV and NAP. Thus, it is vital to take into account how NAP and RSV interact. This study set out to assess how RSV therapy affected the pharmacokinetics of NAP in rats. Methods and Materials Materials

Aurobindo Pharmaceuticals (Jadcherla, Mahaboobnagar) provided a complimentary sample of naproxen. The source of carrageenan was Sigma Aldrich, Bangalore. We purchased RSV from Navachetan in New Delhi, India.
All of the chemicals and reagents utilized in the study are of analytical grade, as are the solvents employed for quantitative analysis (Merck, India).

Animals
The study used albino male Wistar rats weighing between 200 and 250 grams. The animals were purchased from Kakatiya University's major animal facility in Warangal. The rats were kept in groups of no more than five in 38 x 23 x 10 cm polypropylene cages. They were kept in normal lab circumstances with a natural light-dark cycle (14 + 1 h light; 10 + 1 h dark), and they had unlimited access to tap water and a typical dry rat chow. The Institutional Animal Ethics Committee examined and authorized each of the procedures outlined (IAEC/35/UCPSc/KU/2016). Groups of six rats each were created from the rats.

Approach
Induced by carrageenan Model of paw edema
Freshly made 1% w/v carrageenan suspension in regular saline is injected into the left hind paw's subplantar area. The test medication is taken intraperitoneally (i.p.). Using a mercury-filled plethysmograph, the paw volume up to the ankle joint was assessed in both drug-treated and untreated groups three hours after the carrageenan challenge. Edema is identified, and the formula is used to determine the percentage decrease in edema. Mean edema in the control group divided by the mean edema in the treated control group minus the mean edema in the drug-treated group multiplied by 100 is the percentage reduction in edema.
Every animal was split up into V groups, each of which had six animals (n=6). Drug treatment was administered for three weeks to groups III (resveratrol 30 mg/kg p.o.), IV (naproxen 25 mg/kg p.o.), and V (combination). Blood samples were taken from the retroorbital sinus on the twenty-first day of the research at intervals of 0.5, 1, 2, 3, 5, 6, and 7 hours. The samples were then stored at -80ºC until they could be further examined. The following day, a 1% w/v carrageenan suspension was injected into each group's subplantar area for a single day, with the exception of Group (I). The only vehicle given to Group I was Normal Saline. After the inflammation caused by carrageenan, each animal was kept in a different cage for at least half an hour.
Naproxen Determination in Plasma Samples
Standards and stock solutions
Naproxen stock solutions were made by dissolving the drug in methanol, yielding a solution with 1 mg/ml. A workable solution of 50 µg/ml was obtained by diluting this solution 20 times. Ibuprofen was dissolved in methanol to produce a stock solution of the internal standard with a concentration of 1 mg/ml.
Plasma sample treatment
Separately, the 100µl working solutions were moved to dry, clean centrifuge tubes. Each tube was filled with 500 µl of plasma. After two minutes of vortex mixing, 400 µl of methanol was added. Before centrifugation at 5000 rpm for five minutes, these were vortexed together. Before injecting 50 µl into the HPLC system, the supernatant was separated and put into HPLC vials.
Curves of calibration
Rat plasma was used to create calibration curves. In these, plasma samples spiked with different quantities of Naproxen (0.5,1,2,5,10,20, and 40 µg/ml) and a fixed concentration of the internal standard (10 µg/ml) were subjected to duplicate analysis. A plot of the drug's peak area ratio (PAR) to the internal standard as a function of drug concentration (C) represents the naproxen calibration curve.
Analysis of pharmacokinetics
From concentration-time data, the pharmacokinetic parameters, peak serum concentrations [Cmax] and time to

achieve peak concentration [tmax], were directly derived. According to the linear trapezoidal rule, AUC0-t in this study denotes AUC from 0 to 7 hours, and AUC0-∞ denotes AUC from 0 to infinity.

The AUC0-∞ was calculated using the formula AUC0-t +[Clast/ Kcl] where Clast is the concentration in mg/ml at the last time point and Kcl is the elimination rate constant.

Results

During the study period, no serious adverse events related to drug were reported. The pharmacokinetic parameters and mean plasma concentration–time profiles of NAP after pretreatment with RSV are shown in (Table 1) and (Table 2), respectively.

TIME (h)	NAP	NAP+RSV
0	0±0	0±0
1	2.1±0.24	2.8±0.29
2	5.6±0.32	6.1±0.35
4	8.6± 0.72	8.3± 0.68
6	4.3±0.28	8.4±0.31
8	3.2±0.18	4.8±0.20
10	2.1±0.9	3.5±0.12
12	1.3±0.8	2.3±0.2

Table1: Mean serum concentration (ug/ml) of Naproxen and naproxen in presence of resveratrol (SDT & MDT) in inflammatory rats.

PK PARAMETER	Naproxen	NAP+RSV
C_{max} (µg/ml)	1.8±0.72	2.95±0.7**
t_{max} (h)	1.4±0	2.82±0
AUC $_{0-t}$ (µg/ml/h)	4.81±1.8	7.61±2.7***
$t_{½}$ (h)	10.7±0.05	14.3±0.06**
Clearance (l/hr)	14.83±5.45	6.01±2.85***
V_d (ml)	22.92±8.68	12.96±7.32***

Table2: Mean Pharmacokinetic parameters of Naproxen in presence of resveratrol in Inflammatory rats

Mean ± SD: ***significant at p<0.001; ** significant at p<0.01;
*significant at p<0.05 compared to Naproxen control

The plasma NAP concentrations were increased after RSV pretreatment when compared to control phase. The mean Cmax (1.8±0.72 versus 2.95±0.7µg/mL, p<0.05), mean AUC (4.81±1.8 versus 7.61±2.7µgh/mL, p<0.05) and mean t1/2 (10.7±0.05 versus 14.3±0.06 h, p<0.05) values were increased respectively, after RSV pretreatment as compared to that of control phase.On the other hand, mean CL/F (14.83±5.45 versus 6.01±2.85 L/h, p<0.05) and mean Vd/F (22.92±8.68 versus 12.96±57.32 L, p<0.05) values were decreased respectively, after RSV pretreatment as compared to the control phase. However, there was no significant change observed in tmax of NAP between RSV treatment and control phases.

The pharmacodynamic study states that the percentage inhibition of mean paw edema for resveratrol treated group was 51.1±0.1, naproxen treated group was 48.2±0.5, combination of naproxen and resveratrol treated group was 53.1±0.2.

Pharmacodynamic data

	TREATMENT			
Time (h)	Control	RSV	NAP	RSV+NAP
0	31.2±0.4	34.3±0.1	35.1±0.4	36.2±0.5
1	42.3±0.1	51.1±0.1	48.2±0.5	53.1±0.2
2	60.6±0.1	63.2±0.4	59.1±0.3	64.3±0.9
3	58.2±0.3	54.1±0.2	55.1±0.1	59.3±0.1
4	55.3±0.4	52.1±0.3	48.5±0.3	43.2±0.2

Table 3: % Inhibition of Mean Paw edema

Discussions

For a wide range of illnesses, rehabilitation, and medical care, herbal remedies have been utilized extensively as complementary or alternative treatments. Herbal remedies are frequently used in conjunction with numerous prescription medications and contain multiple pharmacologically active ingredients.
It is clear from the literature that RSV was suggested to use nuclear aryl hydrocarbon receptor (AHR) antagonistic action to prevent the transcription of different CYPs. However, by changing the pharmacokinetics of concurrently taken medications, RSV's suppression of CYP activity may result in safety issues.
Therefore, utilizing naproxen as a CYP1A2 substrate, the current investigation assessed the impact of RSV treatment on the pharmacokinetics of naproxen in rats.

Naproxen is a promising CYP1A2 probe substrate to measure the CYP1A2 enzyme activity because of its high tolerance when administered. Changes in the CYP1A2 enzyme's catalytic activity can alter naproxen's pharmacokinetics. In order to measure the CYP1A2 enzyme activity in the investigation, naproxen is utilized as a probe medication.
According to our findings, oral RSV delivery dramatically changed naproxen's pharmacokinetics and increased its bioavailability by inhibiting the CYP1A2 enzyme in rats. In this investigation, we discovered that, in comparison to control, RSV therapy significantly increased mean Cmax, AUC, and T1/2 and significantly decreased mean CL/F and Vd/F of naproxen. Despite an increase in mean naproxen Tmax values following the RSV therapy phase, these changes were not statistically significant. Increased naproxen exposure following RSV therapy is shown by rising Cmax and AUC values. Conversely, the rising T1/2 and falling CL/F ratios show that RSV treatment inhibits the removal of naproxen.
These results suggest that reservetrol inhibits the CYP1A2-mediated metabolism of naproxen in rats. Consequently, CYP1A2 enzyme activity was inhibited to boost naproxen's bioavailability.
Consequently, combining naproxen with RSV may be a novel way to lower the dosage and lessen naproxen's gastrointestinal adverse effects.
A comparison was made between the mean percentage of paw volume in drug-treated and control animals. These results imply that the animals treated with naproxen and reservetrol have a greater suppression of the prolonged phase of paw edema after subplantar injection of carrageenan than the group treated with naproxen alone.
Resveratrol's suppression of the CYP1A2 enzyme may be the cause of these alterations in naproxen's pharmacokinetics and pharmacodynamics when taken together.

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