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EFFECT OF NARINGIN ON PHARMACOKINETIC AND PHARMACODYNAMIC PROFILE OF NIMODIPINE: A HERB–DRUG INTERACTION STUDY IN FRUCTOSE-INDUCED HYPERTENSIVE RATS

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ABSTRACT

Hypertension is a major global health issue and a leading cause of heart-related problems and death. Managing hypertension over the long term often requires using multiple medications. This increases the chances of drug interactions. Naringin, a bioactive flavonoid found in citrus fruits, is known for its ability to lower blood pressure, act as an antioxidant, and modify enzymes. This study aimed to assess how Naringin affects the pharmacokinetics and pharmacodynamics of Nimodipine, a second-generation calcium channel blocker, in a rat model of fructose-induced hypertension. To induce hypertension, male Wistar rats received a 10% fructose solution for 12 days. Rats with systolic blood pressure (SBP) of 140 mmHg or higher were included in the study. They were divided into five groups: a control group, Nimodipine alone (10 mg/kg), Naringin alone (50 mg/kg), a single-dose interaction group (Naringin + Nimodipine), and a multiple-dose interaction group (seven days of Naringin followed by Nimodipine). We conducted pharmacokinetic analysis using a validated RP-HPLC method. We assessed pharmacodynamic activity through the tail-cuff plethysmographic method. The pharmacokinetic results showed that taking Naringin along with Nimodipine significantly increased the C_{max}, AUC_{total}, $t_{1/2}$, and MRT of Nimodipine in both the single and multiple-dose groups. The multiple-dose group had the most significant effects, showing a 2.3-fold increase in AUC and a 1.8-fold increase in C_{max}. Clearance and volume of distribution were significantly lower, indicating better bioavailability and longer systemic exposure. The pharmacodynamic results matched these findings, as the combination therapy resulted in a greater drop in SBP compared to Nimodipine alone. The multiple-dose interaction group showed the highest decrease in SBP (40.9%), suggesting a possible synergistic effect in lowering blood pressure. In conclusion, the study indicates that Naringin significantly improves the pharmacokinetic profile and blood pressure-lowering effectiveness of Nimodipine in hypertensive rats, especially with repeated doses. These results suggest that Naringin could serve as a valuable addition in high blood pressure treatment, possibly enabling dose optimization and better clinical outcomes. Further clinical studies are needed to investigate the potential of this combination in patients with hypertension.

INTRODUCTION

High blood pressure is the leading cause of cardiovascular disease (CVD) and deaths globally [1] Hypertension is a significant risk factor for cardiovascular diseases and a major cause of premature death, which is a global public health problem [2]. According to the Global Health Observatory (GHO), 1.13 billion People in worldwide are affected by hypertension [3]. Management of hypertension generally includes antihypertensive agents, with calcium channel blockers like amlodipine being one of the most prescribed [4]. Nimodipine is a second-generation 1,4-dihydropyridine calcium channel blocker that was originally approved by

the FDA to manage hypertension. (Das JM et al), Naringin, a flavanone glycoside that is formed from the flavanone naringenin and the disaccharide neohesperidose, isone of the main active components of Chinese herbal medicines, such as Drynaria fortunei (DF), Citrus aurantium L. (CA) and Citrus medica L [5, 6]. An extensive literature survey has revealed that naringin possesses antioxidant, anti-inflammatory, anti-apoptotic,anti-ulcer, anti-osteoporotic and anti-carcinogenic properties(Wang et al. 2013). Several lines of investigation suggest that naringin supplementation is beneficial for the treatment of obesity, diabetes, hypertension, and metabolic syndrome [7-9]. In many chronic ailments, the multi-drug therapy may be advocated to mitigate the severity or to avoid the development of possible resistance. There is a possibility of the occurrence of drug-drug interactions when multiple drugs are administered simultaneously [10]. These drug interactions can be explained by alterations in the pharmacokinetic parameters, including inhibition or induction of metabolic enzymes, or by alterations in the pharmacodynamic properties of one or both drugs [11]. Many of the drug interactions occur due to the induction or inhibition of hepatic cytochrome P450 enzymes [12]. MDI therapy is a cornerstone in the management of numerous chronic disorders, employed strategically to alleviate symptom severity and, importantly, to minimize the emergence of drug resistance [13]. This approach is particularly crucial in conditions like hypertension, where the long-term nature of the illness and the interconnectedness of various physiological systems necessitate a comprehensive therapeutic strategy [14]. Individuals with hypertension are at an elevated risk of developing both macrovascular complications, such as myocardial infarction (heart attack) and stroke, and microvascular complications, including diabetic nephropathy (kidney disease), retinopathy (eye disease), and neuropathy (nerve damage) [15]. Therefore, these patients often require a combination of medications to effectively control their blood pressure and mitigate the risk of these debilitating and potentially life-threatening consequences. Furthermore, the inclusion of phytoconstituents, naturally occurring compounds derived from plants, in these multi-drug regimens is increasingly explored for their potential synergistic effects and their ability to address multiple pathophysiological mechanisms simultaneously. These integrated approaches aim to not only lower blood pressure but also to provide broader cardiovascular protection and improve long-term outcomes for hypertensive patients. In the present study is aimed to investigate the influence of Naringin on the pharmacokinetic and pharmacodynamic activity of Nimodipine on fructose-induced hypertensive rats. Naringin was co-administered with nimodipine orally and this may enhance the anti-hypertensive effects of nimodipine. This study could probably provide a potential therapeutic strategy for the management of hypertension.

MATERIALS:

Drugs and chemicals:

Nimodipine (TCI chemicals), Fructose (Hi Media Chemicals, Mumbai, India), Nimesulide (Gift sample from the DMPK research laboratory, Kakatiya University, Warangal), Naringin (Yarrow Chemicals Pvt Ltd). Acetonitrile (HPLC grade), was purchased from Merck Pvt. Ltd., Mumbai. Double-distilled water was collected from the Millipore water system (Direct-Q-UV-3). The chemicals used were of analytical grade.

Experimental Animals:

Before the investigation, all the animal experiments were reviewed and approved by the Institutional Animal Ethical Committee (IEAC), University College of Pharmaceutical Sciences, Kakatiya University, Warangal, India (07/ IAEC /UCPSC/KU/2024). Male Wistar rats weighing 200 ± 20 g were purchased from Systemic Life Sciences, Hyderabad, India. The animals were housed in standard polypropylene cages and maintained under standard laboratory conditions (12 h light and dark cycle; at an ambient temperature of 25 ± 50 °C; 35-60% of relative humidity). The animals were fed with a standard rat pellet diet and water ad libitum.

EXPERIMENTAL DESIGN:

Induction of hypertension:

Hypertension was induced in male Wistar rats by drinking fluid consisting of 10% fructose solution [16-18]. The rats were trained to stay in the rat holder in a calm and nonaggressive state during BP measurement. Table 1 presents blood pressure measurements in control and hypertensive rats for 2 weeks. On day 5, the control rats exhibited a mean blood pressure of 115.43 ± 3.55 mmHg, while the hypertensive rats had a significantly higher pressure of 142.74 ± 5.24 mmHg. By day 10, the control rats' blood pressure slightly increased to 119.11 ± 4.26 mmHg, whereas the hypertensive rats reached 152.37 ± 6.18 mmHg. By day 10, the control rats' blood pressure slightly increased to 119.11 ± 4.26 mmHg, whereas the hypertensive rats reached 152.37 ± 6.18 mmHg.

Table 1: Induction of hypertension

Day	Control Rats (mmHg)	Hypertensive rats (mmHg)
5	115.43 ± 3.55	142.74 ± 5.24
10	119.11± 4.26	152.37± 6.18
11	120.12 ± 3.85	160.08 ± 5.71
12	120.13 ± 3.64	165.26± 6.33

Table 2: Mean Pharmacokinetic parameters of Nimodipine in the presence of Naringin in Hypertensive rats.

PK parameters	ND (HT)	ND+NA (SDI)	ND+ NA(MDI)
C_{max}(µg/mL)	13.92±5.26	18.58± 5.87*	25.54 ± 6.94**
T_{max}(h)	1	1	1
AUC $_{total}$ (µg.h/mL)	58.47±10.87	92.13 ± 15.49*	139.27 ±17.58**
$t_{1/2}$(h)	8.64±4.98	11.19±5.42	13.07± 6.58*
MRT(h)	9.64± 0.92	12.22 ± 0.89	15.23 ± 0.71**
CL (mL/h/kg)	0.62±0.14	0.32±0.09	0.15±0.08*
V_d(mL/kg)	7.72±3.45	5.16±2.48	2.82±0.93*
K_{el}(h-1)	0.08	0.06	0.05

Values are mean ± S.D. n = 6 /group NC+ND: Nimodipine in Normal control; HT+ND: Nimodipine in hypertensive group; ND+NA(SDI): Nimodipine + Naringin (Single Dose Interaction); ND+NA(SDI): Nimodipine + Naringin (Multiple Dose Interaction); ∗ P < 0.05, **P < 0.01; *** P < 0.001 Groups vs. ND (One Way ANOVA followed by Dunnet's Test).

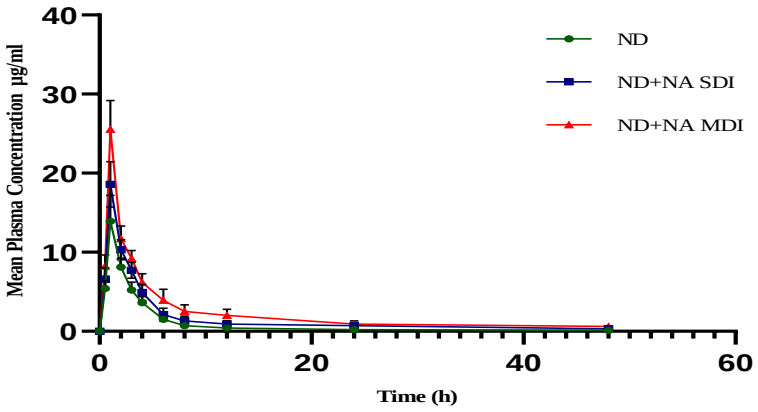


Figure 1: Mean plasma concentrations of Nimodipine in the presence of Naringin in Hypertensive rats.

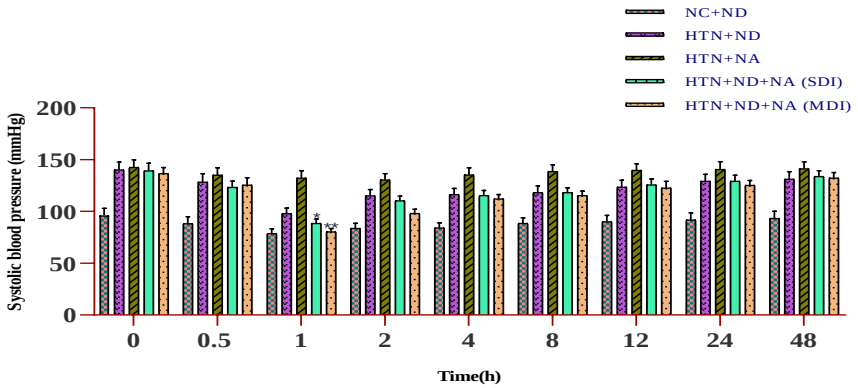
Values are mean ± S.D. n = 6 /group HTN+ND: Nimodipine in hypertensive group; ND+NA(SDI): Nimodipine + Naringin (Single Dose Interaction); ND+NA(SDI): Nimodipine + Naringin (Multiple Dose Interaction); ∗ P < 0.05, **P < 0.01; *** P < 0.001 Groups vs. ND (One Way ANOVA followed by Dunnet's Test).

Table 3: Systolic blood pressure (mmHg) profile of Nimodipine with Naringin in Hypertensive rats.

Group	Treatment	Systolic blood pressure (mmHg) at different time points								
		0 h	0.5 h	1 h	2 h	4 h	8 h	12 h	24 h	48 h
I	NC+ND	96.24±6.72	88.36±6.46	**78.72±4.45 18.2 %**	83.75±4.84	84.12±4.86	88.45±5.42	90.14±6.12	91.81±6.81	93.27±6.81
II	HT+ND	140.18±7.36	128.38±8.10	**97.82±5.29 30.2 %**	115.22±5.82	116.34±5.96	118.26±6.26	123.45±6.67	129.12±6.72	131.21±7.12
III	HT+NA	142.55±7.29	135.22±6.82	132.25±6.95	**130.58±5.82 8.39 %**	135.25±6.86	138.52±6.35	139.62±6.36	140.52±7.57	141.25±6.54
IV	HT+ND+ NA (SDI)	139.23±7.16	123.21±5.92	**88.62±3.95 36.3 %***	110.45±4.23	115.45±4.75	118.26±4.69	125.78±5.52	129.26±5.56	133.84±5.45
V	HT+ND+ NA (MDI)	136.75±5.53	125.56±6.84	**80.34±3.24 40.9 %****	98.15±3.95	112.14±4.25	115.43±4.24	122.64±6.45	125.25±4.52	132.28±5.25

Values are mean ± S.D. n = 6 /group NC+ND: Nimodipine in Normal control; HT+ND: Nimodipine in hypertensive group; ND+NA(SDI): Nimodipine + Naringin (Single Dose Interaction); ND+NA(SDI): Nimodipine + Naringin (Multiple Dose Interaction); ∗ P < 0.05, **P < 0.01; *** P < 0.001 Groups vs. ND (One Way ANOVA followed by Dunnet's Test).

Figure 2: Systolic blood pressure (mmHg) profile of Nimodipine with Naringin in Hypertensive rats



Values are mean ± S.D. n = 6 /group NC+ND: Nimodipine in Normal control; HNT+ND: Nimodipine in hypertensive group; ND+NA(SDI): Nimodipine + Naringin (Single Dose Interaction); ND+NA(SDI): Nimodipine + Naringin (Multiple Dose Interaction); ∗ P < 0.05, **P < 0.01; *** P < 0.001 Groups vs. ND (One Way ANOVA followed by Dunnet's Test).

On day 11, control rats recorded a pressure of 120.12 ± 3.85 mmHg, with hypertensive rats showing a further increase to 160.08 ± 5.71 mmHg. Finally, on day 12, the control rats maintained a similar level at 120.13 ± 3.64 mmHg, while the hypertensive rats' pressure rose to 165.26 ± 6.33 mmHg. These results indicate a progressive elevation of blood pressure in hypertensive rats over the days measured, in contrast to the relatively stable levels observed in control rats. 12 days later, rats with a minimum mean systolic blood pressure (SBP) of 140–145 mm of Hg were selected. They were screened as hypertensive rats and used for the experiment.

The single-dose Treatment (SDT) and multi-dose Treatment (MDT) were used for the pharmacokinetic and pharmacodynamic study.

Group I – Disease Control (DC)

Group II – Nimodipine 10 mg/kg 7 days per orally suspended in 0.5% sodium CMC [19].

Group III – Administered Naringin (50mg/Kg/ Po) suspended in 0.8 ml of DMSO for 8 days [20]

Group IV-was pretreated with Naringin (50mg/Kg Po) followed by ND (10mg/kg/po) for SDI study [21].

Group V – pretreated with Naringin (50mg/kg/po) for 7 days on the 8th day, Naringin followed by ND (10mg/kg/po) for MDI study[21]

HPLC analysis

ND concentrations were estimated in Plasma by RP-HPLC with slight modification of earlier reported methods. The analysis was performed using a High-Performance Liquid Chromatography (Shimadzu, Kyoto, Japan) system with a gradient capillary binary pump (LC-20AD) and the analytical column C18 (2), 250 × 4.6 mm, 5 µ particle size (Luna 5 µ, Phenomenex). The column effluent was measured with a UV-Visible dual wavelength absorbance detector (SPD-M20A) at 254nm. The mobile phase consists of Acetonitrile and Water in the ratio of 52:48 v/v which was delivered isocratic flow rate of 1.5mL/min. The Phenomenex C18 column was utilized to elute the compounds of interest at a λ max = 264 nm[22].

Plasma sample extraction of ND: About 100 µL of Plasma sample, added, 100 µL of Nimesulide at a concentration of 25 µg/mL as IS, and then 100 µL of cold acetonitrile was added as a precipitating agent and vortexed for 1 min and further centrifuged at 13000 g for 15 mins. The supernatant was transferred into a clean labelled tube and was stored at -20 °C for further analysis. The resultant samples were reconstituted in 200 µL of mobile phase, and about 20 µL were injected into HPLC for analysis of ND.

Pharmacodynamic study: By using the tail-cuff method [23] (NIBP, AD instruments, New Zealand), The systolic blood pressure (SBP) of the rats was measured at different time intervals (0, 0.5, 1, 2, 4, 8, 12, 24, and 48 h) for all groups.

Pharmacokinetic study: Various pharmacokinetic parameters like C_{max} , AUC_{total}, $t_{1/2}$, K_{el}, V_d, CL, and MRT were calculated using Kinetica TM software (version 4.4.1, Thermo Fisher Scientific Corporation, USA).

Statistical analysis: All the PK and PD Parameters were expressed as Mean ±SD. The data were statistically evaluated using Student's unpaired t-test using GraphPad Prism 5.03.2011 software. Values corresponding to ($p<0.05$) were considered significant.

RESULTS AND DISCUSSION:

Pharmacokinetic results: From Table 2 and Figure 1 data, the pharmacokinetic parameters of ND in hypertensive rats HTN were significantly altered in the presence of Naringin (NA), both in single-dose (SDI) and multiple-dose (MDI) administrations. The C_{max} of ND increased from 13.92 ± 5.26 µg/mL in the HT group to 18.58 ± 5.87 µg/mL with SDI and 25.54 ± 6.94 µg/mL with MDI, showing 1.3- and 1.8-fold increases, respectively. The T_{max} remained constant at 1 hour across all groups. The AUC_{total} demonstrated a significant increase from 58.47 ± 10.87 µg·h/mL in the ND (HT) group to 92.13 ± 15.49 µg·h/mL with SDI and 139.27 ± 17.58 µg·h/mL with MDI, reflecting 1.5- and 2.3-fold increases, respectively. The $t_{1/2}$ of ND was prolonged from 8.64 ± 4.98 hours in the HT group to 11.19 ± 5.42 hours with SDI and 13.07 ± 6.58 hours with MDI, indicating 1.2- and 1.5-fold increases. The MRT also increased from 9.64 ± 0.92 hours to 12.22 ± 0.89 hours (SDI) and 15.23 ± 0.71 hours (MDI), with 1.2- and 1.5-fold increments. CL decreased from 0.62 ± 0.14 mL/h/kg to 0.32 ± 0.09 mL/h/kg with SDI and 0.15 ± 0.08 mL/h/kg with MDI, showing reductions by 0.5 and 0.2 folds, respectively. The V_d was also reduced from 7.72 ± 3.45 mL/kg to 5.16 ± 2.48 mL/kg (SDI) and 2.82 ± 0.93 mL/kg (MDI), with 0.6- and 0.3-fold decreases. Additionally, the K_{el} declined from 0.08 h^{-1} to 0.06 h^{-1} (SDI) and 0.05 h^{-1} (MDI), indicating reductions of 0.75 and 0.6 folds, respectively. These results suggest that Naringin significantly enhances the bioavailability of Nimodipine, prolongs its half-life, and reduces its clearance, especially with multiple-dose administration,

thereby potentially improving its therapeutic efficacy in hypertensive conditions.

Pharmacodynamic Results: From Table 3 and Figure 2 data, the study evaluated the effects of Nimodipine with Naringin on systolic blood pressure (SBP) in hypertensive rats across different treatment groups and time points. Group I (NC+ND) maintained relatively stable SBP levels, slightly decreasing at 1 hour (78.72 ± 4.45 mmHg), showing an 18.2% reduction. Group II (HT+ND) initially showed an increase in SBP at 0.5 hours, followed by a reduction at 1 hour (97.87 ± 5.29 mmHg), with a 30.2% decrease before gradually rising again. Group III (HT+NA) exhibited a mild drop in SBP at 1 hour (132.25 ± 6.95 mmHg) and a more notable reduction at 2 hours (130.58 ± 5.82 mmHg), marking an 8.39% decrease; however, SBP returned to baseline levels at later time points. In contrast, Group IV (HT+ND+NA (SDI)) demonstrated a significant SBP reduction at 1 hour (88.62 ± 3.95 mmHg), with a 36.3% decrease, suggesting a stronger effect of the combined therapy. The most pronounced effect was observed in Group V (HT+ND+NA (MDI)), where SBP dropped significantly at 1 hour (80.34 ± 3.24 mmHg), marking a 40.9% reduction, confirming the effectiveness of multiple-dose interaction. When compared to previous studies, our findings align with reports highlighting the cardioprotective effects of flavonoids such as Naringin. Prior research has demonstrated that Naringin exhibits antihypertensive properties by improving endothelial function, enhancing nitric oxide bioavailability, and reducing oxidative stress in hypertensive models[24, 25]. A study by [26] found that Naringin supplementation significantly lowered mean arterial pressure and oxidative stress markers in hypertensive rats, supporting the present study's observation of an SBP reduction with Naringin co-administration. Similarly, [27, 28] reported that flavonoids enhance calcium channel blocker (CCB) activity, leading to improved vasodilation and blood pressure regulation, which corroborates our results indicating the enhanced effect of Naringin with Nimodipine. Additionally, earlier investigations on calcium channel blockers (CCBs) like Nimodipine have reported their efficacy in reducing SBP, mainly through vascular smooth muscle relaxation. However, combining CCBs with natural polyphenols such as Naringin has not been extensively studied. Our results provide novel insights into this combination therapy, showing that multiple-dose Naringin administration significantly enhances the blood pressure-lowering effects of Nimodipine compared to its single-dose counterpart. This finding is crucial as it suggests a potential dose-dependent synergistic interaction between Nimodipine and Naringin, which could be explored further for therapeutic applications in hypertensive patients.

CONCLUSION:

In conclusion, our study confirms that Nimodipine, when combined with Naringin, significantly reduces SBP in hypertensive rats, with the multiple-dose regimen demonstrating the highest efficacy. These findings support the use of flavonoids as potential adjuncts to conventional antihypertensive therapy. Future studies should focus on exploring the molecular mechanisms behind this synergistic effect and conducting clinical trials to assess its translational potential in human hypertension management.

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Conflict of interest: The authors do not have any conflicts of interest.

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