

## Article

# Impact of Cumin and Green Tea on Amlodipine Pharmacodynamics and Pharmacokinetics in Hypertensive Rats

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**Abstract:** The main purpose of the current research was to determine the impact of cumin and green tea on the pharmacodynamics and pharmacokinetics of amlodipine in hypertensive rats. Wistar rats were given 40 mg/kg of L-NAME orally every day for two weeks in order to induce hypertension. The groups treated with herbs received L-NAME with a daily oral dose of cumin (200 mg/kg) and green tea (200 mg/kg), respectively. After the treatment for 14 days, blood pressure was measured at specific intervals using a tail-cuff BP-measurement device for 24 h. For oral pharmacokinetics of amlodipine (single dose, 1 mg/kg), the blood samples were collected at predetermined intervals up to 24 h, and plasma samples were analyzed using UPLC-LC MS/MS. In comparison to the hypertensive control group, green tea and cumin significantly decreased systolic and diastolic blood pressures, as well as mean arterial pressures. Green tea has demonstrated a more prominent effect on pharmacodynamic of amlodipine compared to cumin. The rats treated with amlodipine, cumin + amlodipine, and green tea + amlodipine exhibited  $AUC_{0-t}$  of  $38.85 \pm 14.8$  ng h/mL,  $52.05 \pm 10.2$  ng h/mL, and  $114.73 \pm 24.94$  ng h/mL, respectively. In addition, it has been observed that co-administration of green tea and cumin increases the  $C_{max}$  and  $T_{1/2}$  of amlodipine. The results indicated a potential interaction between amlodipine and the investigated herbs in hypertensive rats. Hence, precautions should be taken while concurrently administering amlodipine with the investigated herbs.



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**Keywords:** amlodipine; cumin; green tea; pharmacodynamics; pharmacokinetics

## 1. Introduction

Hypertension (HTN) is one of the most common chronic diseases worldwide and is considered a leading cause of kidney diseases, cardiovascular diseases, and even death [1]. In fact, studies have shown that a corresponding estimate of high blood pressure levels linked to coronary heart disease was 49%, and for stroke it was 62% [2].

HTN is defined and known by an average of systolic blood pressure (SBP)  $\geq 140$  mmHg and diastolic blood pressure (DBP)  $\geq 90$  mm Hg [3,4]. It should be noted that the long-term consequences such as dementia, diabetes mellitus, and many other pathophysiological conditions can occur if blood pressure is not controlled [2]. Furthermore, a recent study found that the rate of controlled HTN (SBP/DBP  $< 140/90$  mm Hg) has dropped 10% over the past few years from 54% in 2014 to 44% in 2018 [5].

The risk factors that can lead to HTN and elevation in blood pressure levels include an unhealthy diet with imbalanced high sodium consumption and low potassium usage, cigarette smoking, drinking alcohol, obesity, and low levels of physical activity [6]. Accordingly, Al-Hanawi et al. reported that people who were overweight or who smoked tobacco were found to have a higher prevalence of HTN [7].

Data show that one and a half billion adults around the world have HTN; this is considered a major global health problem due to its high prevalence and its comorbidities and serious complications [6]. Middle Eastern and Arab countries are estimated to

have a HTN prevalence of 15.2% to 35.8%. Many factors contribute to this variation across the region, for example, health care systems, obesity, smoking, and lifestyle [8]. However, the prevalence is not uniform throughout the world due to socio-economic variations between high-income and low-income communities, which include the accessibility and availability of healthcare services, as well as different lifestyles, habits, and diet [6]. Moreover, based on the updated definition of HTN, in the US population, the prevalence increased from 32% to 45%, and these findings indicate that if the updated guidelines were applied across the globe, HTN prevalence would be much higher than previously estimated [6]. Based on a study, out of 10,735 participants, 15.2% were hypertensive and 40.6% were borderline hypertensive or with high normal blood pressure, whereas 57.8% of hypertensive volunteers were undiagnosed [9]. There are different types of antihypertensive agents available in the market; these medicines are usually used in combination or as monotherapy in order to achieve the treatment goals and to eventually control blood pressure levels [5,10].

Furthermore, there has been a substantial increase in the use of herbal medicines in the past few years for the treatment of many diseases, one of which is HTN [9,11]. There are over 200 different types of plant species that are used in Arab countries, and approximately 80% of people in this region rely on natural medicine to prevent and treat various illnesses [12]. Saudi Arabia is also a country highly influenced by herbal products, with the latest report revealing that 94% of the respondents utilize herbal products as a form of health care [13]. According to Alghamdi et al., around 88% of patients with chronic diseases are taking herbs without consulting their healthcare provider [14]. Since the herbal product users are generally not informing their medical professionals about their usage of herbal products, there is no accurate estimation of the level of utilization of herbal products with conventional medications [15]. The use of herbs and herbal products with conventional drugs could lead to serious complications due to potential interactions. Such interactions can prolong, enhance, or diminish the effects of concurrently administered drugs, and lead to serious consequences such as toxic reactions [16].

Amlodipine is dihydropyridine calcium channel blocker; it is considered as a first-line remedy for the management of HTN whether it is used alone or in combination with another antihypertensive drug. It works selectively on vascular smooth muscles by inhibiting the entry of calcium ions into the cells, causing vasodilation, and reducing peripheral vascular resistance and blood pressure. It is broken down into inactive metabolites mainly via the hepatic oxidation pathway through cytochrome P450 (CYP) 3A4 and, to a lesser extent, through CYP3A5, with an estimated oral bioavailability between 60 and 80% [17,18].

Recent reports have shown that drugs that interfere with CYP3A4 activity may have an impact on the amlodipine pharmacokinetics when administered concurrently; for instance, the co-administration of ritonavir, a strong CYP3A4 inhibitor antiretroviral, with amlodipine had a significant effect on both the pharmacodynamic (PD) and pharmacokinetic (PK) profiles of amlodipine [19]. Moreover, it is important to note that any substances that may interfere with or exert action on the smooth muscle contractility mechanism may either have a positive or negative impact on the PD of amlodipine.

Cumin (*Cuminum cyminum*) belongs to the Apiaceae family. It contains volatile oils like cuminaldehyde, cymene, and terpenoids, and it is rich in monounsaturated fats, proteins, and fibers, as well as vitamins and minerals such as vitamins B and E and iron [20]. Traditionally, cumin seeds have been used in medicine and as dietary supplements. Cumin exhibits anti-diabetic, antioxidant, carminative, diuretic, antibacterial, antifungal, and antihypertensive activity. A possible mechanism for this is the regulation of the nitric oxide pathway, and the reduction in the level of low-density lipoproteins [21,22].

Green tea (*Camellia sinensis*) belongs to the Theaceae family and comprises a plethora of “flavanols (flavan-3-ols) such as catechins, including epigallocatechin-3-gallate (EGCG), epigallocatechin, epicatechin, epicatechin-3-gallate, proanthocyanidins (tannins), and flavonols such as quercetin”, along with a variety of vitamins [23]. It has been reported that green tea constituents have a number of pharmacological effects including antioxidant, antimicrobial,

anticancer, and antidiabetic activity [23]. According to findings, green tea consumption has been shown to lower the blood pressure, and both SBP and DBP [24,25]. Furthermore, administration of green tea has been proven to significantly lower the level of low-density lipoprotein cholesterol in the blood via a variety of suggested mechanisms [26]. The interactions between green tea and several medications have been reported in many studies, affecting both PD and PK properties. A recent *in vivo* as well as *in vitro* study found that co-administration of “epigallocatechin-3-gallate (EGCG)”, green tea’s main constituent with amlodipine resulted in a significant change in PK profile with remarked inhibition of amlodipine metabolism. Moreover, a recent *in vitro* study showed that the EGCG and green tea extracts inhibit CYP3A activity [27]. A study in healthy humans assessed interaction probability between green tea and buspirone CYP3A4 substrate showed increase in the bioavailability of buspirone [28,29]. Another study examined the interaction of EGCG with nadolol, and the results show a decrease in the levels of  $AUC_{0-t}$ ,  $C_{max}$ , and  $T_{max}$  for the investigated drugs [30,31].

Due to the anti-hypertensive properties of cumin and green tea, there is a high chance of using these herbs alone or with anti-hypertensive medications. Furthermore, there is not enough literature available about the PD and PK herb–drug interaction of cumin and green tea with amlodipine in experimentally diseased rats. Hence, in the present study, the impact of cumin and green tea on amlodipine anti-hypertensive activity, as well as on the PK profile of amlodipine, was investigated. During the PD study, the rat’s HR, SBP, DBP, and MAP were recorded in intervals up to 24 h using the Visitech tail-cuff system. In the PK study, on the other hand, the impact of each herb on the “ $C_{max}$  (maximum plasma concentration),  $T_{max}$  (time to reach maximum plasma concentration),  $AUC_{0-t}$  (the area under the curve),  $T_{1/2}$  (the elimination half-life), and  $K_{el}$  (elimination rate constant)” of amlodipine was assessed.

## 2. Materials and Methods

The “green tea and cumin used in this study were purchased from R. Twinning and company limited, Hampshire, England and Bin Menqash store, Riyadh, Saudi Arabia, respectively”. “Amlor<sup>®</sup> (amlodipine besylate, 10 mg capsules) was purchased from Novartis pharma AG, Basel, Switzerland”. “L-NAME (N-nitro L-arginine methyl ester) was bought from Carbosynth limited<sup>®</sup>, Berkshire, UK”. “HPLC-grade methanol and acetonitrile were purchased from Fisher Scientific<sup>®</sup>, MA, USA, and Sigma-Aldrich<sup>®</sup>, St. Louis, MO, USA”, respectively. “Formic acid was bought from Honeywell<sup>®</sup> Charlotte, NC, USA”.

### 2.1. Monitoring Rat Blood Pressure and Pharmacokinetic Study

In this study, two herbs, namely, cumin and green tea, were examined in relation to amlodipine’s PD and PK studies using Wistar rats, each weighing between 250 and 300 g. The rats were housed under well-controlled conditions with a routine light/dark cycle. Animals had full access to a normal animal diet as well as water.

In order to identify the rats, their tails were marked before the experiment began, and trained to sit in a rat restrainer for adaptation and being familiar with experiment conditions. Rats were monitored for blood pressure using “Visitech tail-cuff system (Visitech, BP-2000 series II, USA)”. For two weeks, L-NAME (40 mg/kg daily) was administered orally to Wistar rats to induce HTN [16]. This study consisted of four groups of rats ( $n = 5$ ). Group 1 (without treatment) served as normal control group. HTN was induced in the remaining three groups. Rats with SBP equal to 150 mm Hg or higher are considered hypertensive rats. The hypertensive control group (Group 2) was administered L-NAME alone for two weeks.

For the preparation of herbal medicines, the powdered herbs (cumin and green tea) were precisely weighed and suspended in normal saline in two separate beakers. Each herb suspension was then sonicated. Every day, prior to administration, herbal suspensions were prepared. Rats in the corresponding group were given the suspension orally through rat feeding needles. Amlodipine suspension was also prepared in normal

saline. For 2 weeks, the 3rd and 4th groups of rats were administered L-NAME + cumin (200 mg/kg) [21,32,33] and L-NAME + green tea (200 mg/kg) [34–36], respectively. After two weeks, the rats' heart rates (HR), SBP, DBP, and mean arterial pressure (MAP) were measured up to 24 h and on the 16th day, amlodipine (1 mg/kg, oral single dose) was given to Group 2, Group 3, and Group 4, and blood pressure was again measured up to 24 h [37–43]. After the washout duration of 3 days, a once-daily oral dose of the drug (amlodipine 1 mg/kg) was given again, and samples of blood were drawn at predetermined intervals for a period of 24 h. The plasma sample was then separated from blood samples and analyzed for drug concentrations using the "UPLC (ultra-performance liquid chromatography)-MS/MS method".

## 2.2. Bio-Analytical Method

For amlodipine analysis, plasma samples (200  $\mu$ L) were collected from the blood samples of rats, and then placed into a labeled Eppendorf tube. After that, 20  $\mu$ L of nitrendipine (IS) (100 ng/mL) was then transferred to each Eppendorf tube and mixed well. Acetonitrile (420  $\mu$ L) was added for protein precipitation and samples were vortexed for 25 s, and, centrifuging the samples at 12,000 rpm for 10 min, the supernatant was then withdrawn from each sample and analyzed for drug content using "Waters<sup>®</sup> Acquity H-Class UPLC-tandem quadrupole mass spectrometer UPLC-TQD-MS (Waters, Milford, Connecticut, USA)". UPLC column "UPLC<sup>®</sup> BEH C<sub>18</sub> column (1.7  $\mu$ m, 2.1  $\times$  50 mm)" at a controlled temperature of  $40 \pm 5$  °C was used for analysis. The mobile phase used was water (45%) and acetonitrile (55%), each containing 0.1% formic acid. The auto sampler temperature was set at  $15 \pm 3$  °C. The daughter fragments of amlodipine and nitrendipine were monitored using electrospray ionization positive mode (ESI+) and multiple reaction mode (MRM) at  $m/z$  409.1 > 238 and  $m/z$  409.1 > 294; and at  $m/z$  361.1 > 315.1 and  $m/z$  361.1 > 329.1; respectively. The retention time for amlodipine and IS was 0.49 min and 1.14 min, respectively. The calibration curve was found to be linear from 0.6 to 20 ng/mL with lower limit of quantitation (LOQ) of 0.6 ng/mL [39]. PK solver was used in order to calculate the PK parameters such as,  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-t}$ ,  $T_{1/2}$ , and  $K_{el}$ .

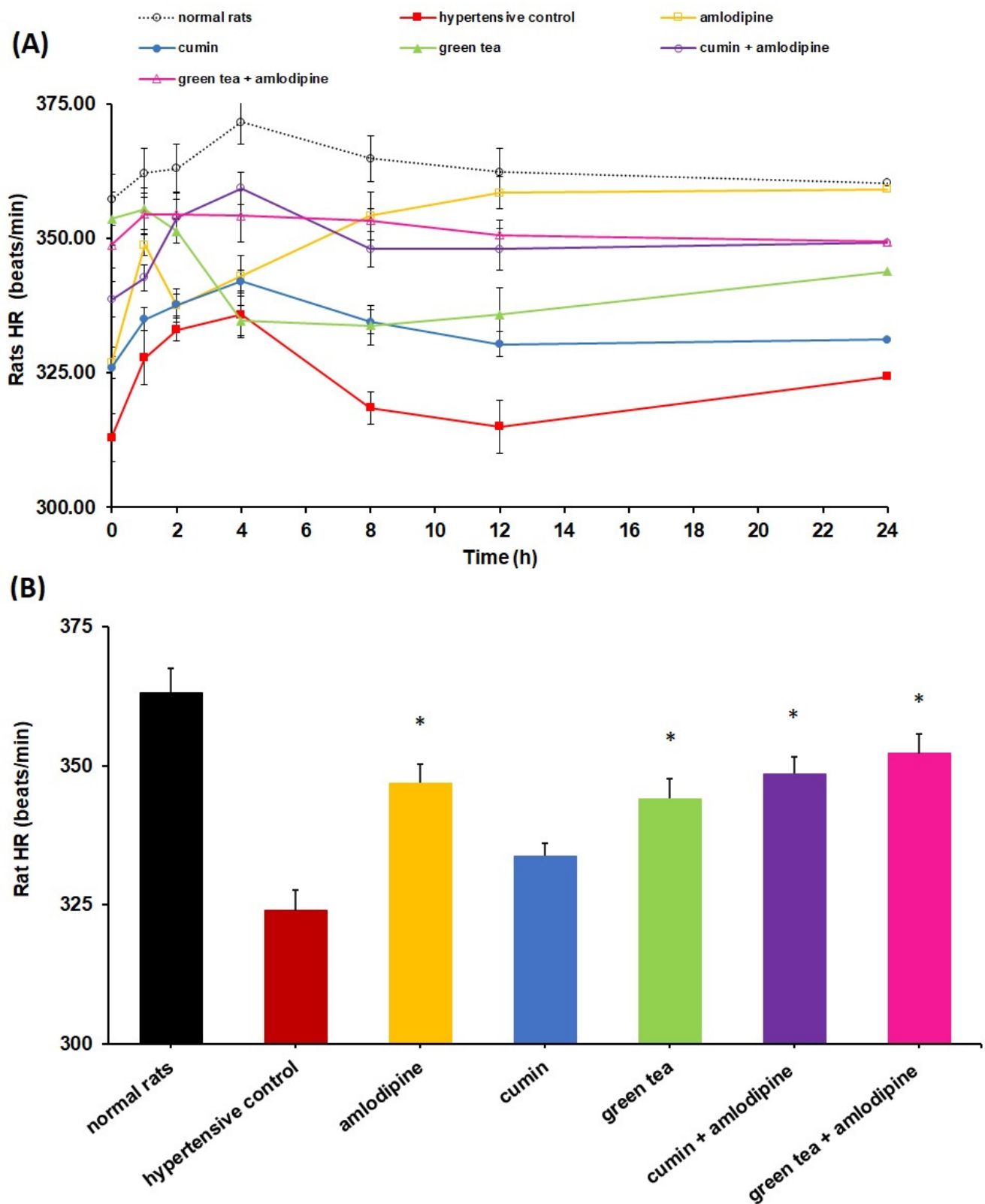
## 3. Statistical Analysis

Statistical "comparison was performed employing the one-way ANOVA Dunnett test with the consideration of significance level as  $p < 0.05$ . GrapPadInStat<sup>®</sup> version 3.06 for Windows was used for statistical analysis".

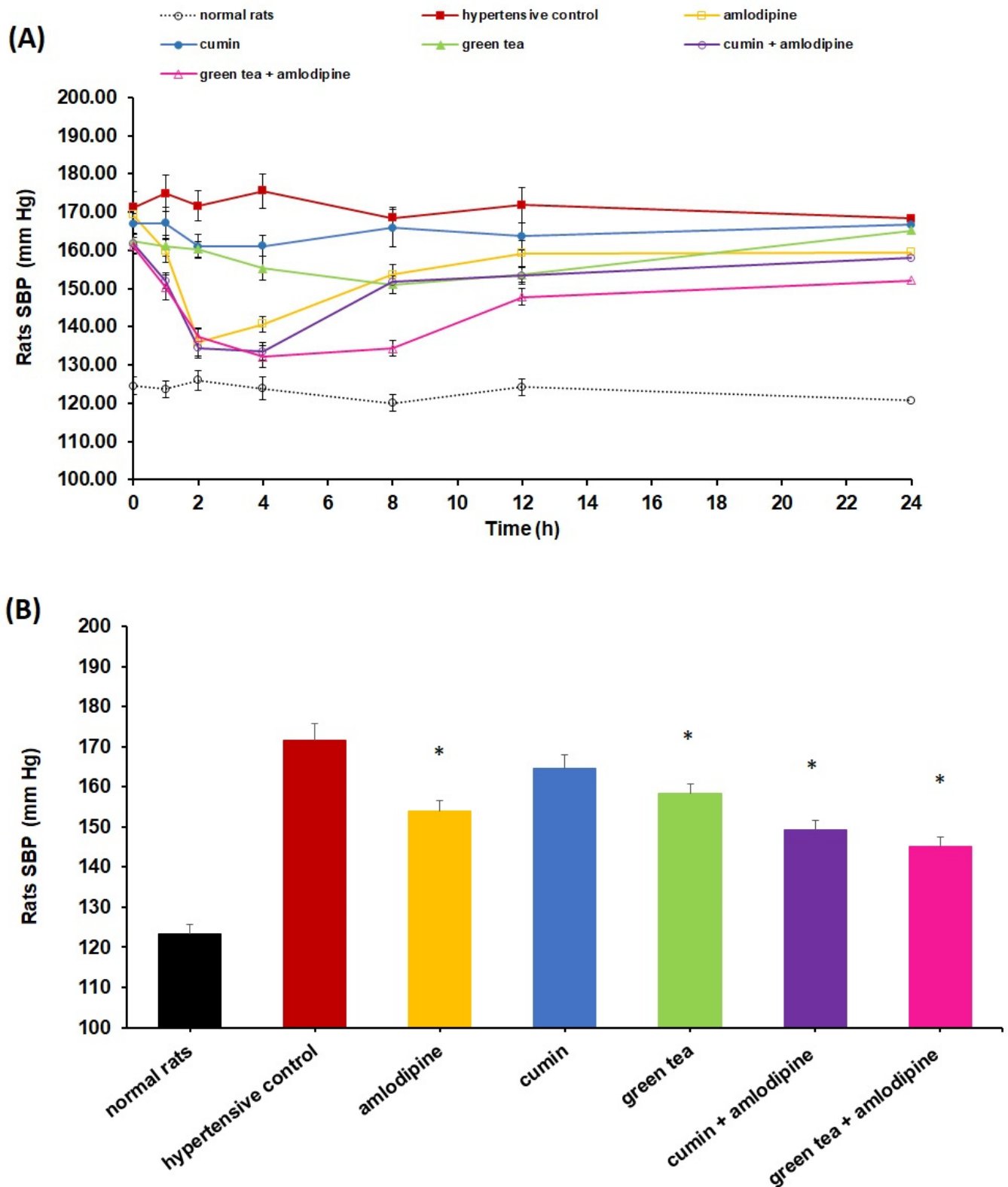
## 4. Results

### 4.1. Impact of Cumin and Green Tea on Amlodipine Pharmacodynamics

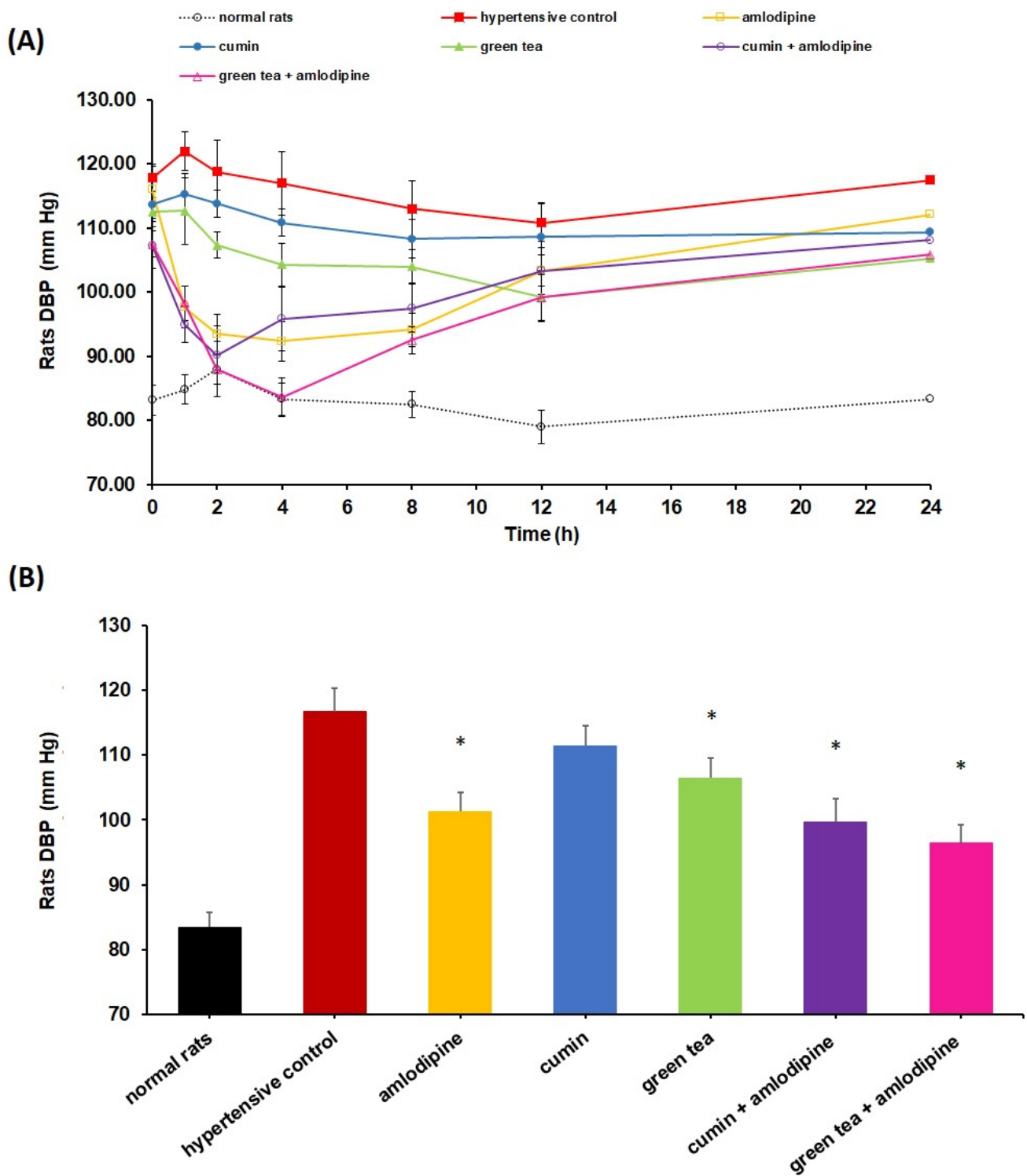
The HR, SBP, DBP, and MAP were recorded in intervals up to 24 h using the Visitech tail-cuff system, and the results were plotted against time (Figures 1–4).



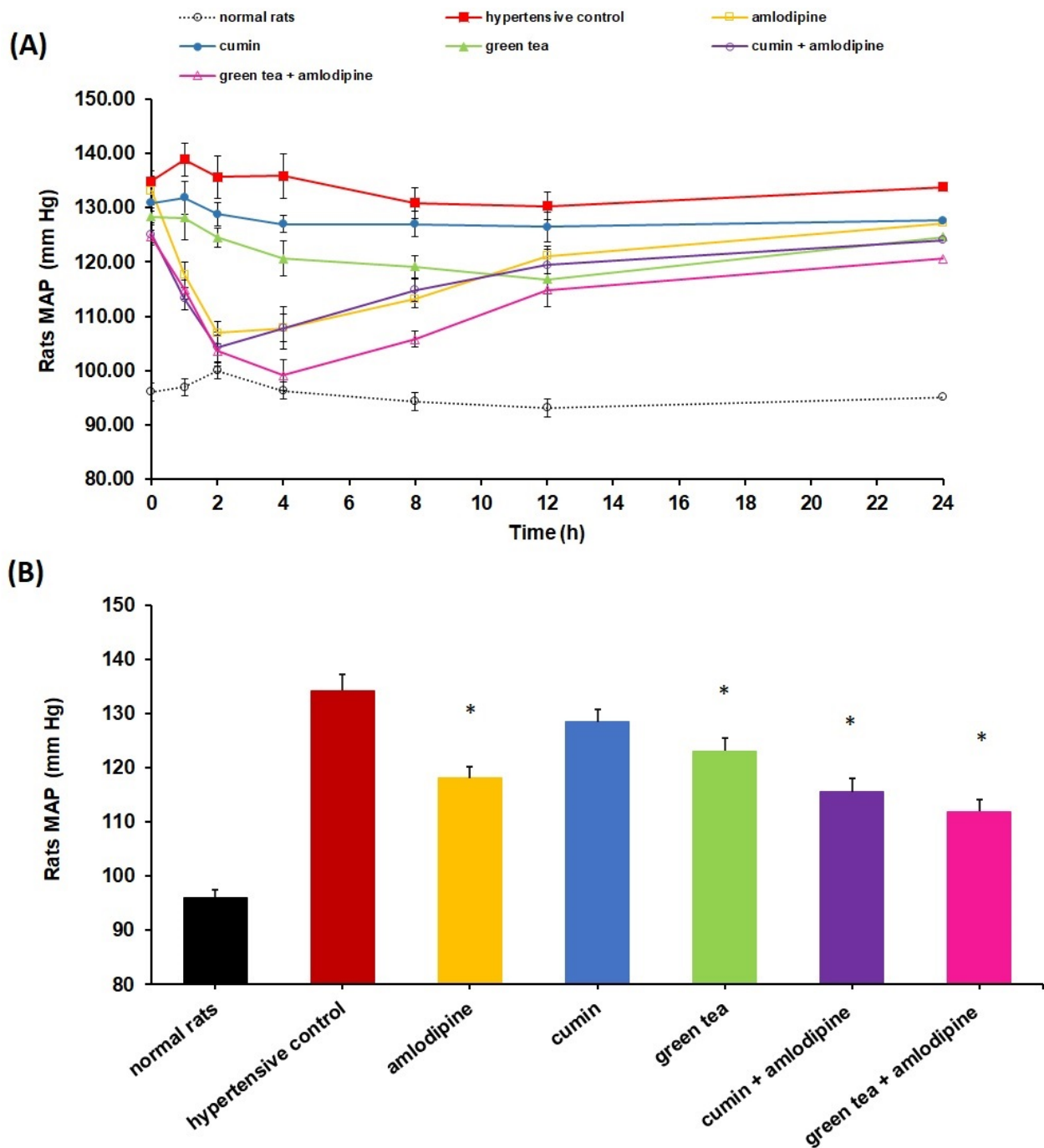
**Figure 1.** Impact of amlodipine, cumin, green tea, cumin + amlodipine, and green tea + amlodipine on HR of hypertensive rats. (A) HR change over the course of 24 h; (B) mean HR over 24 h in response to treatments. (Mean  $\pm$  SEM, \*  $p < 0.05$ ,  $n = 5$ ).



**Figure 2.** Impact of amlodipine, cumin, green tea, cumin + amlodipine, green tea + amlodipine on SBP of hypertensive rats. (A) SBP changes over 24 h in response to treatments; (B) average SBP changes over 24 h in response to treatments. (Mean ± SEM, \*  $p < 0.05$ ,  $n = 5$ ).



**Figure 3.** Impact of amlodipine, cumin, green tea, cumin + amlodipine, and green tea + amlodipine on DBP of hypertensive rats. (A) DBP changes over 24 h in response to treatments; (B) average DBP changes over 24 h in response to treatments (mean ± SEM, \*  $p < 0.05$ ,  $n = 5$ ).



**Figure 4.** Impact of amlodipine, cumin, green tea, cumin + amlodipine, green tea + amlodipine on the MAP of hypertensive rats. (A) MAP changes over 24 h in response to treatments; (B) average MAP changes over 24 h in response to treatments (mean ± SEM, \*  $p < 0.05$ ,  $n = 5$ ).

The HR (0–24 h) of the normal group, hypertensive control group, and amlodipine group was recorded as  $363 \pm 4.47$  beats/min (BPM),  $323.93 \pm 3.71$  BPM, and  $346.86 \pm 3.35$  BPM, respectively (Figure 1).

The mean SBP of the normal group (Group 1) from 0 to 24 h was found to be  $123.26 \pm 2.4$  mm Hg, while the mean SBP of the hypertensive control group (Group 2) was  $171.69 \pm 4.1$  mm Hg (Figure 2). L-NAME oral administration raised SBP in rats significantly ( $p < 0.05$ ).

The mean baseline of DBP for the normal group and hypertensive control group was  $83.45 \pm 2.3$  mm Hg and  $116.71 \pm 3.64$  mm Hg, respectively. The difference in DBP of normal



rats and after administration of L-NAME was found significant ( $p < 0.05$ ). In addition, the average of MAP was equal to  $96.02 \pm 1.56$  mm Hg for the normal group, while it was  $134.3 \pm 2.89$  mmHg for the hypertensive control group (Figure 3). In hypertensive-control-treated animals (Group 2), administration of amlodipine orally (1 mg/kg) reduces the mean SBP (0–24 h) to  $154.02 \pm 2.6$  mm Hg, DBP (0–24 h) to  $101.31 \pm 2.93$  mm Hg, and MAP to  $118.17 \pm 2.11$  mm Hg. The maximum reduction in SBP by 19.68% was seen after 2 h of amlodipine administration ( $169.33 \pm 1.76$  mm Hg to  $136 \pm 3.66$  mm Hg). At the 4 h time point, the SBP of L-NAME + amlodipine-treated animals started rising to  $140.67 \pm 2.12$  mm Hg, and reached  $159.5 \pm 1.85$  mm Hg at 24 h. However, a reduction in the SBP by 5.25% was noted in comparison with the SBP of rats of hypertensive control group at 24 h. Regarding DBP, the rats in hypertensive control and amlodipine had a DBP of  $117.83 \pm 2.18$  mm Hg and  $116 \pm 3.67$  mm Hg at 0 h, respectively. The maximum reduction was observed 4 h after amlodipine dosing, by 20.4%, where the level of DBP decreased to  $92.33 \pm 3.13$ . Moreover, it was found that after 24 h, the rats taking amlodipine showed a DBP of  $112.17 \pm 2.32$  mm Hg, with a reduction of 4.54% in comparison with hypertensive control rats,  $117.5 \pm 3.07$  mm Hg.

Similarly, rats receiving amlodipine displayed decreased MAP overall on average compared to the hypertensive control rats (from  $134.31 \pm 2.89$  to  $118.17 \pm 2.11$  mm Hg) (Figure 4). There was a statistically significant difference between the two groups ( $p < 0.05$ ).

In L-NAME + cumin-treated animals, Group 3, the mean SBP (0–24 h) after consumption of cumin extract for 14 days was found to be  $164.64 \pm 3.34$  mmHg, DBP (0–24 h)  $111.43 \pm 3.1$  mmHg, and MAP  $128.52 \pm 2.31$  mm Hg. The maximum reduction in SBP was observed after 2 h following cumin administration and extended up to 4 h  $161 \pm 3.12$  mm Hg. After 24 h of cumin consumption, the SBP of rats was  $166.67 \pm 2.22$  mm Hg. In contrast, following amlodipine administration, the SBP of the cumin + amlodipine group decreased to its maximum level  $133.5 \pm 2.35$  mm Hg at 4 h, with a reduction of 5.1% in comparison with the SBP of amlodipine group at 4 h time point. Cumin administration resulted in the greatest decrease in DBP ( $108.33 \pm 3.04$  mm Hg) after 8 h, with noticeable extended impact up to 24 h. As a result of amlodipine administration (1 mg/kg) to the cumin + amlodipine-treated group, the mean SBP (0–24 h) decreased to  $149.26 \pm 2.49$  mm Hg, the mean DBP (0–24 h) was  $99.62 \pm 3.72$  mmHg, and the mean MAP was recorded as  $115.57 \pm 2.53$  mmHg. Compared with the hypertensive control group, all three measures demonstrated significant differences ( $p < 0.05$ ). At 24 h, the rats administered with L-NAME + cumin + amlodipine had an average SBP of  $158.00 \pm 2.74$  mm Hg, which was comparable to the average SBP of the amlodipine-treated group. No statistically significant ( $p > 0.05$ ) differences between the two groups were noted. For the cumin + amlodipine group, the maximum reduction of DPB  $92.33 \pm 3.14$  mm Hg was observed at 4 h after amlodipine administration. Additionally, it was found that at 24 h, the animals treated with cumin + amlodipine showed a DBP of  $108.17 \pm 2.63$ . Compared to the amlodipine group, those treated with cumin + amlodipine exhibited a slight decrease of 2% in the average MAP (0–24 h); statistics did not show a significant difference ( $p > 0.05$ ). The HR (0–24 h) of cumin-treated and cumin + amlodipine-treated animals were  $333.81 \pm 2.24$  BPM and  $348.52 \pm 3.08$  BPM, respectively.

In L-NAME + green tea-treated animals, Group 4, the mean SBP (0–24 h) decreased after consumption of green tea for 14 days to  $158.43 \pm 2.39$  mm Hg, and DBP (0–24 h)  $106.48 \pm 3.12$  mm Hg, as well as MAP  $123.19 \pm 2.35$  mm Hg. The statistical test indicated significant variations ( $p < 0.05$ ) in all three parameters when contrasted with the hypertensive control group. The maximum reduction in SBP was observed after 8 h ( $151 \pm 2.32$  mm Hg). At 24 h, the SBP of rats was  $165.17 \pm 2.38$  mm Hg. Moreover, the maximum decrease in DBP was observed 12 h after green tea consumption ( $99.17 \pm 3.68$  mm Hg) and after 24 h, the DBP of rats reached  $105.33 \pm 2.63$ . In contrast, the green tea + amlodipine-treated group showed the maximum reduction in SBP ( $132.17 \pm 2.81$  mm Hg) at 4 h, which indicates a reduction of more than 6% in SBP in rats treated with green tea + amlodipine compared with the amlodipine group, while the mean SBP (0–24 h) was found to be

145.05 ± 2.41 mm Hg, and the mean DBP (0–24 h) decreased to 96.43 ± 2.91 mm Hg. After 24 h, the average SBP of the green tea + amlodipine-treated group was 152.17 ± 2.09 mm Hg, which is relatively lower than the SBP (165.17 ± 2.39 mm Hg) for animals treated with green tea only. Furthermore, the maximum reduction in DPB (83.67 ± 3.0 mm Hg) was observed 4 h after amlodipine administration, which is lower by 3.96% compared to the group treated with amlodipine alone at the 4 h point. A noticeable reduction of 5.24% in the MAP mean (0–24 h) was seen in rats treated with green tea + amlodipine. The mean HR (0–24 h) of animals treated with green tea and green tea + amlodipine-treated animals was found to be 344.10 ± 3.53 BPM and 352.19 ± 3.55 BPM, respectively.

#### 4.2. Impact of Cumin and Green Tea on Amlodipine Pharmacokinetics

The impact of cumin and green tea on amlodipine plasma concentration and its PK parameters were investigated using the UPLC-MS/MS method. It is extremely advantageous to use the LC-MS/MS analysis method as well as the sensitivity and selectivity provided by the MRM mode, since it can detect only the daughters or charged fragments that are generated when the compound of interest is ionized, thus eliminating interference from other impurities. As reported in previous study [39], “positive ionization mode was used along with optimized mass spectrometry parameters, such as source temperature, extractor, capillary voltage, desolvation temperature, RF Lens, desolvation gas flow, cone gas flow, low mass resolution (LMR1), (LMR2), high mass resolution (HMR1), (HMR2), ion energy IE1, IE2, gain, entrance and exit, and collision gas flow conditions”.

The charged fragments of amlodipine were monitored at mass-to-charge ratio ( $m/z$ ) 409.1 > 238 and  $m/z$  409.1 > 294 with an optimum collision energy of 8 eV and 12 eV, respectively (Figure 5).

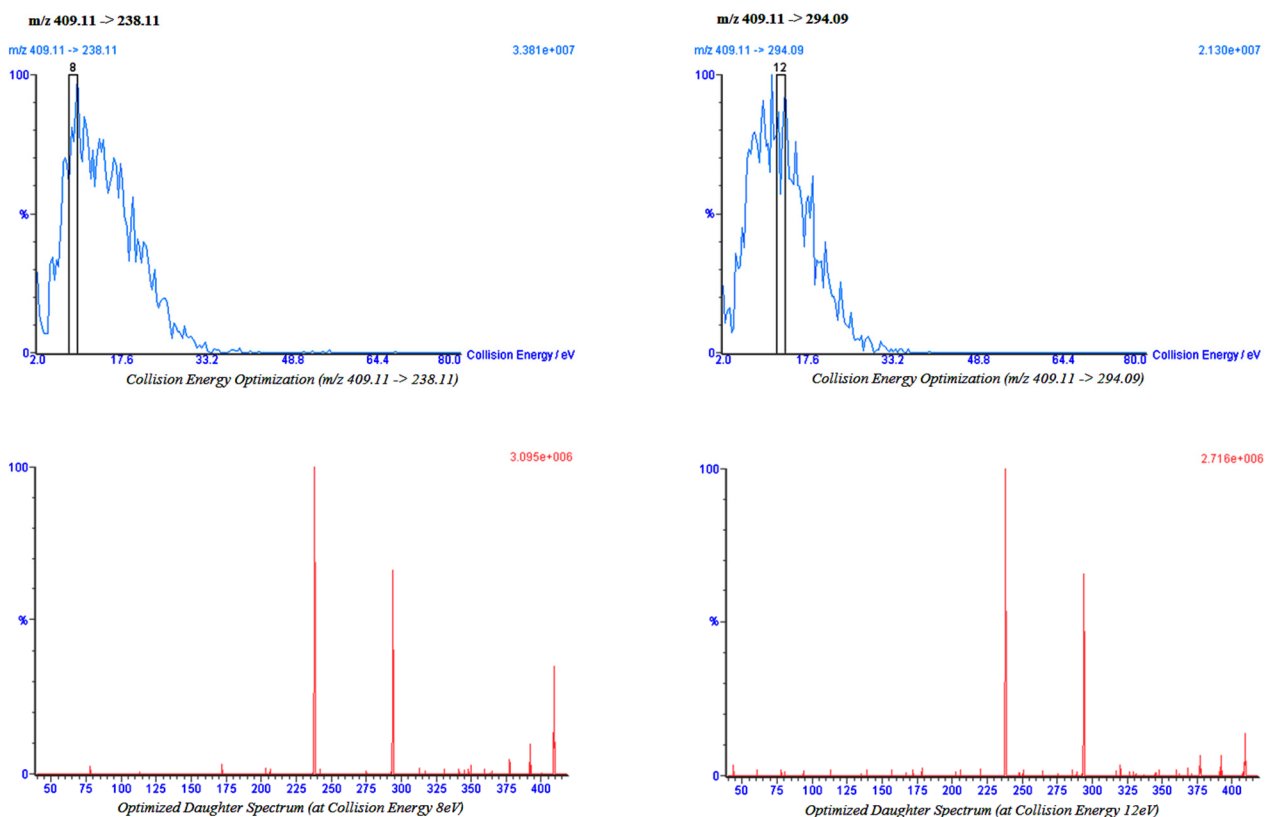
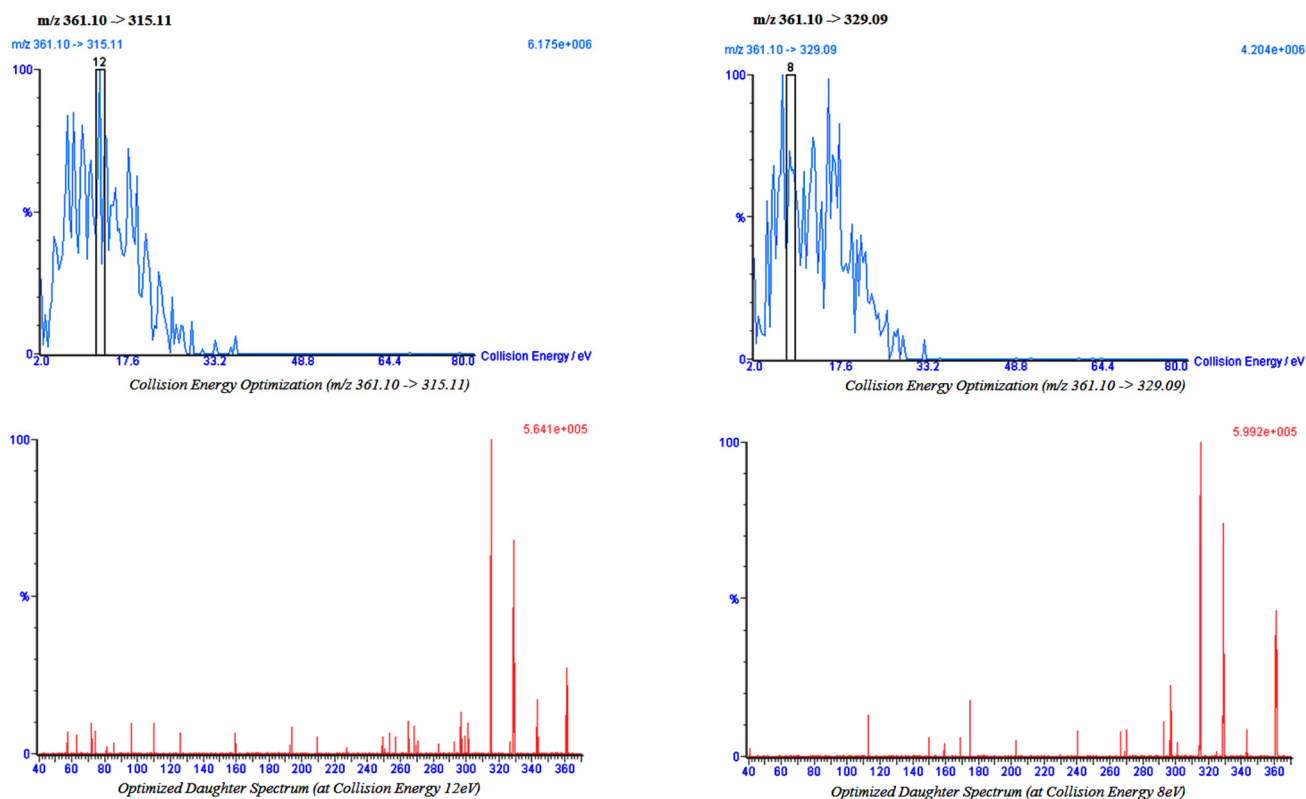


Figure 5. Daughter spectra for amlodipine with optimum collision energy.

While the optimized collision energy for IS daughters monitored at  $m/z$  361.1 > 315.1 and  $m/z$  361.1 > 329.1 was 12 eV, 8 eV, respectively (Figure 6).



**Figure 6.** Daughter spectra for amlodipine with optimum collision energy.

The representative chromatograms of amlodipine daughters and IS daughters were shown in Figure 7. Additionally, the calibration curve for the analytical method exhibited strong linearity between 0.6 and 20 ng/mL, with correlation coefficient ( $r^2$ ) equal to 0.99 (Figure 8).

The plasma concentrations profile and PK parameters of amlodipine are displayed in Figures 9 and 10, respectively. The study revealed that the  $C_{max}$  of the amlodipine group was  $3.94 \pm 0.99$  ng/mL with a  $T_{max}$  of  $2.6 \pm 1.34$  h, while the  $AUC_{0-t}$  is  $38.85 \pm 14.8$  ng h/mL. The  $T_{1/2}$  and  $K_{el}$  were found to be  $7.96 \pm 4.6$  h and  $0.11 \pm 0.06$  h, respectively (Figure 10). The group treated with cumin + amlodipine displayed a slight increase in  $C_{max}$  compared to the amlodipine group, with a value of  $4.92 \pm 1.46$  ng/mL. The  $T_{max}$  for this group was found to be the longest among all groups, with a mean of  $6.00 \pm 2.83$  h. The  $AUC_{0-t}$  for the cumin-treated group was  $52.05 \pm 10.2$  ng h/mL. In addition, the  $T_{1/2}$  and  $K_{el}$  for the cumin + amlodipine group were  $9.93 \pm 3.49$  h and  $0.08 \pm 0.03$  h, respectively.

The results showed that the green tea + amlodipine-treated group demonstrated the most significant impact on amlodipine PK parameters compared to the other groups. The  $C_{max}$  of amlodipine in rats was found to be the highest, with a value of  $9.12 \pm 1.4$  ng/mL after treatment with green tea. The green tea + amlodipine-treated rats also exhibited lowest  $T_{max}$  value  $1.00 \pm 0.0$  h. The  $AUC_{0-t}$  of amlodipine was found highest in the green tea + amlodipine-treated rats, with a value of  $114.73 \pm 24.94$  ng h/mL. Furthermore, the  $T_{1/2}$  was found to be the longest in the green tea + amlodipine-treated group, with a value of  $20.57 \pm 12.42$  h, and the  $K_{el}$  was  $0.05 \pm 0.02$  h (Figure 10).

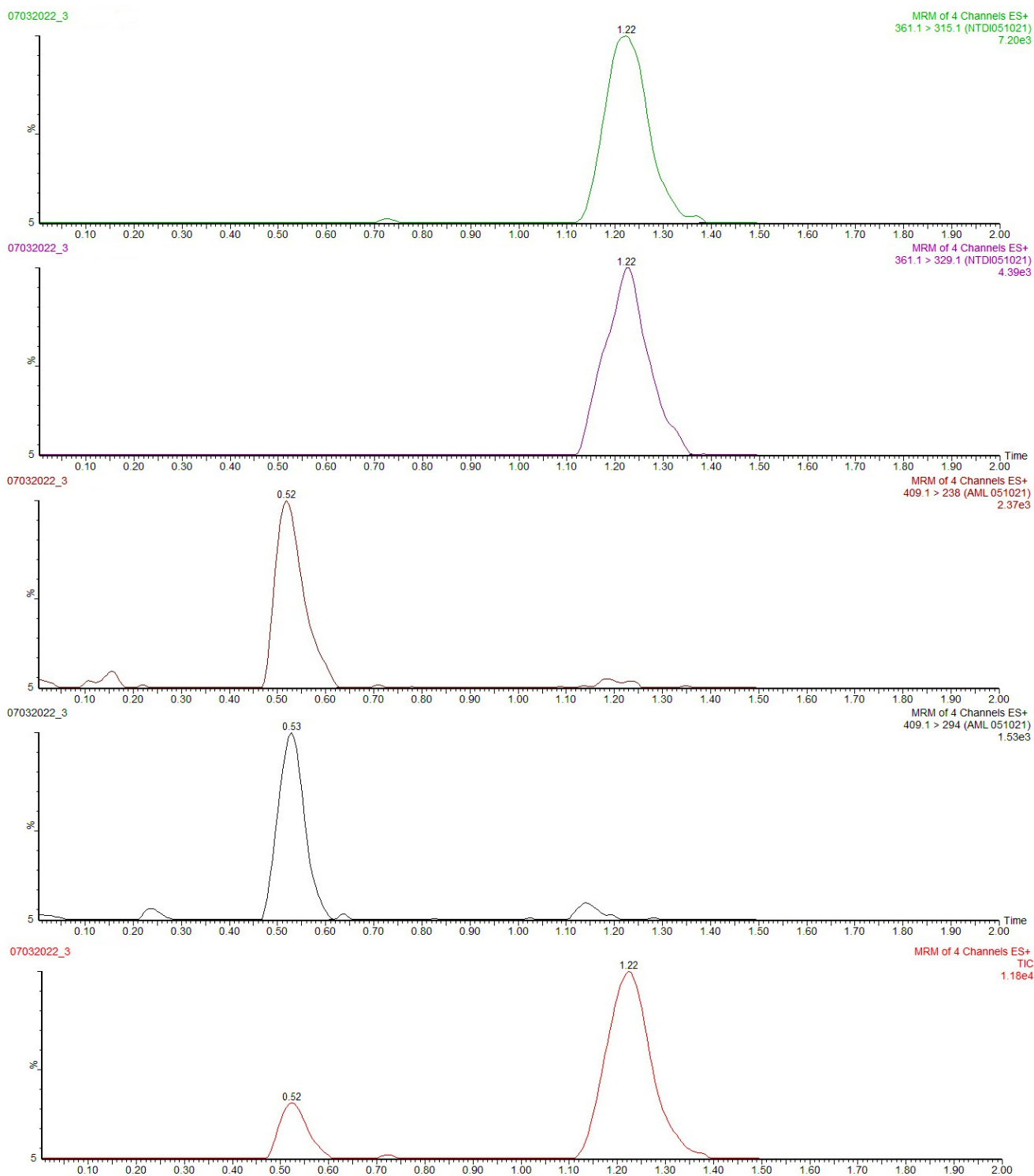


Figure 7. The chromatogram of amlodipine daughters, IS daughters, and total ion chromatogram.

Compound name: AML  
 Correlation coefficient  $r = 0.993925$ ,  $r^2 = 0.987887$

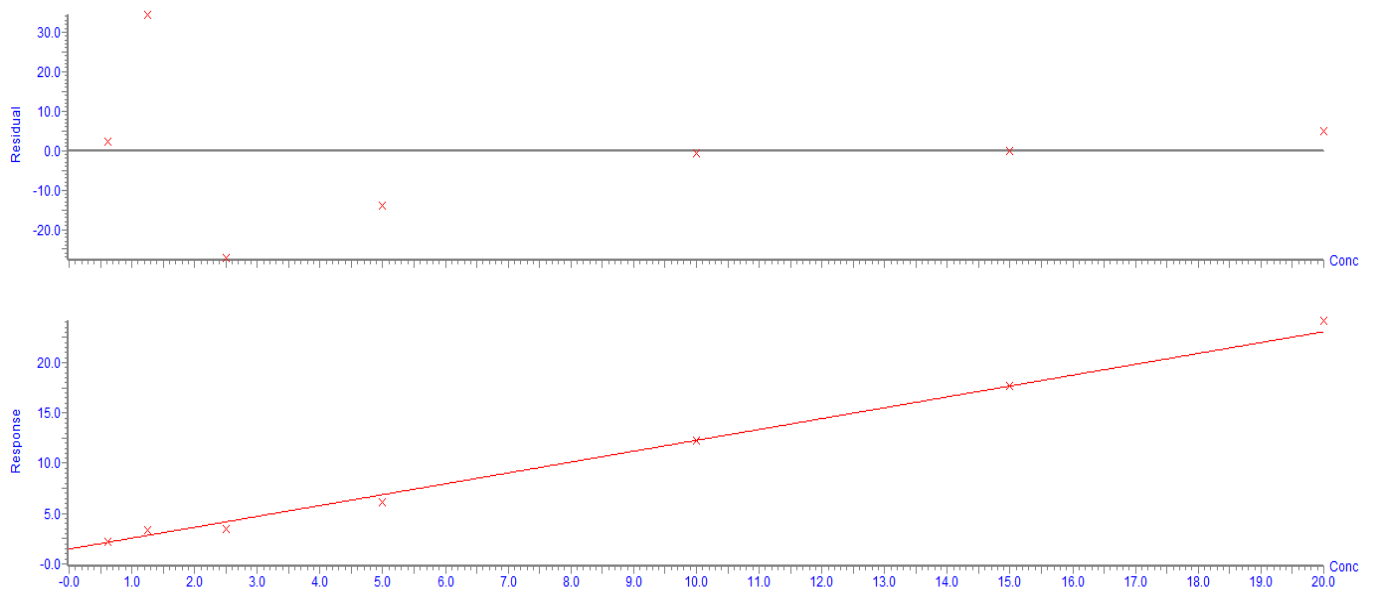


Figure 8. Presenting amlodipine calibration curve in plasma.

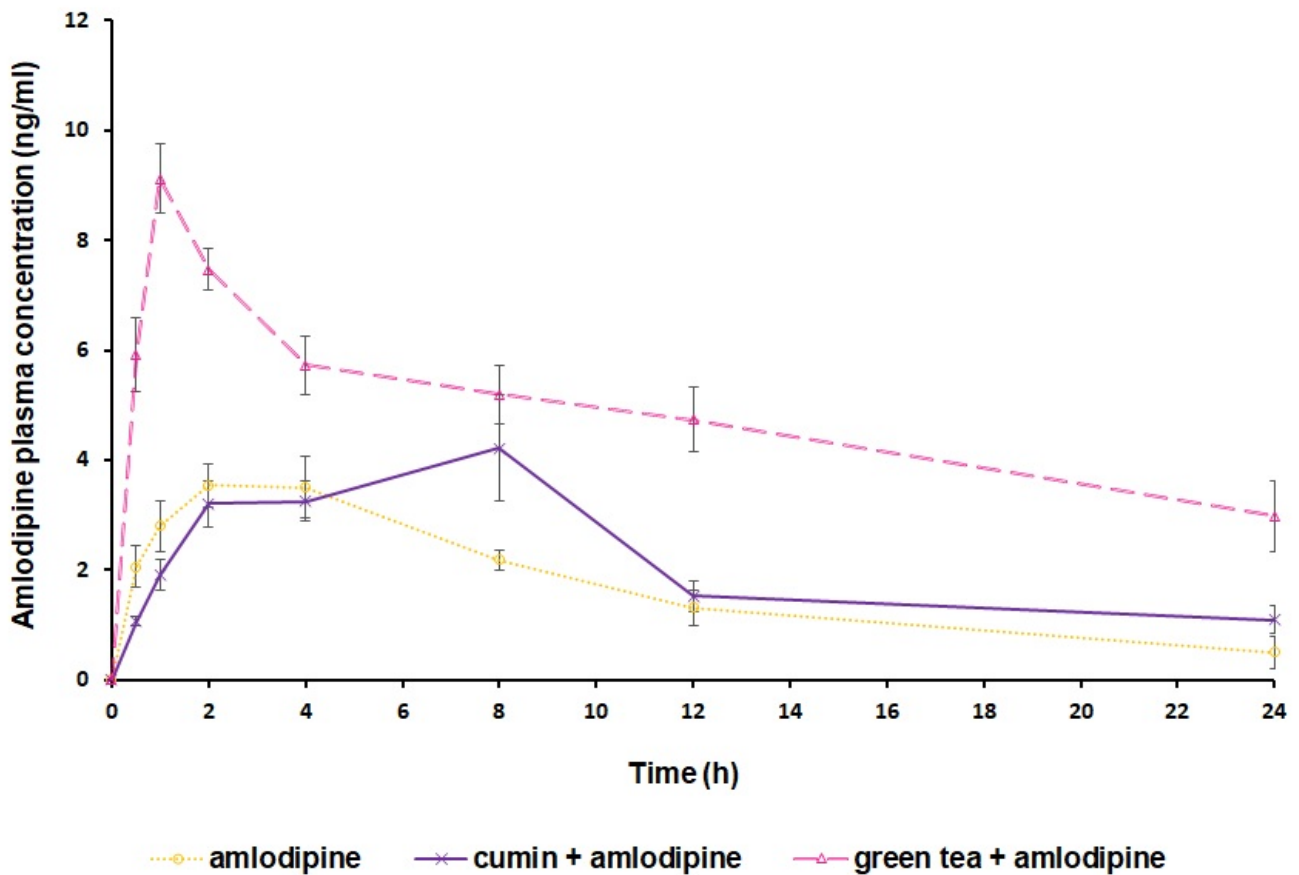
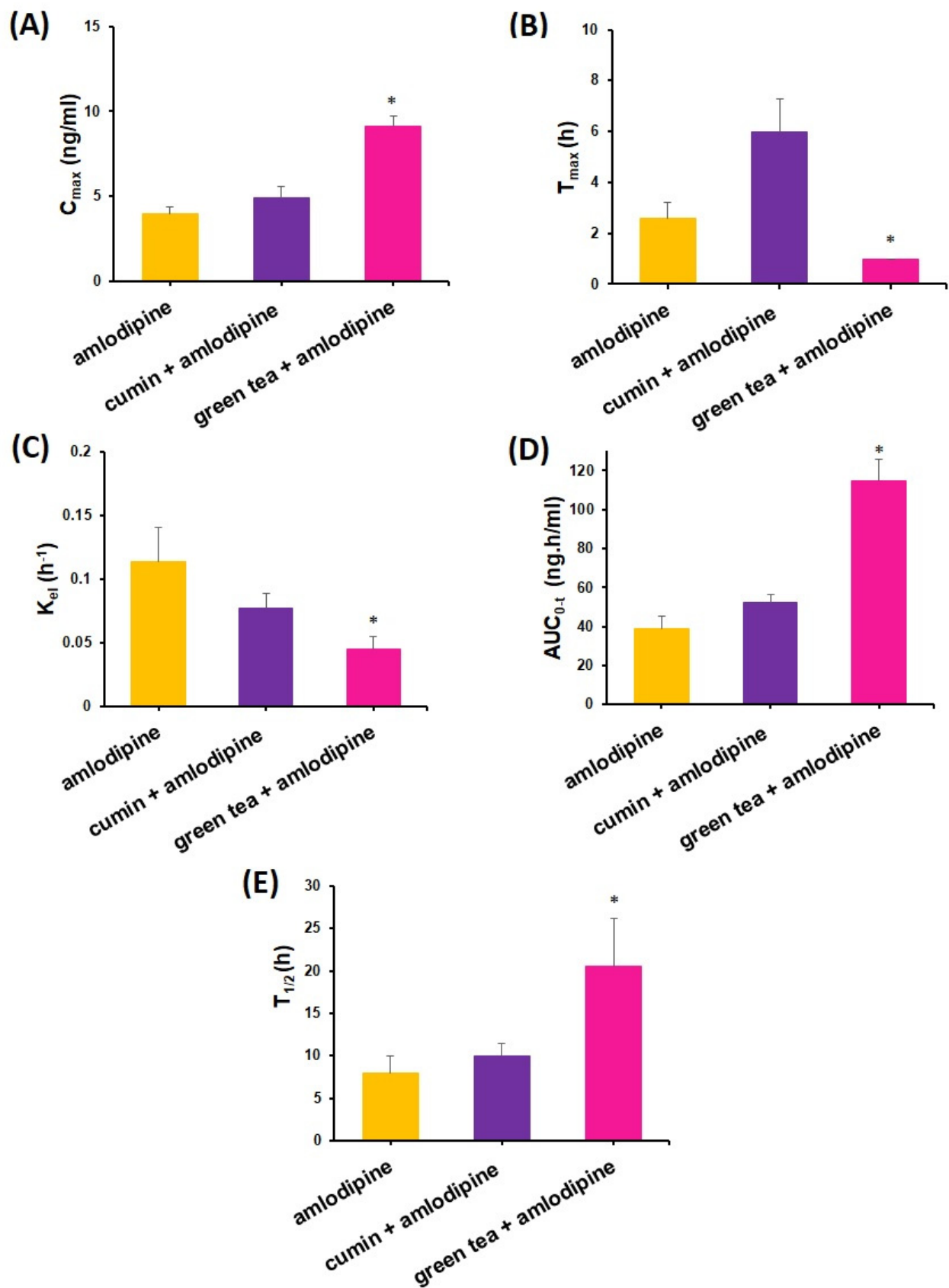


Figure 9. Plasma drug concentration-time curve in rats treated with amlodipine, cumin + amlodipine, and green tea + amlodipine.



**Figure 10.** Pharmacokinetics parameters (A)  $C_{max}$ , (B)  $T_{max}$ , (C)  $K_{el}$ , (D)  $AUC_{0-t}$ , and (E)  $T_{1/2}$  of amlodipine in hypertensive rats treated with amlodipine, cumin + amlodipine, and green tea + amlodipine (mean  $\pm$  SEM, \*  $p < 0.05$ ,  $n = 5$ ).

## 5. Discussion

The study was aimed to observe the influence of investigated herbs such as cumin and green tea on the amlodipine PD and PK in L-NAME-induced hypertensive rats. When comparing blood pressure profiles of the normal group (Group 1) to the hypertensive control group (Group 2), it indicates that rats in Group 2 became hypertensive as a result of L-NAME administration and remained hypertensive till the end of the experiment. The SBP of Group 2 ranged between 161 and 181, with an average of (0–24 h)  $171.69 \pm 4.10$ , while the DBP was found to be  $116.71 \pm 3.64$ . In contrast, the amlodipine dose reduces the mean SBP (0–24 h) to  $154.02 \pm 2.61$  mmHg and DBP (0–24 h) to  $101.31 \pm 2.93$  mmHg. Generally, it could also be said that amlodipine administration has been successful in lowering the SBP, DBP and subsequently the MAP in all groups. Low levels of reduction were shown for the SBP, DBP, and MAP for the cumin group. Noticeably the effect of cumin was observed more than 2 h from administration and lasted for almost 24 h. However, the reduction in SBP, DBP, and MAP as a result of treatment with cumin was not statistically significant compared to the hypertensive control group. The utmost reductions in SBP and DBP were seen at 4 h for the amlodipine group, whereas they were seen at 2 h for the cumin + amlodipine group.

In the present study, green tea has shown a notable blood-pressure-lowering effect in terms of SBP, DBP, and MAP when it is consumed alone, whilst the combination of green tea + amlodipine shows significant differences regarding SBP, DBP, and MAP in comparison with the hypertensive control group. The HR was improved significantly by treatment with green tea in comparison with the hypertensive control group, while the consumption of cumin did not show similar effects regarding HR. Several possible mechanisms of antihypertensive effect of green tea have been reported, including the direct regulation of vascular function by modulating the production and expression of vasoactive substances such as endothelin-1, prostaglandins, and prostacyclin [44,45]. Likewise, green tea has an inhibitory effect on inflammatory factors like tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), and other cytokines play a major role in lowering SBP [46]. In green tea and cumin, there are many types of polyphenols including EGCG and cuminol, as well as minerals and vitamins, that may exert antioxidant activity by increasing the activity of nitric oxide synthase and the concentration of nitric oxide in the body, thereby lowering the blood pressure by reducing oxidative stress [21,45].

In the present study, both herbs substantially altered the plasma concentration of amlodipine in hypertensive rats when compared to amlodipine group. It has been shown that the  $C_{max}$  and  $AUC_{0-t}$  of amlodipine in the cumin + amlodipine-treated group have not been significantly ( $p > 0.05$ ) changed. However, both parameters were increased 0.25-fold and 0.34-fold, respectively, as compared to the control group. Cumin increased the  $T_{max}$  of amlodipine considerably from  $2.6 \pm 1.34$  to  $6.0 \pm 2.83$ , which is a 1.31-fold increase, although the difference was not statistically significant ( $p > 0.05$ ). Evidently, this indicates a delay in the absorption process. In contrast, the green tea + amlodipine group had a shorter  $T_{max}$  value than the amlodipine group, suggesting that green tea may enhance the absorption of amlodipine. Additionally, green tea has been shown to increase amlodipine  $C_{max}$  1.31-fold in comparison to the  $C_{max}$  obtained for amlodipine group. Furthermore, the  $AUC_{0-t}$  in green tea + amlodipine was significantly ( $p < 0.05$ ) increased 1.95-fold in comparison to the  $AUC_{0-t}$  of the amlodipine-treated group. Additionally, the  $T_{1/2}$  of amlodipine increased significantly ( $p < 0.05$ ); this may account for the long duration of action of the drug, as shown in pharmacodynamic studies. These results support the findings of Han et al., who reported the significant effect of the active constituent of green tea EGCG on PK parameters [27]. It was observed that the  $T_{1/2}$  of green tea + amlodipine was increased 1.58-fold ( $p < 0.05$ ) in comparison to the  $T_{1/2}$  of the amlodipine group. Additionally, green tea also significantly ( $p < 0.05$ ) decreases the  $K_{el}$  of amlodipine; this PK interaction could be caused by the inhibition of CYP3A4 activity in the presence of green tea [27]. Therefore, the longer  $T_{1/2}$  and lower  $K_{el}$  observed in the green tea + amlodipine

group compared to the amlodipine group suggest that green tea may slow down the elimination of amlodipine from the body.

The  $T_{max}$  was also delayed in the cumin + amlodipine group compared to the amlodipine group, indicating that cumin may slow down the absorption of amlodipine, while it appears that cumin has a moderate effect on the  $K_{el}$  of amlodipine compared to the amlodipine group. The  $K_{el}$  value for the cumin group ( $0.08 \pm 0.03$  h) was lower than that of the amlodipine group ( $0.11 \pm 0.06$  h), suggesting a slower elimination of amlodipine in the presence of cumin. However, the difference in  $K_{el}$  values between the cumin + amlodipine group and the amlodipine group was not statistically significant ( $p > 0.05$ ). It is worth noting that the  $T_{max}$  was considerably delayed in the cumin + amlodipine group compared to the amlodipine group ( $6.00 \pm 2.83$  h vs.  $2.6 \pm 1.34$  h). This may suggest that cumin interferes with the absorption of amlodipine, leading to a slower rate of absorption and delayed  $T_{max}$ .

Taking into account the results of this study, amlodipine PD and PK may be altered by both investigated herbs. Increased plasma concentrations of amlodipine in the presence of green tea and cumin could be the reason for enhanced and prolonged antihypertensive effect of amlodipine. Despite the beneficial effect of medicinal herbs, untoward consequences could be expected when co-administered with antihypertensive agent(s). Furthermore, in order to understand the mechanism by which interactions occur, more studies need to be conducted in future.

## 6. Conclusions

In this study, HTN was effectively induced in Wistar rats by oral delivery of L-NAME. The administration of both herbs, namely green tea and cumin, effectively lowered the blood pressure in rats. In comparison to cumin, green tea has a more profound impact on the pharmacodynamics of amlodipine. The rats treated with cumin and green tea demonstrated higher  $C_{max}$ ,  $T_{1/2}$ , and  $AUC_{0-t}$  of amlodipine in comparison to the control group. The findings of the present study demonstrated a substantial interaction among amlodipine and examined herbs in L-NAME-induced hypertensive rats. As a result, it is imperative that precautions be taken when administering amlodipine together with herbs which have been investigated in the present study.

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