Saudi Pharmaceutical Journal 31 (2023) 101737

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Saudi Pharmaceutical Journal

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Original article

Cinnamon modulates the pharmacodynamic & pharmacokinetic of amlodipine in hypertensive rats

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ARTICLE INFO

Article history:
Received 2 July 2023
Accepted 1 August 2023
Available online 7 August 2023

Keywords:
Cinnamon
Cinnamomum zeylanicum
Amlodipine
Pharmacodynamic
Pharmacokinetic

ABSTRACT

The objective of this study was to investigate the effects of cinnamon on the pharmacodynamic (PD) & pharmacokinetic (PK) of amlodipine in hypertensive rats. The hypertensive control group of Wistar rats received L-NAME (40 mg/kg, daily, orally) only. The cinnamon group of rats was treated with cinnamon (200 mg/kg, daily, orally) along with L-NAME. Following 14 days treatment period, blood pressures of rats were monitored at designated intervals over 24 h utilizing a tail-cuff system for measuring blood pressure. To assess the oral PK; amlodipine was administered as a single oral dose of 1 mg/kg to rats and blood samples were collected at specified intervals over 24 h and analysed by UPLC-LC MS/MS.

Synergistic decreased in rat's blood pressure was observed in presence of cinnamon + amlodipine. Simultaneous administration of cinnamon ameliorates the C_{max} and AUC_{0-t} of amlodipine, the C_{max} and AUC_{0-t} was 11.04 ± 1.01 ng/ml and 113.76 ± 5.62 ng h/ml for the cinnamon + amlodipine group as compared to 4.12 ± 0.49 ng/ml and 48.59 ± 4.28 ng h/ml for the amlodipine alone group. The study demonstrates that the use of cinnamon considerably decreases the blood pressure levels and enhances the PK parameters of amlodipine in hypertensive rats.

1. Introduction

The practice of herbal treatment has been on the rise globally, and it is more common among patients with chronic diseases to incorporate them alongside their prescribed medications. This tendency can be attributed to the pursuit of enhancing the therapeutic effects or as a means to mitigate certain side effects associated with conventional medication consumption (Posadzki et al. 2013; Sen Samanta 2015). Hypertension is a widespread due to its high prevalence and it is chronic medical condition characterized by elevated blood pressure, which affects millions of people globally (Kearney et al. 2005; Mills et al. 2020). It is one of the risk factors for cardiovascular diseases, including heart attacks and strokes, which are among the leading causes of death worldwide (Mills et al. 2016; Mills et al. 2020). There are several classes of antihypertensive agents are available in market (Ali et al. 2017; Azizi et al. 2019). As a first-line option among the myriad antihypertensive agents, amlodipine is highly recommended (van Zwieten 1994). Amlodipine is one of the frequently used medications for hypertension treatment due to its efficacy in lowering blood pressure belongs to dihydropyridine calcium channel blocker, act via relaxing the blood vessels and improving blood flow (Ananchenko et al. 2012; Meredith Elliott 1992). Amlodipine is mainly metabolized via liver cytochrome P450 (CYP) enzymes system, with CYP3A4 being one of the main enzymes involved in its metabolism (Abernethy 1992; Zhang et al. 2014; Zhu et al. 2014). The reported oral bioavailability of amlodipine is 60–65% (Ahad et al. 2013; Meredith Elliott 1992). In comparison with other cardiovascular agents, amlodipine appears to be well tolerated. It is common for people taking amlodipine to experience oedema and flushing after taking the medication. It ranges from mild to moderate in severity. This may be caused by the drug's vasodilatory action. Some other adverse effects reported with amlodipine therapy includes anxiety, cramps in the muscles, erectile dysfunction, eye irritation, frequent urination (nocturia), respiratory problems, and wheezing. Although these reactions are uncommon, few have been sev-

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2023.101737

ere enough to require treatment to be discontinued (Ananchenko et al. 2012; Murdoch Heel 1991). The efficacy and safety profile of amlodipine can be influenced by drug-drug or drug-herb interactions, especially those that involve modulation of the CYP3A4 enzyme. It is therefore essential to understand the potential interactions of amlodipine with other substances to avoid alterations in drug pharmacodynamic (PD) and pharmacokinetic (PK), which could lead to ineffective therapy or adverse reactions (Höcht et al. 2019; Tarirai et al. 2010).

Cinnamon (*Cinnamomum Zeylanicum*) belongs to the Lauraceae family. The most prominently constituents found in cinnamon herb include coumarin, eugenol, and cinnamaldehyde which has been reported to possess several properties such as antibacterial, anti-inflammatory, antidiabetic, and antioxidant activities which can be responsible for hypotensive effect of cinnamon (Gruenwald et al. 2010; Hadi et al. 2020; Hariri Ghiasvand 2016; Mousavi et al. 2020; Ranasinghe et al. 2013; Yanakiev 2020). Antecedent studies have indicated that cinnamon have antihypertensive activity and hold significant effect in managing blood glucose levels (Akilen et al. 2012; Leach Kumar 2012; Preuss et al. 2006). It was reported the hypotensive effect of cinnamon could be due to improvement of lipid profile characteristics and the high potassium content of cinnamon (Alsoodeeri et al. 2020; Hadi et al. 2020; Mousavi et al. 2020). Some clinical researches have also reported that cinnamon has a potential to lower the raised blood pressure (Akilen et al. 2013; Hadi et al. 2020; Wainstein et al. 2011). This can be attributed to cinnamaldehyde one of the various components in cinnamon, which has vasodila-

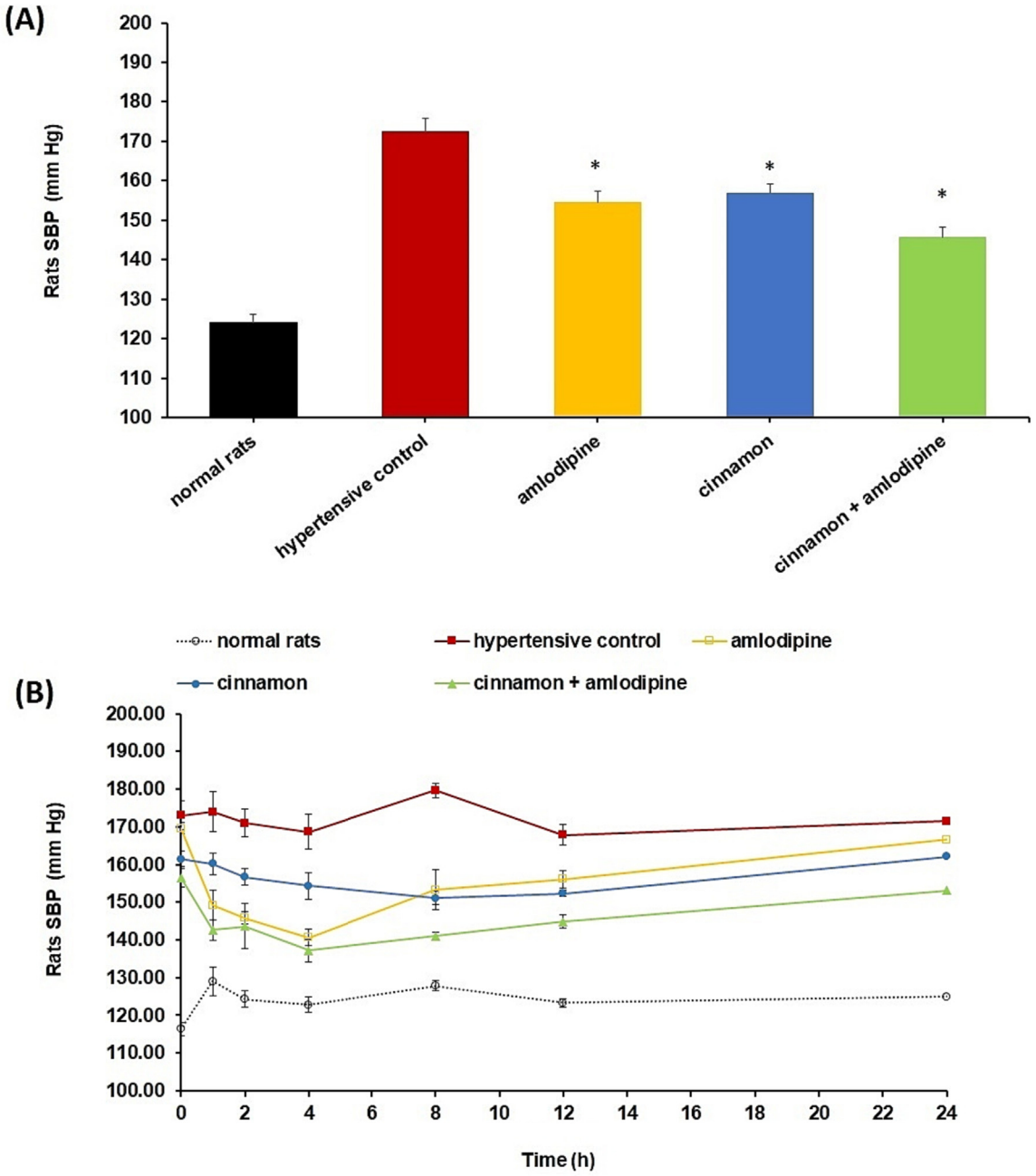

Fig. 1. Illustrating the influence of amlodipine, cinnamon and combinations of cinnamon + amlodipine on SBP of hypertensive rats. (A) Displays the average changes in SBP over a 24 h period in response to the treatments. (B) Presents the variations in SBP across a 24 h following treatments. (*$p < 0.05$, $n = 5$, Mean ± SEM). *In relation to the hypertensive control group.

tion activity and blood pressure reduction property (El-Bassossy et al. 2011; Xue et al. 2011).

Based on above literature, this study aimed to assess the potential impact of cinnamon on the PD and PK of amlodipine in an animal model. In this study, it is hypothesized that cinnamon might potentiate the effects of amlodipine due to their possibly similar mechanisms of action on blood vessels (Lu et al. 2022; Nyadjeu et al. 2011; Shen et al. 2012). This could result in an exaggerated antihypertensive effect and potentially lead to decrease blood pressure. Furthermore, cinnamon might also interact with the PK of amlodipine, potentially altering its absorption or metabolism, which could either enhance or attenuate the drug's therapeutic effect. However, the research literature on the herb-drug interaction between cinnamon and amlodipine in the context of hypertension is sparse and further research is needed to draw definitive conclusions. It will help the healthcare workers to optimize dosage regimen and ensure patient safety.

2. Materials and methods

The cinnamon bark powder was procured from "Bin Menqash Store Riyadh, Saudi Arabia". Amlodipine besylate (Amlor®, 10 mg) was purchased from "Novartis Pharma AG in Basel, Switzerland". L-NAME was acquired from "Carbosynth Limited® in Berkshire, UK". Formic acid was procured from Honeywell®, based in Charlotte, North Carolina, USA. Methanol and acetonitrile HPLC grade were obtained from "Fisher Scientific®, Massachusetts, USA" and Sigma-Aldrich®, "St. Louis, Missouri, USA" respectively.

2.1. Assessment of role of cinnamon in modulating the PD of amlodipine

This study was conducted following the protocol approved by the "Research Ethics Committee at King Saud University and ethical approval number KSU-SE-18–27, dated 24 December 2018". For

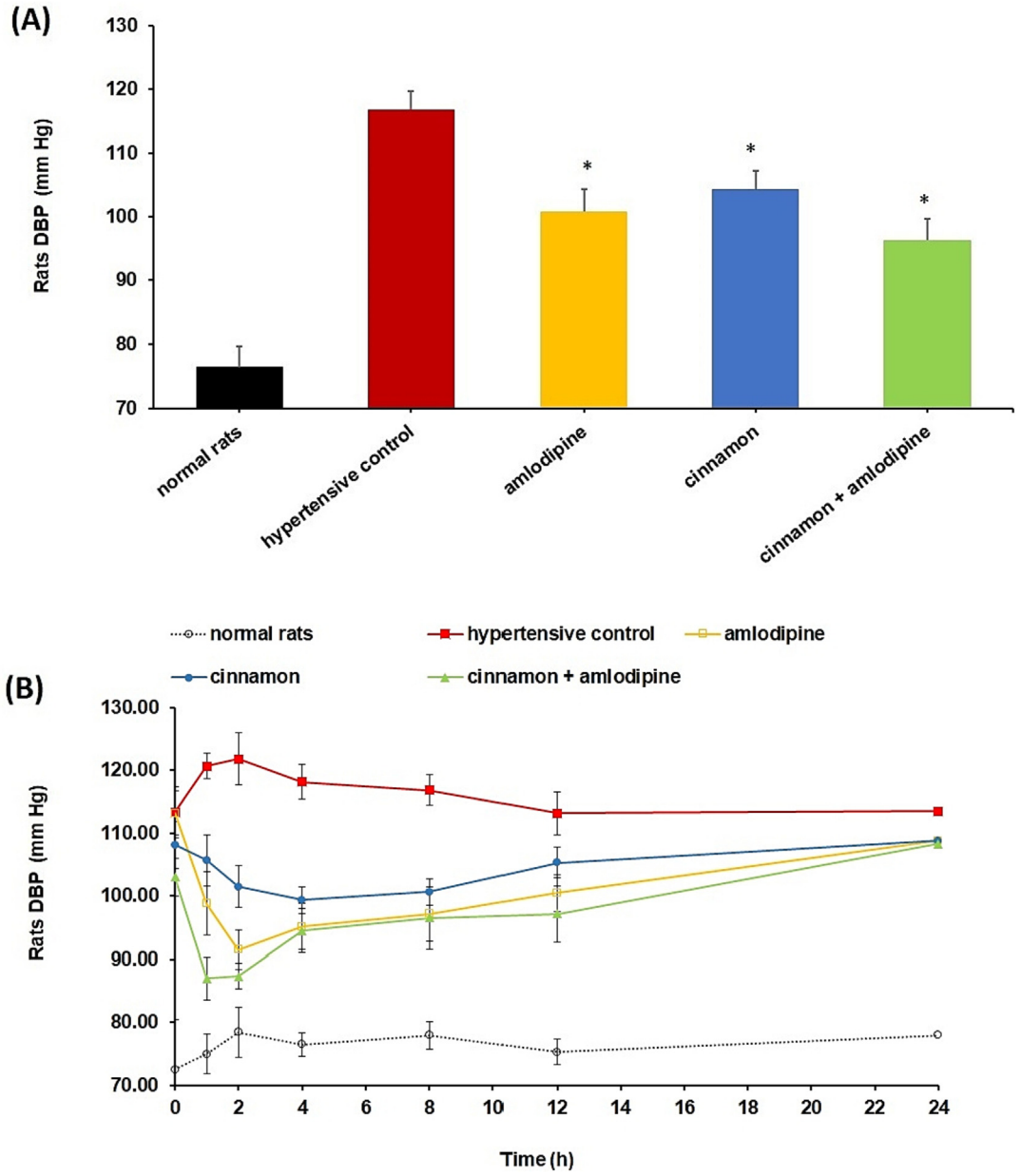

Fig. 2. Illustrating the influence of amlodipine, cinnamon and combinations of cinnamon + amlodipine on DBP of hypertensive rats. (A) Displays the average changes in DBP over a 24 h period in response to the treatments. (B) Presents the variations in SBP across a 24 h following treatments. (*$p < 0.05$, $n = 5$, Mean ± SEM). *In relation to the hypertensive control group.

PD study, Wistar rats (~250 g) were randomly divided into two groups (n = 5). Rats were trained for 5 days to sit in the restrained so they become familiar with the machine and experiment prior the actual recording (Ahad et al. 2017; Ahad et al. 2018). The blood pressure of normal rats (baseline blood pressure) was recorded, and subsequently hypertension was induced in both hypertensive control group and cinnamon group by oral administration of L-NAME 40 mg/kg daily for two weeks (Adaramoye et al. 2012; Adedapo et al. 2020; Ahad et al. 2022; Alam et al. 2021; Alam et al. 2020; Metchi Donfack et al. 2021; Sung et al. 2013). The cinnamon group received oral dose of cinnamon 200 mg/kg daily for two weeks in addition to L-NAME (Abdeen et al. 2019; Farazandeh et al. 2022; Jain et al. 2015; Sayad-Fathi et al. 2020; Sharafeldin Rizvi 2015). After two weeks, the measurement of animal blood pressure was conducted by Visitech tail-cuff system (Visitech, BP-2000 Series II, USA) at 0, 1, 2, 4, 8, 12, 24 h (Ahad et al. 2022). On next day, amlodipine (1 mg/kg, oral single dose) (Alam et al. 2021; Alam et al. 2020, 2022; Han et al. 2019; Jiang et al. 2020) was administered to hypertensive control group, cinnamon group, and blood pressure was again determined at 0, 1, 2, 4, 8, 12, 24 h.

2.2. Assessment of role of cinnamon in modulating the PK of amlodipine

For Pk study, a single oral dose of amlodipine 1 mg/kg was given to Wistar rats following a 3 days washout period and blood samples were obtained at specific time intervals 0.5, 1, 2, 4, 8, 12, and 24 h post-administration. Plasma was isolated from the samples and analysed for amlodipine content by LC-MS-MS method. In brief, the Pk analysis of amlodipine was conducted using the Waters® Acquity H-Class UPLC-tandem quadrupole mass spectrometer (UPLC-TQD-MS) manufactured by Waters®, Milford, USA (Alam et al. 2020). The UPLC® BEH C_{18} column (1.7 μm

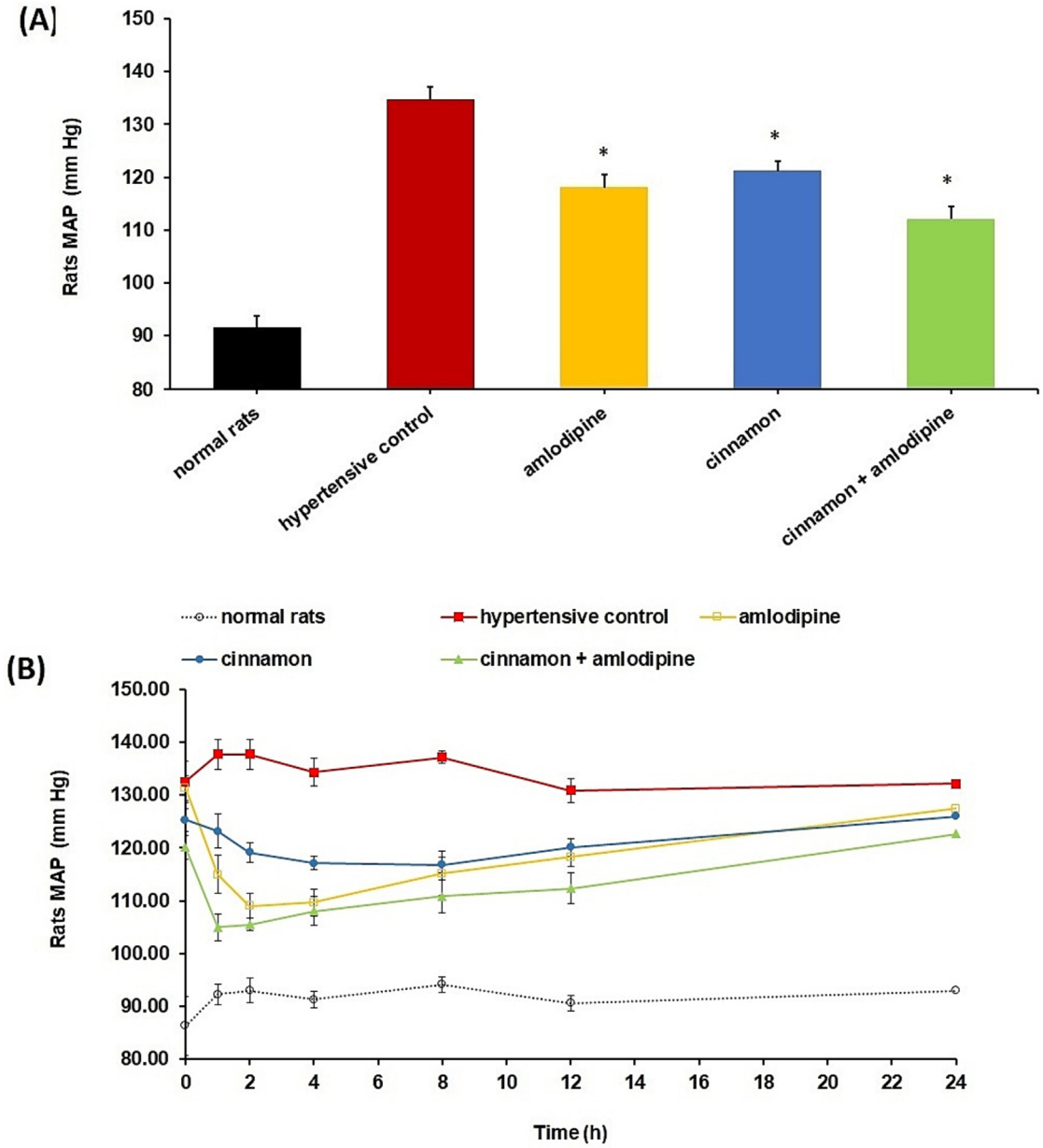

Fig. 3. Illustrating the influence of amlodipine, cinnamon and combinations of cinnamon + amlodipine MAP of hypertensive rats. (A) Displays the average changes in SBP over a 24 h period in response to the treatments. (B) Presents the variations in MAP across a 24 h following treatments. (*p < 0.05, n = 5, Mean ± SEM). *In relation to the hypertensive control group.

and 2.1 × 50 mm) was used for analysis at a controlled column temperature of 40 ± 5 °C (Alam et al. 2021; Alam et al. 2022). A plasma sample of 200 µL was placed into a labelled Eppendorf tube. Subsequently, 20 µL of a nitrendipine (IS) solution with a stock concentration of 100 ng/mL in methanol was precisely added into the plasma sample in the Eppendorf tube and mixed using a vortex. Acetonitrile (420 µL) was then added to the mixture to induce protein precipitation, which was further vortexed for 25 s. The resulting mixture was centrifuged at 12,000 rpm for 6 min. The supernatant was withdrawn, injected into the UPLC-TQD-MS system, and subsequently analysed. The mobile phase used in the analysis was a mixture of water with 0.1% formic acid (45%) as phase A, and acetonitrile with 0.1% formic acid (55%) as phase B. The temperature of the auto sampler was kept within the range of 15 ± 3 °C throughout the analysis. For PK analysis, the daughter fragments of amlodipine and IS were monitored using electrospray ionization positive mode (ESI +) and multiple reaction mode (MRM). The monitored *m*/*z* values for amlodipine and nitrendipine were 409.1 > 238 and 409.1 > 294, respectively. Similarly, the *m*/*z* values for the daughter fragments of amlodipine and nitrendipine were 361.1 > 315.1 and 361.1 > 329.1, respectively. The retention times for amlodipine and the IS were 0.49 min and 1.14 min respectively. The calibration curve exhibited linearity within the range of 0.6 to 20 ng/mL,

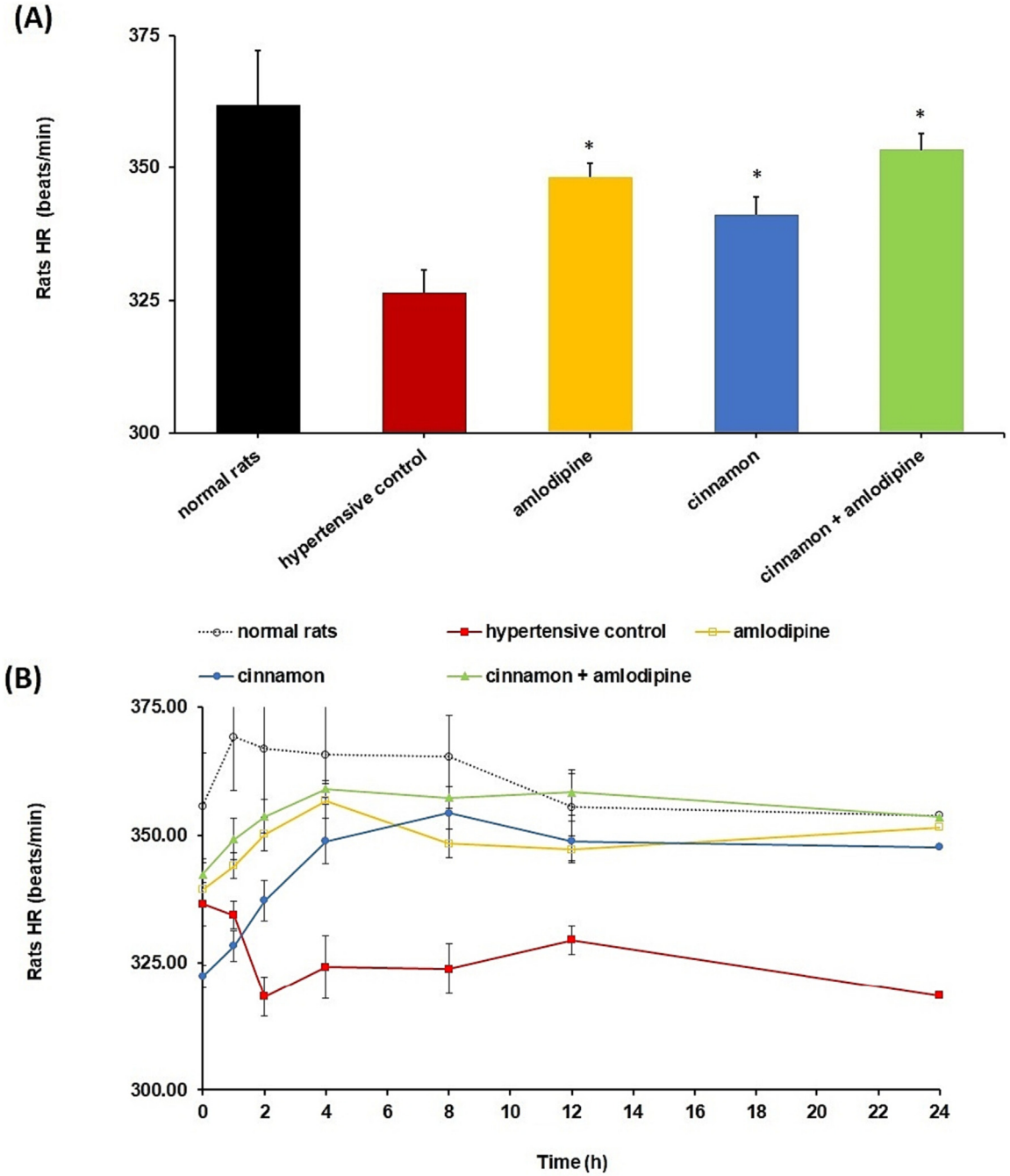

Fig. 4. Illustrating the influence of amlodipine, cinnamon and combinations of cinnamon + amlodipine on HR of hypertensive rats. (A) Displays the average changes in HR over a 24 h period in response to the treatments. (B) Presents the variations in HR across a 24 h following treatments. (*p < 0.05, *n* = 5, Mean ± SEM). *In relation to the hypertensive control group.

with a lower limit of quantitation (LOQ) set at 0.6 ng/mL (Alam et al. 2020).

2.3. Statistical analysis

"Statistical analysis was done by unpaired *t*-test using GraphPad Prism 6.00 (GraphPad Software, Inc, CA, USA). *P vales < 0.05 was considered as significant".

3. Results

3.1. Role of cinnamon in modulating the PD of amlodipine

The measurements of SBP, DBP, mean arterial pressure (MAP) and heart rate (HR) over 24 h were monitored in intervals using the "Visitech tail-cuff system", and shows in Figs. 1-4.

The normal group shows a mean SBP of 124.09 ± 1.99 mmHg (Fig. 1A), while the DBP was 73.26 ± 3.30 mmHg (Fig. 2A). In addition, the MAP equal to 91.55 ± 2.18 mmHg (Fig. 3A) and HR equal to 361.71 ± 10.42 beat/min (Fig. 4A). After 14 days of treatment with L-NAME alone for hypertensive control group the blood pressure was measured. For hypertensive control group the SBP (0–24 h) was 172.24 ± 2.49 mmHg (Fig. 1A), and the DBP and MAP were 116.79 ± 3.02 mmHg (Fig. 2A), 134.62 ± 2.55 mmHg (Fig. 3A) respectively. The HR was found 326.45 ± 4.12 beat/min (Fig. 4A). Animals subjected to cinnamon treatment shows slightly blood pressure lowering effect with SBP of 156.91 ± 2.21 mmHg (Fig. 1A), DBP 104.21 ± 2.98 mmHg (Fig. 2A) and MAP was 121.1 2 ± 1.9 mmHg (Fig. 3A), which is lower by 8.9%, 10.77%, 10.03% respectively as compared to hypertensive control group. The HR was found 341.07 ± 3.47 beat/min for cinnamon group (Fig. 2A). There was a notable effect of cinnamon throughout the 24 h period, but the maximum effect on SBP was observed 8 h after administration of the herb, the SBP was found 151.17 ± 1.82 mmHg at 8 h (Fig. 1B). The maximum reduction of DBP to 99.33 ± 2.06 mmHg at 4 h of the study (Fig. 2B). At the end of 24 h, SBP, DBP of rats was found 162.17 ± 2.3 mm Hg (Fig. 1B) and 108.83 ± 3.15 mm Hg (Fig. 2B) respectively.

At 0 h time point, the SBP and DBP was found 169.67 ± 1.43 mm Hg (Fig. 1B), and 113.17 ± 3.49 mm Hg (Fig. 2B) respectively in L-NAME + amlodipine group. At 24 h, the SBP and DBP were found 154.5 ± 2.74 mm Hg (Fig. 1B) and 100.74 ± 3.52 mm Hg (Fig. 2B) for L-NAME + amlodipine group. The average of MAP was found 118.00 ± 2.62 mmHg (Fig. 3A) while the HR improved to 348.17 ± 2.74 beat/min after amlodipine administration in L-NAME + amlodipine group (Fig. 4A). The maximum reduction of SBP was found 140.67 ± 2.14 mm Hg at 4 h (Fig. 1B) and DBP was found 91.5 ± 3.03 mm Hg at 2 h (Fig. 2B). After that the SBP start to rise and reached 166.67 ± 2.43 mm Hg (Fig. 2A), as well as DBP reached to 108.83 ± 2.14 mm Hg at the end of 24 h (Fig. 2B). At 0 h the SBP and DBP was found 156.5 ± 2.36 mm Hg (Fig. 1B) and 103.00 ± 3.01 mm Hg (Fig. 2B) for cinnamon + amlodi pine group. Rats treated with cinnamon + amlodipine showed an average of SBP 145.57 ± 2.6 mmHg (Fig. 1A) lower by 15.48% and 5.77% compared to hypertensive control group, and L-NAME + amlodipine group respectively. The DBP over 24 h was 96.26 ± 3.38 mm Hg (Fig. 2A) indicating to 17.58% and 4.45% reduction in comparison with hypertensive control and L-NAME + amlodipine treated group respectively. The MAP was also lowered to 112.07 ± 2.31 mm Hg (Fig. 3A). While the HR or rats improved to 353.33 ± 3.11 beat/min (Fig. 4A). Furthermore, in the group treated with cinnamon + amlodipine, the maximum reduction of SBP was 137.17 ± 2.99 mm Hg at 4 h (Fig. 1B) and around 3% reduction compare to animal treated with L-NAME + amlodipine. Approx. 12% reduction in DBP at 1 h (98.83 ± 4.99 mm Hg to 87.00 ± 3.43 mm Hg) (Fig. 2B) was noted. The most reduction in MAP was exhibited at 1 h and the reduction was found to be 8.69% less compared to MAP of L-NAME + amlodipine group (115.00 ± 3.54 mm Hg to 105.00 ± 2.56 mm Hg) (Fig. 3B). At the end of experiment the SPB was 153.17 ± 1.33 mm Hg (Fig. 1B) decreased by 11% in compared with hypertensive control group and 8% compared to L-NAME + amlodipine group. The DBP and MAP at 24 h were 108.33 ± 3.15 mm Hg (Fig. 2B) and 122.67 ± 1. 49 mm Hg (Fig. 2B), respectively.

3.2. Role of cinnamon in modulating the PK of amlodipine

The amlodipine plasma concentrations versus time curve and PK parameters are presented in Fig. 5 and Fig. 6. In the control group, the C_{max} was observed to be 4.12 ± 0.49 ng/ml (Fig. 6A),

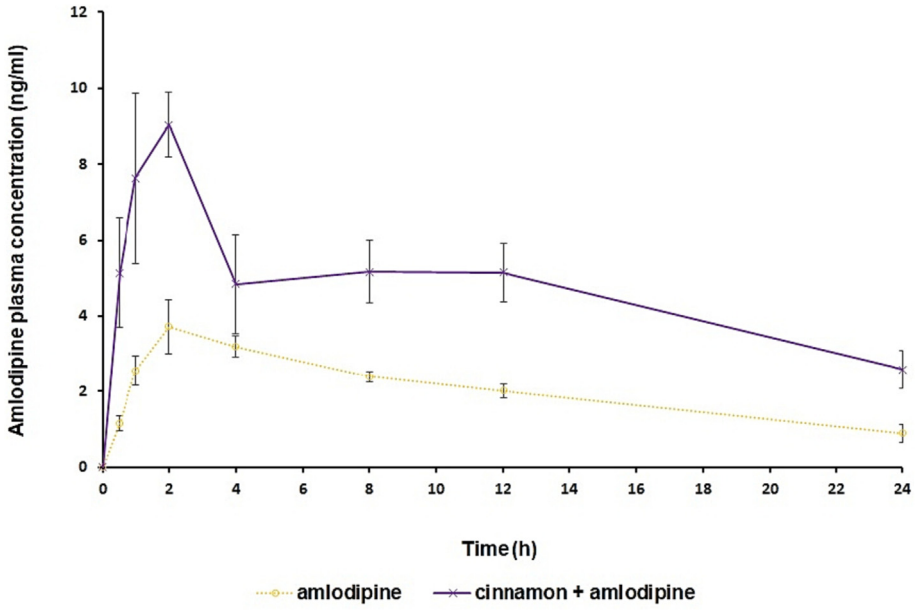

Fig. 5. Plasma drug concentration–time curve for rats treated with amlodipine alone, cinnamon + amlodipine.

and T_{max} was 2.20 ± 0.49 h (Fig. 6B). The AUC_{0-t} was approximately 48.59 ± 4.28 ng·h/ml (Fig. 6C). The $T_{1/2}$ and K_{el} was found to be 10. 34 ± 1.88 h (Fig. 6D) and 0.09 ± 0.03 h (Fig. 6E) respectively. The results demonstrated that the group receiving cinnamon exhibited

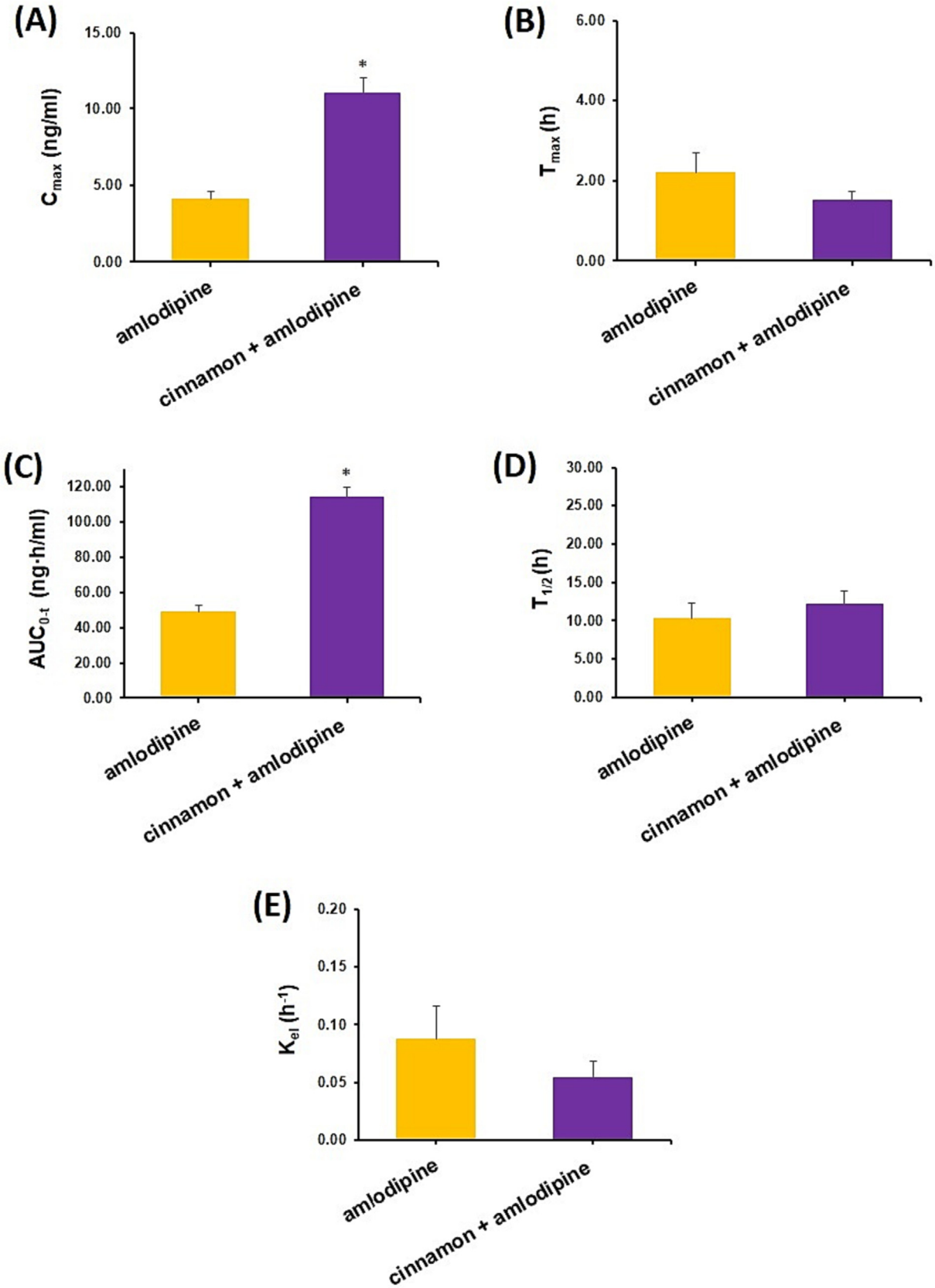

Fig. 6. Pharmacokinetics parameters (A) C_{max}, (B) T_{max}, (C) AUC_{0-t}, (D) $T_{1/2}$, (E) K_{el} of amlodipine in groups treated with amlodipine alone and cinnamon + amlodipine (*$p < 0.05$, $n = 5$, mean ± SEM). *In relation to the amlodipine group.

a noteworthy alteration in the PK parameters of amlodipine in comparison to the group receiving amlodipine alone. In the cinnamon group, the C_{max} of amlodipine was markedly elevated and raised to 11.04 ± 1.01 ng/ml (Fig. 6A). Moreover, this group experienced a comparatively reduced T_{max}, with an average value of 1.5 ± 0.22 h (Fig. 6B). The AUC_{0-t} was also substantially greater in the cinnamon group, and reached to 113.76 ± 5.62 ng·h/ml (Fig. 6C). Additionally, the $T_{1/2}$ was observed to be more prolonged in the cinnamon group, and extend to 12.09 ± 1.84 h (Fig. 6D), and the K_{el} was noted at 0.05 ± 0.01 h (Fig. 6E).

4. Discussion

In this study, the monitoring of SBP, DBP, MAP, and HR over a period of 24 h brought some remarkable observations. The control group, which was subjected to L-NAME treatment, exhibited a mean SBP of 172.24 ± 2.49 mmHg (Fig. 1A). In contrast, the group receiving cinnamon displayed a blood pressure lowering effect, with a significant reduction in the SBP, DBP, and MAP, by approximately 8.9%, 10.77%, and 10.03% respectively compared to the control group. Such findings are consistent with earlier studies suggesting the potential antihypertensive properties of cinnamon (Nyadjeu et al. 2011; Ranasinghe et al. 2013).

It was reported that the herb constituent contributes to hypotension by blocking calcium release or influx (Xue et al. 2011). Previously, it was reported that the chemical constituents of the cinnamon either indirectly inhibit/stimulate the renin angiotensin system, angiotensin converting enzyme, or diuretic properties or directly cause vasodilation (Ajebli Eddouks 2020). In another report, it was mentioned that phytoconstituent of cinnamon demonstrated hypotensive activity in guinea pigs and dogs by causing peripheral vasodilation (Harada Yano 1975). The hypotensive effect of cinnamon might be attributed to its high potassium content and improvement in lipid profile characteristics (Alsoodeeri et al. 2020; Hadi et al. 2020; Mousavi et al. 2020).

Furthermore, the maximum reduction in SBP was observed 8 h post-administration of cinnamon, suggesting a delayed, but sustained, effect of cinnamon on blood pressure modulation. The combination resulted in an even more substantial decrease in blood pressure. Notably, this combination of cinnamon and amlodipine achieved an average SBP of 145.57 ± 2.6 mmHg (Fig. 1A), which is markedly lower than the hypertensive control group and the L-NAME + amlodipine group. This suggests the possible synergistic effects of cinnamon and amlodipine in lowering blood pressure level.

From a PK point of view, a notable alteration in amlodipine's parameters was observed in animal treated with cinnamon. The increase in C_{max} and the AUC_{0-t} suggests that cinnamon could possibly affect the absorption and metabolism of amlodipine. This might be attributed to the interaction of cinnamon with the CYP3A4 enzyme, which is crucial in the metabolism of amlodipine (Mamindla et al. 2017). These findings implicate that the concurrent administration of cinnamon and amlodipine may alter the PD and PK parameters, which warrants further investigations and such interactions must be cautiously considered. Research investigators and health practitioners should be aware of such potential herb-drug interactions.

5. Conclusion

Based on the data presented, it is evident that cinnamon (*Cinnamomum Zeylanicum*) exhibits promising antihypertensive properties and can potentially enhance the efficacy of amlodipine in reducing blood pressure. The synergistic effect of co-administration with amlodipine was even more pronounced, with SBP lowered to an average of 145.57 ± 2.6 mmHg, which is a substantial 15.48% reduction compared to the hypertensive control group. Moreover, the PK analysis revealed that cinnamon influences the metabolism of amlodipine. The study exhibited a considerable increase in the C_{max} (11.04 ± 1.01 ng/ml) and AUC_{0-t} (113.76 ± 5.62 ng·h/ml) of investigated drug in cinnamon plus amlodipine treated group and indicated a greater exposure of the drug. This suggests that cinnamon may alter the PK of amlodipine, possibly through the modulation of the CYP3A4 enzyme activity. Despite the promising findings of combining amlodipine and cinnamon for hypertension management, the substantial alterations of PD and PK could have negative effect on therapeutic outcome, therefore, future studies are needed and caution should be exercised when investigated herb is administered with investigated drug.

Funding

"The authors are thankful to the Researchers Supporting Project (RSPD2023R541) at King Saud University, Riyadh, Saudi Arabia, for funding this project".

CRediT authorship contribution statement

Ibrahim Abdelsalam Abdelrahman: Formal analysis, Writing – original draft, Writing – review & editing. **Abdul Ahad:** Conceptualization, Supervision, Formal analysis, Writing – original draft, Writing – review & editing. **Mohammad Raish:** Formal analysis, Writing – review & editing. **Yousef A. Bin Jardan:** Conceptualization, Supervision, Writing – review & editing. **Mohd Aftab Alam:** Formal analysis, Writing – review & editing. **Fahad I. Al-Jenoobi:** Conceptualization, Supervision, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abdeen, A., Abdelkader, A., Abdo, M., Wareth, G., Aboubakr, M., Aleya, L., Abdel-Daim, M., 2019. Protective effect of cinnamon against acetaminophen-mediated cellular damage and apoptosis in renal tissue. Environ. Sci. Pollut. Res. Int. 26, 240–249.

Abernethy, D.R., 1992. Pharmacokinetics and pharmacodynamics of amlodipine. Cardiology 80 (Suppl 1), 31–36.

Adaramoye, O.A., Nwosu, I.O., Farombi, E.O., 2012. Sub-acute effect of N(G)-nitro-l-arginine methyl-ester (L-NAME) on biochemical indices in rats: Protective effects of Kolaviron and extract of Curcuma longa L. Pharmacogn Res 4, 127–133.

Adedapo, A.D.A., Ajayi, A.M., Ekwunife, N.L., Falayi, O.O., Oyagbemi, A., Omobowale, T.O., Adedapo, A.A., 2020. Antihypertensive effect of Phragmanthera incana (Schum) Balle on NG-nitro-L-Arginine methyl ester (L-NAME) induced hypertensive rats. J. Ethnopharmacol. 257, 112888.

Ahad, A., Al-Jenoobi, F.I., Al-Mohizea, A.M., Aqil, M., Kohli, K., 2013. Transdermal delivery of calcium channel blockers for hypertension. Expert Opin. Drug Deliv. 10, 1137–1153.

Ahad, A., Al-Saleh, A.A., Al-Mohizea, A.M., Al-Jenoobi, F.I., Raish, M., Yassin, A.E.B., Alam, M.A., 2017. Pharmacodynamic study of eprosartan mesylate-loaded transfersomes Carbopol((R)) gel under Dermaroller((R)) on rats with methyl prednisolone acetate-induced hypertension. Biomed. Pharmacother. 89, 177–184.

Ahad, A., Raish, M., Al-Jenoobi, F.I., Al-Mohizea, A.M., 2018. Sorbitane monostearate and cholesterol based niosomes for oral delivery of telmisartan. Curr. Drug Deliv. 15, 260–266.

Ahad, A., Raish, M., Abdelrahman, I.A., Jardan, Y.A.B., Alam, M.A., Al-Mohizea, A.M., Al-Jenoobi, F.I., 2022. Changes in pharmacokinetics and pharmacodynamics of losartan in experimental diseased rats treated with Curcuma longa and Lepidium sativum. Pharmaceuticals (Basel) 16.

Ajebli, M., Eddouks, M., 2020. Phytotherapy of hypertension: An updated overview. Endocr Metab Immune Disord Drug Targets 20, 812–839.

Akilen, R., Tsiami, A., Devendra, D., Robinson, N., 2012. Cinnamon in glycaemic control: Systematic review and meta analysis. Clin. Nutr. 31, 609–615.
Akilen, R., Pimlott, Z., Tsiami, A., Robinson, N., 2013. Effect of short-term administration of cinnamon on blood pressure in patients with prediabetes and type 2 diabetes. Nutrition 29, 1192–1196.
Alam, M.A., Bin Jardan, Y.A., Raish, M., Al-Mohizea, A.M., Ahad, A., Al-Jenoobi, F.I., 2020. Effect of Nigella sativa and fenugreek on the pharmacokinetics and pharmacodynamics of amlodipine in hypertensive rats. Curr. Drug Metab. 21, 318–325.
Alam, M.A., Bin Jardan, Y.A., Alzenaidy, B., Raish, M., Al-Mohizea, A.M., Ahad, A., Al-Jenoobi, F.I., 2021. Effect of Hibiscus sabdariffa and Zingiber officinale on pharmacokinetics and pharmacodynamics of amlodipine. J. Pharm. Pharmacol. 73, 1151–1160.
Alam, M.A., Bin Jardan, Y.A., Raish, M., Al-Mohizea, A.M., Ahad, A., Al-Jenoobi, F.I., 2022. Herb-drug interaction: pharmacokinetics and pharmacodynamics of anti-hypertensive drug amlodipine besylate in presence of Lepidium sativum and Curcuma longa. Xenobiotica 52, 177–185.
Ali, M.A., Rizvi, S., Syed, B.A., 2017. Trends in the market for antihypertensive drugs. Nat. Rev. Drug Discov. 16, 309–310.
Alsoodeeri, F.N., Alqabbani, H.M., Aldossari, N.M., 2020. Effects of cinnamon (Cinnamomum cassia) consumption on serum lipid profiles in albino rats. J Lipids 2020, 8469830.
Ananchenko, G., Novakovic, J., Lewis, J., 2012. Amlodipine besylate. Profiles Drug Subst Excip Relat Methodol 37, 31–77.
Azizi, M., Rossignol, P., Hulot, J.S., 2019. Emerging drug classes and their potential use in hypertension. Hypertension 74, 1075–1083.
El-Bassossy, H.M., Fahmy, A., Badawy, D., 2011. Cinnamaldehyde protects from the hypertension associated with diabetes. Food Chem. Toxicol. 49, 3007–3012.
Farazandeh, M., Mahmoudabady, M., Asghari, A.A., Niazmand, S., 2022. Diabetic cardiomyopathy was attenuated by cinnamon treatment through the inhibition of fibro-inflammatory response and ventricular hypertrophy in diabetic rats. J. Food Biochem. 46, e14206.
Gruenwald, J., Freder, J., Armbruester, N., 2010. Cinnamon and health. Crit. Rev. Food Sci. Nutr. 50, 822–834.
Hadi, A., Campbell, M.S., Hassani, B., Pourmasoumi, M., Salehi-Sahlabadi, A., Hosseini, S.A., 2020. The effect of cinnamon supplementation on blood pressure in adults: A systematic review and meta-analysis of randomized controlled trials. Clin Nutr ESPEN 36, 10–16.
Han, X., Zhang, H., Hao, H., Li, H., Guo, X., Zhang, D., 2019. Effect Of epigallocatechin-3-gallate on the pharmacokinetics of amlodipine in rats. Xenobiotica 49, 970–974.
Harada, M., Yano, S., 1975. Pharmacological studies on Chinese cinammon. II. Effects of cinnamaldehyde on the cardiovascular and digestive systems. Chem Pharm Bull (Tokyo) 23, 941–947.
Hariri, M., Ghiasvand, R., 2016. Cinnamon and chronic diseases. Adv. Exp. Med. Biol. 929, 1–24.
Höcht, C., Bertera, F.M., Santander Plantamura, Y., Parola, L., Del Mauro, J.S., Polizio, A.H., 2019. Factors influencing hepatic metabolism of antihypertensive drugs: impact on clinical response. Expert Opin. Drug Metab. Toxicol. 15, 1–13.
Jain, S., Sangma, T., Shukla, S.K., Mediratta, P.K., 2015. Effect of Cinnamomum zeylanicum extract on scopolamine-induced cognitive impairment and oxidative stress in rats. Nutr. Neurosci. 18, 210–216.
Jiang, N., Zhang, M., Meng, X., Sun, B., 2020. Effects of curcumin on the pharmacokinetics of amlodipine in rats and its potential mechanism. Pharm. Biol. 58, 465–468.
Kearney, P.M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P.K., He, J., 2005. Global burden of hypertension: analysis of worldwide data. Lancet 365, 217–223.
Leach, M. J., Kumar, S., 2012. Cinnamon for diabetes mellitus. Cochrane Database Syst Rev 2012, CD007170.
Lu, L., Xiong, Y., Zhou, J., Wang, G., Mi, B., Liu, G., 2022. The therapeutic roles of cinnamaldehyde against cardiovascular diseases. Oxid. Med. Cell. Longev. 2022, 9177108.
Mamindla, S., Koganti, V.S.R.G.P., Ravouru, N., Koganti, B., 2017. Effect of Cinnamomum cassia on the pharmacokinetics and pharmacodynamics of pioglitazone. Curr. Clin. Pharmacol. 12, 41–49.
Meredith, P.A., Elliott, H.L., 1992. Clinical pharmacokinetics of amlodipine. Clin. Pharmacokinet. 22, 22–31.
Metchi Donfack, M.F., Atsamo, A.D., Temdie Guemmogne, R.J., Ngouateu Kenfack, O. B., Dongmo, A.B., Dimo, T., 2021. Antihypertensive effects of the Vitex cienkowskii (Verbenaceae) stem-bark extract on L-NAME-induced hypertensive rats. Evid. Based Complement. Alternat. Med. 2021, 6668919.
Mills, K.T., Bundy, J.D., Kelly, T.N., Reed, J.E., Kearney, P.M., Reynolds, K., Chen, J., He, J., 2016. Global disparities of hypertension prevalence and control: A systematic analysis of population-based studies from 90 countries. Circulation 134, 441–450.
Mills, K.T., Stefanescu, A., He, J., 2020. The global epidemiology of hypertension. Nat. Rev. Nephrol. 16, 223–237.
Mousavi, S.M., Karimi, E., Hajishafiee, M., Milajerdi, A., Amini, M.R., Esmaillzadeh, A., 2020. Anti-hypertensive effects of cinnamon supplementation in adults: A systematic review and dose-response Meta-analysis of randomized controlled trials. Crit. Rev. Food Sci. Nutr. 60, 3144–3154.
Murdoch, D., Heel, R.C., 1991. Amlodipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in cardiovascular disease. Drugs 41, 478–505.
Nyadjeu, P., Dongmo, A., Nguelefack, T. B., Kamanyi, A., 2011. Antihypertensive and vasorelaxant effects of Cinnamomum zeylanicum stem bark aqueous extract in rats. J Complement Integr Med 8.
Posadzki, P., Watson, L., Ernst, E., 2013. Herb-drug interactions: an overview of systematic reviews. Br. J. Clin. Pharmacol. 75, 603–618.
Preuss, H.G., Echard, B., Polansky, M.M., Anderson, R., 2006. Whole cinnamon and aqueous extracts ameliorate sucrose-induced blood pressure elevations in spontaneously hypertensive rats. J. Am. Coll. Nutr. 25, 144–150.
Ranasinghe, P., Pigera, S., Premakumara, G.A., Galappaththy, P., Constantine, G.R., Katulanda, P., 2013. Medicinal properties of 'true' cinnamon (Cinnamomum zeylanicum): a systematic review. BMC Complement. Altern. Med. 13, 275.
Sayad-Fathi, S., Zaminy, A., Babaei, P., Yousefbeyk, F., Azizi, N., Nasiri, E., 2020. The methanolic extract of Cinnamomum zeylanicum bark improves formaldehyde-induced neurotoxicity through reduction of phospho-tau (Thr231), inflammation, and apoptosis. EXCLI J. 19, 671–686.
Sen, T., Samanta, S.K., 2015. Medicinal plants, human health and biodiversity: a broad review. Adv. Biochem. Eng. Biotechnol. 147, 59–110.
Sharafeldin, K., Rizvi, M. R., 2015. Effect of traditional plant medicines (Cinnamomum zeylanicum and Syzygium cumini) on oxidative stress and insulin resistance in streptozotocin-induced diabetic rats.
Shen, Y., Jia, L.N., Honma, N., Hosono, T., Ariga, T., Seki, T., 2012. Beneficial effects of cinnamon on the metabolic syndrome, inflammation, and pain, and mechanisms underlying these effects - a review. J. Tradit. Complement. Med. 2, 27–32.
Sung, J.H., Jo, Y.S., Kim, S.J., Ryu, J.S., Kim, M.C., Ko, H.J., Sim, S.S., 2013. Effect of lutein on L-NAME-induced hypertensive rats. Korean J. Physiol. Pharmacol. 17, 339–345.
Tarirai, C., Viljoen, A.M., Hamman, J.H., 2010. Herb-drug pharmacokinetic interactions reviewed. Expert Opin. Drug Metab. Toxicol. 6, 1515–1538.
van Zwieten, P.A., 1994. Amlodipine: an overview of its pharmacodynamic and pharmacokinetic properties. Clin. Cardiol. 17, III3-6.
Wainstein, J., Stern, N., Heller, S., Boaz, M., 2011. Dietary cinnamon supplementation and changes in systolic blood pressure in subjects with type 2 diabetes. J. Med. Food 14, 1505–1510.
Xue, Y.L., Shi, H.X., Murad, F., Bian, K., 2011. Vasodilatory effects of cinnamaldehyde and its mechanism of action in the rat aorta. Vasc. Health Risk Manag. 7, 273–280.
Yanakiev, S., 2020. Effects of cinnamon (Cinnamomum spp.) in dentistry: A review. Molecules 25.
Zhang, Y.P., Zuo, X.C., Huang, Z.J., Cai, J.J., Wen, J., Duan, D.D., Yuan, H., 2014. CYP3A5 polymorphism, amlodipine and hypertension. J. Hum. Hypertens. 28, 145–149.
Zhu, Y., Wang, F., Li, Q., Zhu, M., Du, A., Tang, W., Chen, W., 2014. Amlodipine metabolism in human liver microsomes and roles of CYP3A4/5 in the dihydropyridine dehydrogenation. Drug Metab. Dispos. 42, 245–249.