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The Acute and Chronic Effects of Co-Administration of Turmeric and Black Pepper Extracts in Genetic Hypertension

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Abstract

High blood pressure is the main risk factor for cardiovascular diseases, it affects many people worldwide and is a public health problem. This study explored the acute and chronic actions of a mixture of turmeric (95% curcumin) plus black pepper (95% piperine) extracts, in the blood pressure pattern in spontaneously hypertensive rats (SHR) along they age. For the acute study male adult (4 - 7 months old) SHR and their control Wistar Kyoto rats (WKY) were used. A single oral dose of the mixture of turmeric/black pepper extracts (200 mg/2mg, respectively) suspension was administered. Tail-cuff was used to determine blood pressure during 180 min. For the chronic study, young (1-month-old) male SHR and their control WKY rats were fed with standard chow, or standard chow combined with cocoa, or combined with cocoa plus the mixture of turmeric/black pepper extracts; tail-cuff was used to determine blood pressure once a week, along 12 weeks. In a second chronic assay adult (5 months old) male SHR and their control WKY rats were fed with standard chow, or standard chow combined with cocoa, or combined with cocoa plus the mixture of turmeric/black pepper extracts; tail-cuff was used to determine blood pressure once a week, along 12 weeks. In all three studies, a decrease in systolic, diastolic and mean blood pressure was observed, being higher in SHR and negligible in WKY rats. The mixture of turmeric/black pepper extracts showed antihypertensive actions in SHR rats with no effect on WKY rats. The mixture delayed the onset of hypertension in young SHR rats.

Keywords

Curcuma longa L., *Peper nigrum* L., Hypertension, Polyphenol, SHR

1. Introduction

High blood pressure (HBP) is the most prevalent risk factor for the appearance of cardiovascular (CVD) and other diseases; primary or essential HBP is of unknown origin and affects 90% - 95% of hypertensive persons; while secondary HBP is of known etiology, for example, after kidney disease, diabetes and others, and also from risk factors as high salt intake, smoking, alcohol drinking and so [1]. Approximately 1.28 billion adults aged over 30 years show this condition, and two-thirds of them live in middle- and low-income countries [1]. It has been projected that in 2025 the prevalence of HBP will be 26.9% of adults worldwide [2]; while in Mexico, a middle-income country, data from the Ministry of Health indicates that 25.5% of the population 20 years and older had been diagnosed with HBP. This percentage increased to 26.3% in 70 years and older people [3].

Among the factors involved in the genesis of HBP, oxidative stress (ROS) is found to induce endothelial dysfunction, by reducing the availability of nitric oxide (NO), and increasing the amount of superoxide radical (O_2^-) [4] [5] [6] [7]. Furthermore, there is a decrease in antioxidant enzymes and the higher ROS, which appear to be associated with cardiovascular hypertrophy and hyperplasia [5] [6] [7] [8]. It is widely recognized that the consumption of high- antioxidant food, such as those containing polyphenols plays a beneficial role in health, mainly in the prevention and treatment of chronic degenerative diseases such as cardiovascular, neurodegenerative disorders, respiratory diseases, and even cancer [9] [10] [11] [12].

The curcumin (diferuloylmethane) is a polyphenolic compound found in the root of turmeric (*Curcuma longa* L). This compound is associated with different biological effects including anti-inflammatory, hepatoprotective, and antioxidant properties, cancer prevention, depression reduction, and stress prevention, among others [11] [12] [13] [14] [15]. Preclinical studies have shown that curcumin can improve the cardiovascular system, and upgrade the left ventricle functioning in rabbits, inhibition of atherosclerosis development in mice, and facilitates the relaxation of pig coronary artery [15]-[20]. These cardiovascular protective actions of the curcumin suggest the involvement of several pathways, such as endothelial NO production, and guanylyl cyclase-cGMP, and muscular β-adrenoceptors as well as sodium channel blockade [17] [18] [19] [20]. This evidence shows that curcumin is a pleiotropic agent, impacting various targets involved in the genesis and maintenance of HBP [4] [5] [6] [7]. In addition to its pharmacodynamic actions, it is also known that curcumin, due to its low absorption, is rapidly metabolized resulting in a discrete bioavailability [21] [22] [23]. However, its bioavailability can be enhanced when curcumin is combined

with other compounds, such as phospholipids or alkaloids like piperine, which is found in black pepper (*Piper nigrum*) [22] [24] [25] [26].

Piperine is a pleiotropic agent responsible for the itching of black pepper, and possesses various pharmacological effects. Although research on black pepper and its biological effects is scarce, studies have shown that intravenous administration of piperine in rats enhances the adrenal glands' activity and ROS production; while low doses can decrease blood pressure and exhibit antioxidant effects [24] [25] [26] [27]. Hlavačková *et al.* found that oral administration of piperine significantly decreased blood pressure in rats with L-NAME-induced hypertension, starting from the third week of daily piperine administration [24] [25]. One of the effects of piperine is its ability to enhance the bioavailability of other substances, *i.e.*, the bioavailability of curcumin is improved when it was co-administered with piperine [22] [26]. Even though the actions of curcumin and piperine, both individually and in combination, had been reported their beneficial impact on hypertension remains a matter of controversy. Therefore, we aimed to explore both the acute effect of a single oral dose of the turmeric and black pepper extracts mixture, and the chronic effect of the mixture when combined with food.

2. Materials and Methods

2.1. Animals and Ethical Statement

The Spontaneously Hypertensive Rats (SHR) and their Wistar Kyoto (WKY) controls were obtained from the breeding colony of the Institute of Cell Physiology (UNAM). The rats were housed in three per cage and maintained in a pathogen-free environment under controlled conditions (22˚C ± 2˚C, 40% - 60% humidity, 12-h/12-h light/dark cycle), with food and water *ad libitum*. All the experimental procedures followed the National Institutes of Health guide for the care and use of laboratory animals (8th edition, 2011), and the care of the animals was in accordance with the Official Mexican Norm for the use and care of experimental animals (NOM-062-ZOO-1999, SAGARPA, Mexico); the protocol was approved by the Institutional Ethics Committee (Protocol number 1368, FESI, UNAM).

2.2. Materials

The standardized extracts of turmeric and pepper were purchased from a supplier (AMFHER Foods, Mexico City), both extracts with purity report of 95%. Cocoa was purchased from a local source. The equipment to measure the arterial blood pressure was a tail-cuff non-invasive system (Automatic Blood Pressure Computer, Model LE 5007, Letica, Panlab, Spain).

2.3. Procedures

Treatment and measurement

Acute effect

Two groups of adult rats each were formed (20 to 39 weeks of age, n = 3), one group of SHR and the other one of WKY rats. Rats were trained for 1 week inside a plastic restrainer at 37˚C; then, the blood pressure (BP) in the tail was measured using plethysmography (LE 5007 Panlab), before and after oral administration of the test dose (200 mg of turmeric/2 mg black pepper mixture). An average of three readings for each rat was used to obtain BP, as described [28]; in each series, BP measurements were taken at times 0, 45, 60, 75, 90, 105, 120, 150 and 180 minutes. For drug administration, we prepared a suspension of the 200 mg turmeric/2 mg black pepper mixture in 1 mL of oleo-aqueous suspension. Throughout the test period, the animals had free access to standard chow and water.

Chronic effect

Five weeks old rats were randomly separated, and eight groups were formed (n = 3 rats each). These included four groups of SHR rats and four groups of WKY rats, as detailed in Table 1. The rats were treated with turmeric/black pepper mixture for a period of 12 weeks, and the BP was measured weekly and subsequently euthanized. Rats in groups 1 and 4 were kept alive and used as control groups for groups 7 and 8, then measured for a further 12 weeks (reaching adulthood, similar to those in the acute assay), prior to being euthanized.

For food preparation, we used powdered standard rat food (Purina chow™, Mexico), cocoa powder, and the mixture of 200 mg turmeric/2 mg black pepper extracts for every 30 g of the prepared food pellets.

2.4. Statistical Analysis

Data are presented as the mean ± standard error of the mean (SEM) of three rats per group. Differences between baseline and final systolic, diastolic, and mean arterial blood pressure in each group were evaluated with Wilcoxon matched-pairs, the differences in percentage change between groups with two-way ANOVA,

Table 1. Rat groups.

Group	Rat	Age (weeks)	food
1	SHR	5	Standard chow
2	SHR	5	Standard chow + cocoa
3	SHR	5	Standard Chow + cocoa +Turmeric/Black paper mixture
4	SHR	5	Standard chow
5	WKY	5	Standard chow + cocoa
6	WKY	5	Standard Chow + cocoa +Turmeric/Black paper mixture
7	WKY	20	Standard Chow + cocoa +Turmeric/Black paper mixture
8	WKY	20	Standard Chow + cocoa +Turmeric/Black paper mixture

Rat groups per age were subjected to a diet added with cocoa or cocoa plus turmeric/black pepper extracts (200 mg/2mg, respectively) per ounce of solid food.

and also linear regression was performed. All analyses were considered two-tailed, with a p-value < 0.05 considered statistically significant. And data were analyzed using GraphPad Prism Software, ver.7.0 (GraphPad Software, Inc., San Diego, CA, USA).

3. Results

3.1. Acute Study

The three measures of blood pressure systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MBP) data were collected for both test groups, and plotted (**Figure 1**). A significant variation in the blood pressure between the test groups was observed (*p = 0.008); subsequently, the % change in BP was calculated per group and plotted. Upon performing linear regression, a significant difference between the lines of both groups was observed (*p = 0.005). An antihypertensive effect of ~20% change was observed at the longest time evaluated in the SHR; however, the percent change was not significant in the WKY rats throughout the assay (**Figure 1**). When compared using a Wilcoxon *t*-test for paired data, the probability observed was statistically significant for the three parameters (*p = 0.008).

The two-way ANOVA test was used to compare baseline (T0) and final (T180) values of the treatment effect. The results were statistically significant for the SHR group (*p = 0.005), but not significant for the WKY group (p = 0.087). The baseline of SHR at T0 with CI95% confidence interval (CI) yielded values between 154 - 172 mm Hg, and at T180 the 95% CI values were 125 - 153 mm Hg. For the WKY rats, the values at T0 with 95% CI were between 104 - 122 mm Hg, and at T180 the 95% CI ranged from 98 - 116 mm Hg.

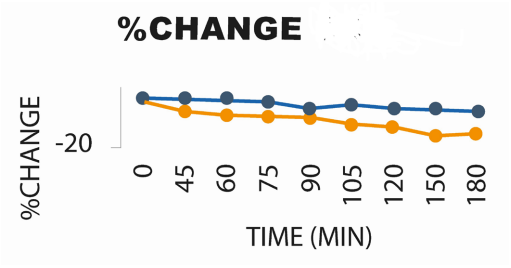
3.2. Chronic Study 1

The data of SBP, DBP, and MBP were collected for each test group, the average per group per week of treatment was obtained. These data were then plotted and analyzed using the Wilcoxon test for paired samples. SHR rats in groups 1, 2, and 3 received standard chow, standard chow with cocoa, and standard chow with cocoa plus turmeric/black pepper extracts, respectively (it should be mentioned that cocoa was used as a flavor modifier). BP was measured for 12 weeks starting at 5 weeks of age, when the SHR rats are not yet hypertensive (SBP < 130 mm Hg). We observed a difference in the SBP pattern among all groups, *i.e.*, the control SHR group 1 exhibited a sudden increase in SBP at the 6th week of age (1st week of assay/treatment); however, in groups 2 and 3 this increase was delayed by 1 and 2 weeks, respectively (**Figure 2**). Furthermore, the rise in SBP was less pronounced over time, with group 3 recording lower SBP values than groups 1 and 2 (**Figure 2(a)**). Wilcoxon tests showed a significant difference between group 1 *vs.* 3 (*p = 0.001), and between group 2 *vs.* 3 (*p = 0.001), but not between group 1 *vs.* 2 (p = 0.093).

In addition, the pattern observed for DBP also showed a delay in the onset of hypertension in groups 2 and 3, as well as a statistical difference in the Wilcoxon

tests (*p < 0.05); whereas the MBP did not show significant differences (Figure 2(b), Figure 2(c)).

The WKY rats in groups 4, 5, and 6 were fed with standard chow, chow with cocoa, and chow with cocoa plus turmeric/black pepper mixture, respectively. We measured BP throughout 12 weeks starting at 5 weeks of age (Figure 3); there were no observed differences in SBP pattern between the control group 4 *vs.* group 5, nor between group 4 *vs.* group 6. However, a significant difference was detected between the groups 5 *vs.* 6 (*p = 0.029), using the Wilcoxon test (Figure 3(a)).



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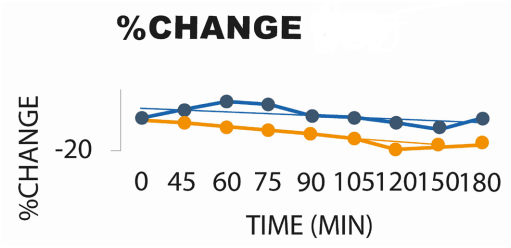

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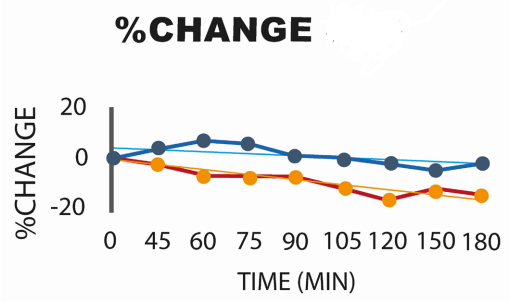
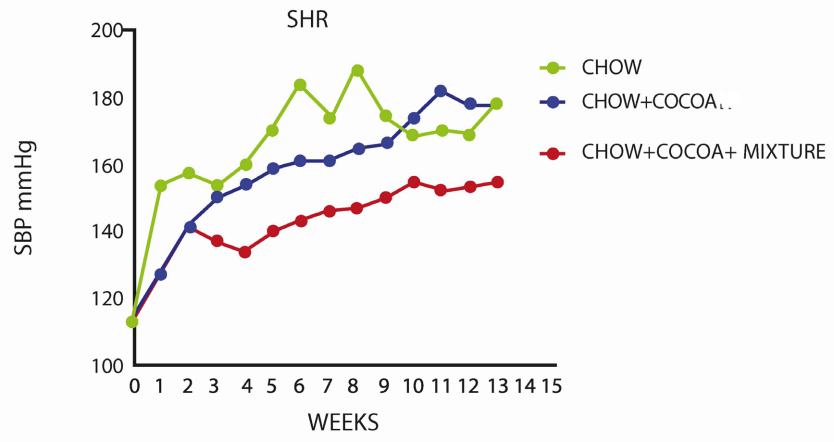


(c)

Figure 1. Time-course of blood pressure after administration of turmeric/black pepper mixture, acute assay. (a) % Change in Systolic Blood Pressure: SHR red (linear regression, y = −1.7132x − 0.393, R^2 = 0.921), WKY blue (linear regression, y = −0.7647x + 1.4216, R^2 = 0.907) *p = 0.008; (b) % Change in Diastolic Blood Pressure: SHR red (linear regression, y = −2.25x + 1.3611, R^2 = 0.856), WKY blue (linear regression, y = −1.1833x + 8.1389, R^2 = 0.354) *p = 0.008; (c) % Change in Mean Blood Pressure SHR Red (linear regression, y = −1.8667x, R^2 = 0.857), WKY blue (linear regression, y = −1.1x + 5.7222, R^2 = 0.552) *p = 0.008. T0 values of SHR red CI95% 154 - 172 mm Hg and T180 values 125 - 153 mm Hg, two-way ANOVA T0 *vs.* T180 values SHR red group *p = 0.005. T0 values of WKY blue CI95% 104 - 122 mm Hg and T180 values 98 - 116 mm Hg, two-way ANOVA T0 *vs.* T180 values WKT blue group *p = 0.087. *p between groups.



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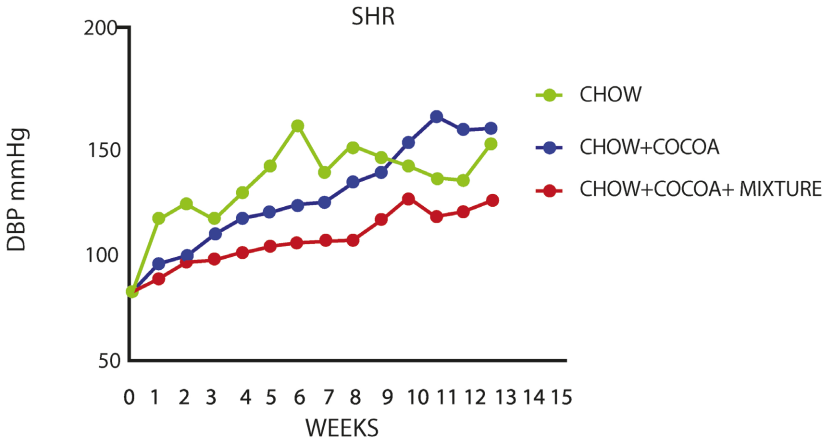

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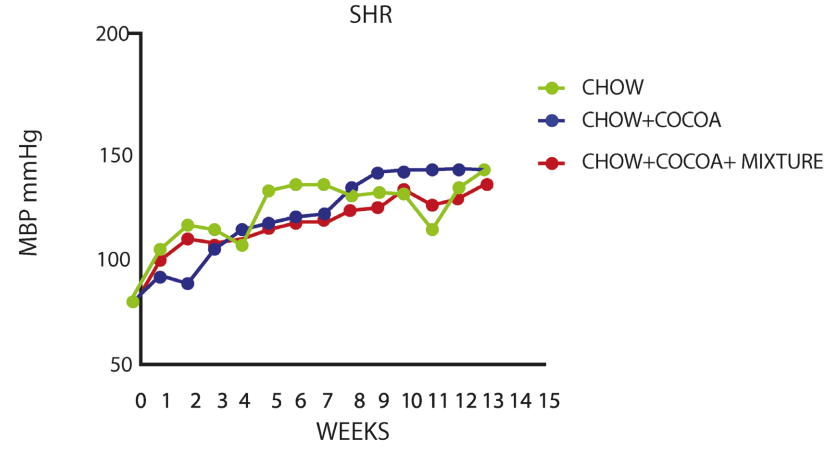
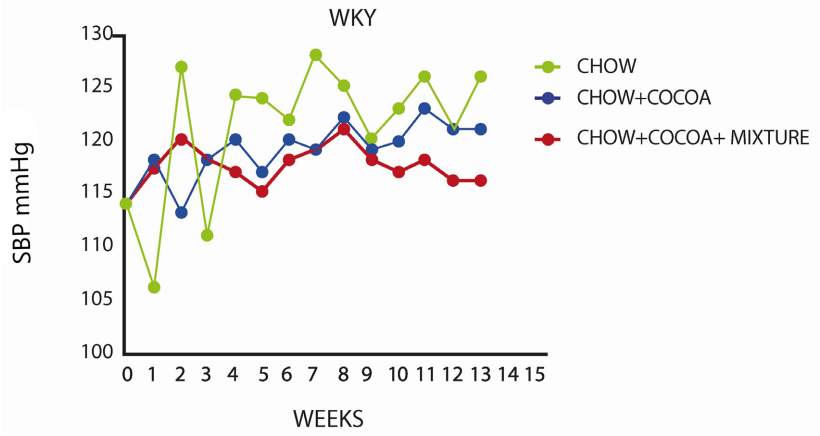


(c)

Figure 2. Time-course of blood pressure in SHR groups of rats fed with standard chow (green), standard chow + cocoa (blue), and standard chow + cocoa + turmeric/black pepper mixture (red). (a) SBP of groups 1 *vs.* 3 *p = 0.001, 2 *vs.* 3 *p = 0.001, 1 *vs.* 2 p = 0.0928. Two-way ANOVA between three groups *p < 0.001; (b) DBP of groups 1 *vs.* 3 *p = 0.001, 2 *vs.* 3 *p = 0.001, 1 *vs.* 2 p = 0.398. Two-way ANOVA between three groups *p < 0.001; (c) MBP of groups 1 *vs.* 3 p = 0.113, 2 *vs.* 3 p = 0.080, 1 *vs.* 2 p = 0.888. Two-way ANOVA between three groups *p > 0.05. *p between groups.



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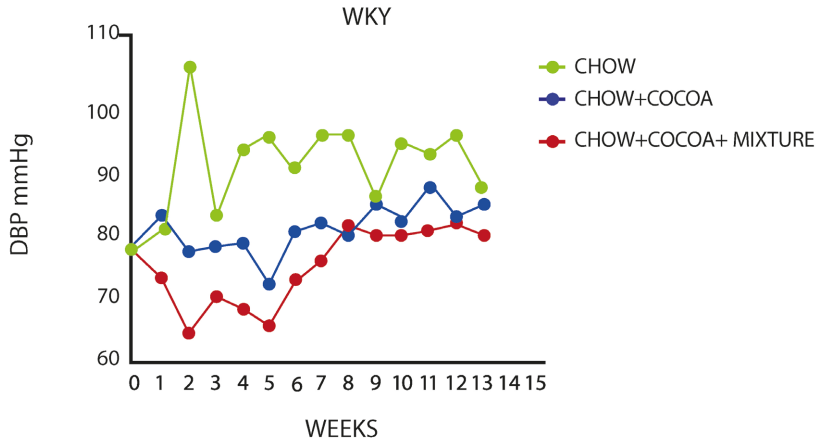

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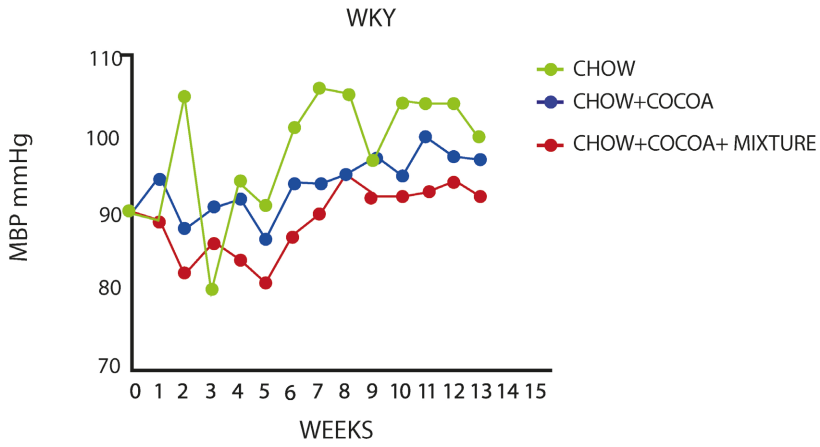


(c)

Figure 3. Time-course of blood pressure in WKY groups of rats fed with standard chow (4, green), standard chow + cocoa (5, blue), and standard chow + turmeric/black pepper mixture (6, red). (a) SBP of groups 5 *vs.* 6 *p = 0.029, 4 *vs.* 6 p = 0.260, 4 *vs.* 5 p = 0.385. Two-way ANOVA between three groups p = 0.527; (b) DBP of WKY groups 4 *vs.* 5 *p = 0.0161, 4 *vs.* 6 *p = 0.004, 5 *vs.* 6 *p = 0.001. Two-way ANOVA between three groups *p = 0.001; (c) MBP of WKY 4 *vs.* 6 *p = 0.026, 5 *vs.* 6 *p = 0.001, 4 *vs.* 5 p = 0.236. Two-way ANOVA between three groups *p = 0.012. *p between groups.

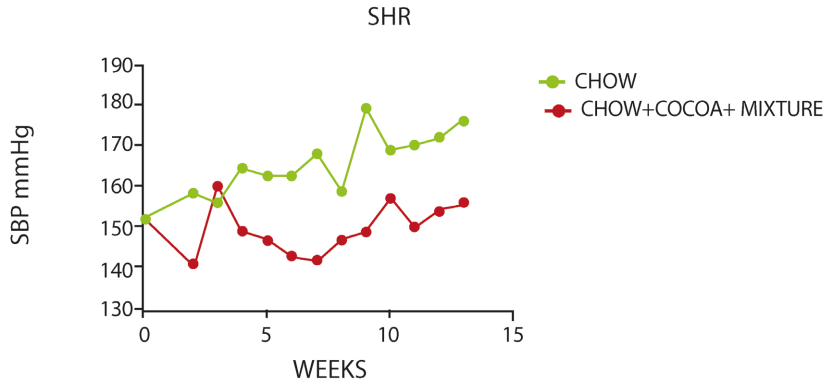
In relation to DBP the Wilcoxon tests revealed differences between all groups (*p < 0.05, Figure 3(b)). As for MBP, the Wilcoxon test showed significant differences between group 4 *vs.* group 6 (* p = 0.026), as well as between group 5 *vs.* group 6 (0.001), but nor between group 4 *vs.* 5 (p = 0.236) (Figure 3(c)).

3.3. Chronic Study 2

The SHR and WKY rats from groups 1 and 4 served as the controls for groups 7 (SHR) and 8 (WKY). These groups were continuously measured as older rats from 20 weeks of age over a period of 12 weeks. For this experiment, groups fed with standard chow + cocoa were omitted. Figures 4(a)-(c) show the recorded values of SBP, DBP and MBP of groups 1 and 7, both SHR rats. Upon analyzes using a Wilcoxon test for paired data, all values were statistically significant (*p < 0.05).

In contrast, the WKY rats (groups 4 and 8) demonstrated no significant difference in SBP and DBP, as displayed in Figure 5(a) and Figure 5(b), respectively. However, Figure 5(c) shows a statistically significant difference (*p = 0.003) in MBP between the same groups.

For a summarized view of data from two chronic assays, the area under the curve (AUC) is shown in Table 2. As observed, the turmeric/black pepper mixture reduced the AUC in SHR but not in WKY rats.



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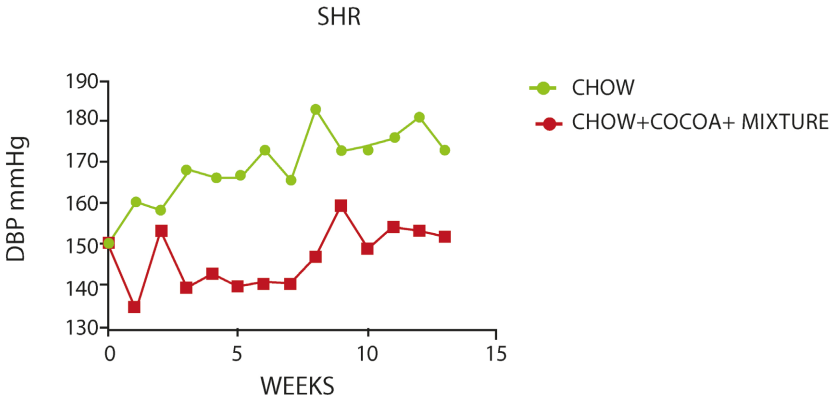

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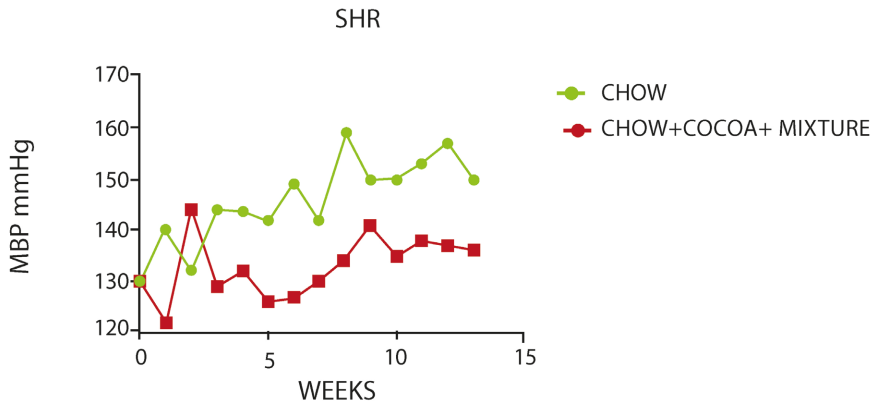
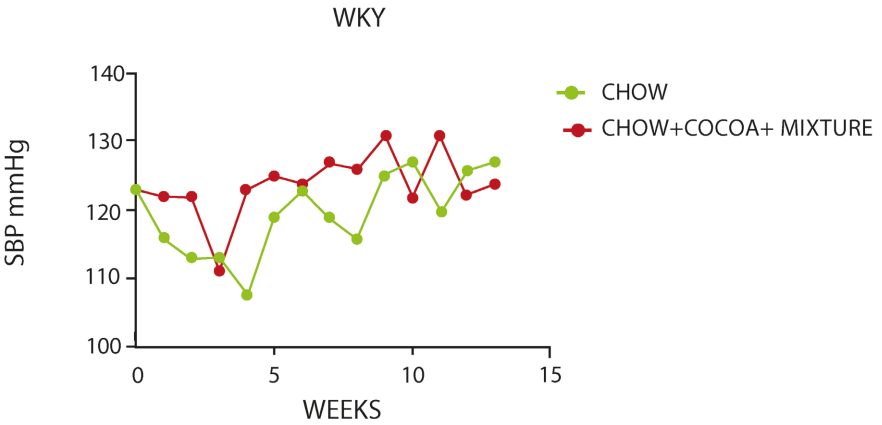


(c)

Figure 4. Time-course of blood pressure in SHR groups of rats fed with standard chow (1, green), and standard chow+ cocoa + turmeric/black pepper mixture (7, red). (a) SBP of SHR groups 1 *vs.* 7 *p = 0.004. Two-way ANOVA between two groups *p = 0.001; (b) DBP of SHR groups 1 *vs.* 7 *p = 0.001. Two-way ANOVA between two groups *p < 0.001; (c) MBP of SHR groups 1 *vs.* 7 *p = 0.002. Two-way ANOVA between two groups *p = 0.001. *p between groups.



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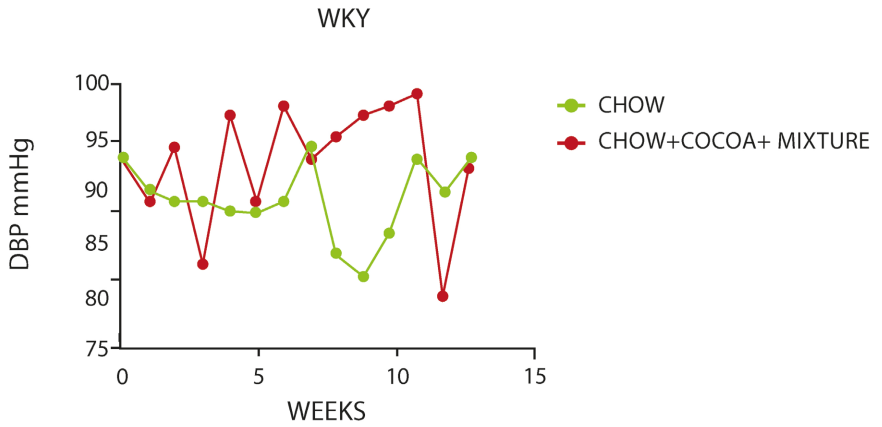

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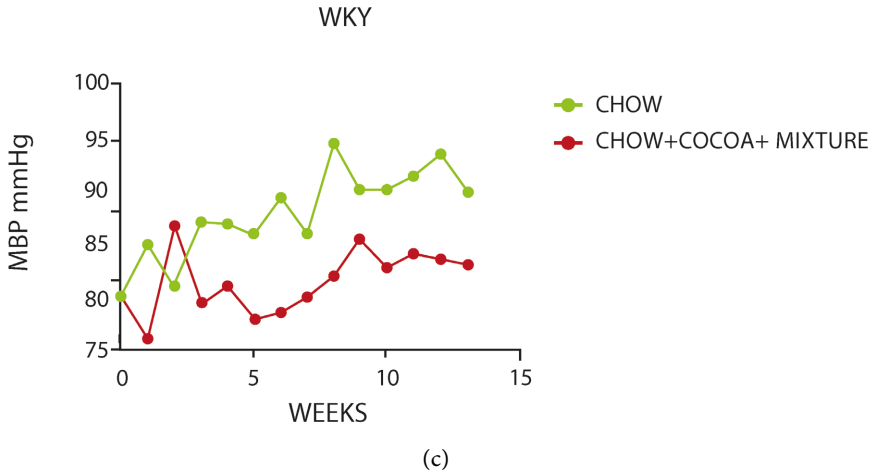

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Figure 5. Time-course of blood pressure in WKY groups of rats with standard chow (1, green), and standard chow + cocoa + turmeric/black pepper mixture (8, red). (a) SBP of WKY groups 4 *vs.* 8 p = 0.067. Two-way ANOVA between two groups p = 0.069; (b) DBP of WKY groups 4 *vs.* 8 p = 0.235. Two-way ANOVA between two groups p = 0.170; (c) MBP of WKY groups 4 *vs.* 8 *p = 0.003. Two-way ANOVA between two groups *p = 0.003. *p is between groups.

Table 2. Area under the curve (AUC) for cronic assays.

Group	Description	Age (weeks)	AUC (SBP)	AUC (DBP)	AUC (MBP)
1	SHR Standard chow	5 - 17	2166	1745	1609
2	SHR Standard chow + cocoa	5 - 17	2069	1664	1598
3	SHR Standard Chow + cocoa +Turmeric/Black paper mixture	5 - 17	1856	1393	1546
4	WKY Standard chow	5 - 17	1569	1190	1267
5	WKY Standard chow + cocoa	5 - 17	1554	1059	1224
6	WKY Standard Chow + cocoa +Turmeric/Black paper mixture	5 - 17	1531	973	1157
1	SHR Standard chow	20 - 33	2153	1800	1899
4	WKY Standard chow	20 - 33	1552	1157	1210
7	SHR Standard Chow + cocoa +Turmeric/Black paper mixture	20 - 33	1954	1521	1731
8	WKY Standard Chow + cocoa +Turmeric/Black paper mixture	20 - 33	1608	1203	1329

Area under the curve (AUC) for the 2 assays: chronic starting at 5 weeks of age (groups 1 - 6), and chronic starting at 20 weeks of age (groups 1, 4, 7, 8).

4. Discussion

The results of this study indicate a reduction in the blood pressure of SHR rats, without significant change in WKY rats, when treated with the turmeric/black pepper mixture (200 mg/2mg, respectively). The antihypertensive effect was observed during the acute phase of the study. Given the pleiotropic actions of both

major constituents of the turmeric/black pepper mixture, namely curcumin and piperine, a combination of influences could contribute to reducing blood pressure. These influences include antioxidant, anti-dyslipidemic, anti-inflammatory, Na^+ channel blocking, interference with renin-angiotensin system, and interaction with β_2-adrenoceptors [4] [8] [16] [17] [18] [19] [20]. The potential actions of minor components in the mixture, such as flavonoids and curcuminoids, among others [12] [15], might also be a contributing factor. Furthermore, piperine has been shown to enhance the bioavailability of curcumin since piperine inhibits curcumin glucuronidation in the gut and the liver [22] [26]. Moreover, in the acute study, we observed that the blood pressure reduction persisted until the final measurement, which was taken 3 h after administering the mixture.

According to the study conducted by Shoba *et al.*, curcumin concentrations started to decline between 2 and 3 hours after administration [26]. Conversely, Suresh and Srinivasan reported in their study with albino rats that curcumin values were still high at 24 h post-co-administration with piperine. These values began to decrease after this point, but were still detectable on the eighth day after administration, which could explain the sustained effect observed in our chronic study [22].

In our chronic study spanning 12 weeks and commencing at the age of 5 weeks, we observed a reduction in SBP, DBP, and MBP in SHR rats. Hlavačková *et al.* reported similar findings, but their measurements were limited to SBP over a 5-week period, in a model of hypertension induced by nitric oxide synthase inhibition, *i.e.*, the absence of nitric oxide as a vasorelaxant agent, in young adult Wistar rats (12 weeks of age) [24] [25]. In contrast, our study had a longer time course and used a model of genetic hypertension, similar to human primary hypertension, initiated in pre-hypertensive stage of the SHR. The study demonstrated the blood pressure-lowering effect of the turmeric/black pepper mixture from the start of the assay.

Another discovery from this study is the blood pressure-reducing action of the turmeric/black pepper mixture in older rats, a finding that could be comparable to what has been reported for elderly humans [8]. The mixture began its effect shortly after the SHR consumed the food. These results underscore the beneficial effects of the turmeric/black pepper mixture, as well as its safety, even in advanced ages [4] [8].

Any hypotensive effect observed in age-matched WKY rats, could be attributed to the antioxidant and anti-inflammatory properties that had been previously demonstrated for turmeric [9] [11] [12] [13] [14]. It is possible that the delay in the onset of hypertension observed in the SHR groups, treated during the chronic study, is related to the mild hypotensive effect seen in the WKY rats.

5. Conclusion

The turmeric/black pepper mixture exhibited a biological capacity to lower blood pressure in SHR rats, with a negligible effect on their WKY control coun-

terparts. The antihypertensive effect was maintained over time, and the mixture also delayed the onset of hypertension in young SHR rats.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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