The effect of resveratrol on hypertension: A clinical trial

MARIOS THEODOTOU[1], KONSTANTINOS FOKIANOS[2], ALEXIA MOUZOURIDOU[3], CORNELIA KONSTANTINOU[1], ANDREA ARISTOTELOUS[1], DAFNI PRODROMOU[3] and ASIMINA CHRYSIKOU[1]

[1]Riegler, Ltd., Institute of Medical Clinical Trials, Limassol 3020; [2]Department of Mathematics and Statistics, University of Cyprus, Nicosia 20537; [3]Agios Efrem, Advanced Medical Diagnostic Center, Limassol 3020, Cyprus

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Abstract. The aim of this clinical trial was to investigate the effects of Evelor, a micronized formulation of resveratrol (RESV; 3,5,4'-trihydroxy-trans-stilbene), in patients with primary hypertension. RESV is a stilbenoid and phytoalexin produced by several plants in response to injury or attack by pathogens, such as bacteria and fungi. Patients included in the clinical trial were split into the following two groups, based on the severity of their disease: Group A (n=46), stage I hypertension [systolic blood pressure (SBP), 140-159 mmHg; diastolic blood pressure (DBP), 90-99 mmHg] and Group B (n=51), stage II hypertension (SBP, 160-179 mmHg; DBP, 100-109 mmHg). Each group was divided into two subgroups: A1 and B1, patients treated with standard antihypertensive therapy (A1, 10 mg Dapril; B1, 20 mg Dapril), and A2 and B2, patients treated with antihypertensive therapy (Dapril) plus Evelor. The present study aimed to determine the effects of Evelor, in addition to the standard hypertension treatment, and its effect on the hepatic enzymes serum glutamate-pyruvate transaminase (SGPT) and gamma-glutamyl transferase (gamma-GT). Following the trial, which lasted two years (October 2010 to October 2012), the mean blood pressure of both groups lay within the normal range, indicating that blood pressure was efficiently controlled. The results of the present study demonstrate that the addition of RESV to standard anti-hypertensive therapy is sufficient to reduce blood pressure to normal levels, without the need for additional antihypertensive drugs. In addition, statistical analysis of the results identified a significant reduction in plasma concentration levels of SGPT ($P<0.001$) and gamma-GT ($P<0.001$) with the addition of RESV, indicating that RESV prevents liver damage.

Correspondence to: Dr Marios Theodotou, Riegler, Ltd., Institute of Medical Clinical Trials, 181 Leontiou A, Limassol 3020, Cyprus
E-mail: info@mariostheodotou.com

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Introduction

Hypertension is defined as abnormally high systolic and diastolic arterial pressure, which remains consistently elevated throughout the day. If hypertension remains untreated it can lead to a number of health problems, including coronary heart disease, stroke, nephropathy, retinopathy and other ophthalmic diseases (1). The majority (90%) of cases of hypertension are characterized as idiopathic, for which the exact cause remains unclear. However, hypertension is associated with an unhealthy lifestyle, including smoking, a diet high in unsaturated fatty acids and salt, a lack of exercise and obesity. In addition, some cases are related to genetic factors (2-5). In the remaining 10% of cases, hypertension results from another chronic condition, such as kidney failure (6).

Hypertension is typically treated using antihypertensive drugs. There are various classes of these drugs, which act via different mechanisms to produce the same end-result. This mechanism is vasodilatation, which is essential to lower blood pressure (BP). In the current study, Dapril was used. The active ingredient in Dapril is lisinopril, an angiotensin-converting-enzyme (ACE) inhibitor, which prevents vasoconstriction by inhibiting angiotensin I.

Resveratrol (RESV; 3,5,4'-trihydroxy-trans-stilbene), the active ingredient of Evelor, is a naturally occurring flavonoid phytoalexin, which has antioxidant properties and is useful in the treatment of numerous diseases because of its cardioprotective, antidiabetic and neuroprotective effects. In addition, previous studies have shown that RESV has vasoprotective properties (7,8). The therapeutic benefits of moderate red wine consumption have been linked by numerous studies with RESV, which is found in red grapes, and in plants that can survive harsh environmental conditions (9-11). RESV is categorized as a food supplement by EFSA and so can be taken without a doctor's prescription or recommendation (12).

RESV is thought to be useful in the control of blood pressure when added to a standard antihypertensive therapy by increasing the production of nitric oxide (NO), an endogenous and potent vasodilator. NO is produced in the endothelium lining blood vessels, where it facilitates vasodilation through activating the enzyme guanylate cyclase (GC) (13,14). GC then initiates a signaling cascade, which results in relaxation of the smooth muscle layer and vasodilatation. Vasodilation decreases peripheral resistance, which directly affects arterial pressure and lowers BP.

The aim of this clinical trial was to demonstrate that the addition of RESV to standard antihypertensive therapy reduces blood pressure to normal levels. A secondary aim was to demonstrate that there is no need for additional antihypertensive drugs.

Materials and methods

Study participants and overview. The present study was approved by the Cyprus National Bioethics Commitee, Nicosia, Cyprus (file no. ΕΕΒΚ/ΕΠ/2010/12; date 14/07/2010). Informed consent was obtained in writing from all the patients prior to entering the study. A number of parameters were used as criteria to select the study participants (Table I). Patients were selected following the first diagnosis of hypertension. A total of 97 patients were included in the present study, which lasted two years (October 2010-October 2012). Based on the severity of hypertension measured by initial tests (electrocardiogram, thoracic x-ray, blood tests and 24 h blood pressure measurements), participants were divided into one of two groups; group A (n=46) and group B (n=51). Within group A, 25 of the patients (54.5%) were male and 21 (45.6%) were female. Within group B, 32 (62.7%) were male and 19 (37.2%) were female. Then, the patients in these groups were evenly divided in a random manner into two further subgroups; one that would receive standard treatment (Dapril) alone and one that would receive standard treatment plus Evelor.

Patients with one or more of the following features were excluded: i) Malignant tumor or any other diseases which significantly decreases lifespan; ii) surgery in the last 3 months; ii) psychiatric disorders; iii) symptoms of heart failure or acute coronary syndrome; iv) hormone medication, such as corticosteroids or estrogens; v) abuse of alcohol, tobacco or caffeine; and vi) participation in similar studies currently or within the last 6 months. In addition, participants were not allowed to consume any food supplements for 2 weeks prior to commencing treatment or during the 6 month observation period.

Study treatment. Participants underwent a clinical examination (at times 1-4), electrocardiogram (time 1), thoracic X-ray (time 1) and 24 h BP monitoring (times 1 and 4). Time 1 is at the beginning of the trial, time 2 is at the end of the second month, time 3 is at the end of the forth month and time 4 is at the end of the sixth month. In addition, blood tests were performed measuring the following parameters: Hemoglobin (Hb), white blood cells (WBC), platelets (PLT), erythrocyte sedimentation rate (ESR), glucose (Glu), urea (Ur), creatinine (Cr), electrolytes, such as sodium (Na), potassium (K), calcium (Ca) and phosphorus (P), total cholesterol levels (Chol), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, liver enzymes serum glutamic pyruvic transaminase (SGPT) and gamma-glutamyl transpeptidase (gamma-GT), thyroid stimulating hormone (TSH), free thyroxine (fT4) and mid-stream urine (MSU) (times 1 and 4).

Based on the severity of hypertension measured by these initial tests, participants were divided into two groups: Group A, for those with stage I hypertension [systolic blood pressure (SBP), 140-159 mmHg; diastolic blood pressure (DBP), 90-99 mmHg] who would received lower doses of antihypertensive therapy and group B, for those with stage II hypertension (SBP, 160-179 mmHg; DBP, 100-109 mmHg) who received higher doses of antihypertensive therapy. Then, the patients in these groups were evenly divided in a random manner into two further subgroups; one that would receive standard treatment (Dapril) alone, and one that would receive standard treatment plus Evelor. Thus, groupings were as follows: Group A_1, treated with 10 mg Dapril; group A_2, treated with 10 mg Dapril plus 50 mg Evelor; group B_1, treated with 20 mg Dapril; and group B_2, treated with 20 mg Dapril plus 50 mg Evelor. All patients took the appropriate doses once a day for six months. During this period, the effects of treatment were measured. In months 2 and 4 of treatment patients underwent a clinical examination. In months 1 and 6 of treatment patients underwent a clinical examination, blood tests and a 24 h measurement of BP.

The results obtained in the present study were used to examine the following parameters: i) The time at which a response was observed; ii) duration of the response; and iii) the count of liver enzymes SGPT and gamma-GT.

Statistical analysis. The results and their interpretation were reviewed using statistical methods and hypothesis testing. The following processes were used to review the results. SBP and DBP were compared for each group separately, at the beginning and end of the study, using an ordinary *t*-test, a paired sample *t*-test and a Mann-Whitney U test. The effect of Evelor and time was investigated by using two-way analysis of variance. The factors were time with two levels (beginning and end of study), treatment (without/with Evelor) and their interaction. The comparisons were made by treatment. SGPT and gamma-GT enzymes, as percentages, were compared for each group separately, at the beginning and end of the study using a *t*-test. All results were obtained by using the statistical programming language R (https://www.R-project.org/).

Results

Clinical and demographic characteristics of patients. The clinical and demographic characteristics of patients are shown in Table II. Tables III and IV present a summary of these characteristics within each group separately.

Prior to treatment, at time 1, the DBP and SBP of patients were measured for 24 h. SBP ranged between 142.7 and 178.6 mmHg (median, 160.8 mmHg). Prior to treatment the female participants had slightly higher SBP values than the males. About 85% of the males tested had SBP between 143 and 155 mmHg, while 83% of the females tested had SBP between 145 and 157 mmHg. DBP measurements ranged between 91.7 and 108.9 mmHg (median, 100.3 mmHg). About 82% of the males participants had DBP ranging between 95 and 100 mmHg, while 80% of the female patients had measurements ranging between 85 and 90 mmHg.

Mean values of SBP and DBP at the beginning and end of the study. At time 4, the end of the study, SBP and DBP were measured during a 24 h period. Table V shows the mean measurements of SBP and DBP, along with the P-values obtained from carrying out three statistical tests (ordinary *t*-test, paired *t*-test and Mann Whitney U test). All tests point to that SBP and DBP decreased between time 1 (the beginning

Table I. Inclusive criteria for participants.

Criteria	Men	Women
Age, years	40-70	50-70
Weight, kg	70-90	60-80
Height (cm)	160-190	150-180
BMI, kg/m^2	20-30	20-30
SBP, mmHg	>140	>140
DBP, mmHg	>90	>90
HR, bpm	60-90	60-90

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Table II. Clinical and demographic characteristics of study participants in groups A and B.

Characteristic	Mean ± SD
Age, years	50.87±10.60
Weight, kg	81.34±9.94
Height, cm	169.5±7.91
BMI, kg/m^2	23.89±2.55
Hb, g/dl	13.62±1.74
Glucose, mg/dl	99.32±21.77
Total cholesterol, mg/dl	210.8±37.05
HDL, mg/dl	47.76±12.25
LDL, mg/dl	133.9±33.12
SGPT, U/l	34.31±17.42
gamma-GT, U/l	31.44±23.01
SBP, mmHg	160.8±18.1
DBP, mmHg	100.3±8.6

SD, standard deviation; BMI, body mass index; Hb, hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SGPT, serum glutamic pyruvic transaminase; gamma-GT, gamma-glutamyl transpeptidase; SBP, systolic blood pressure; DBP, diastolic blood pressure.

of the study) and time 4 (the end of the study). P<0.001 was considered to indicate a statistically significant difference.

Tables VI and VII present comparisons of SBP and DBP, along with the P-values for each comparison; the values are compared for each group separately.

Prior to treatment, group A had a lower average DBP and SBP compared with Group B (Tables VI and VII). However, following treatment the average DBP and SBP values for both groups lay within the normal range (normal range: SBP, ≤120-139 mmHg; DBP, ≤80-89 mmHg) (Tables VI and VII), indicating that the blood pressure was efficiently controlled. This decrease in DBP and SBP was statistically significant in both groups (all P<0.001).

Effect of Evelor and time to different variables. The effect of Evelor and time was investigated. All variables (SBP, DBP, Hb, Glu, Chol, HDL, LDL, SGPT and gamma-GT) were compared with time and treatment (Tables VIII-XVI). Time refers to a factor with two levels (beginning and end of study) and treatment refers to a factor with two levels (control and Evelor). The comparison is made between A1 vs. A2 (group A), B1 vs. B2 (group B) and A1 + B1 vs. A2 + B2. The following tables used the P-value to determine whether there was a statistically significant reduction in the measurement made at the end and the beginning of the study for participants who had, and hadn't, been treated with Evelor. The statistical methodology used was a two-way analysis of the variance test and the important variable is the interaction between time and Evelor.

The above tables determine that there was a statistically significant reduction in the measurement of SBP and DBP made at the end and the beginning of the study for participants who had, and hadn't, been treated with Evelor.

Effect of Evelor to SGPT and gamma-GT. In addition, the present study aimed to test whether Evelor affects the level of the liver enzymes SGPT and gamma-GT. Tables XVII and XVIII show the P-values comparing the levels of the enzyme at the beginning and at the end of the study in groups treated, and not treated, with Evelor.

There was a significant decrease in SGPT and gamma-GT observed in patients treated with Evelor (P<0.001; Tables XVII and XVIII).

Discussion

Previous studies demonstrate that the global burden of hypertension is an important and increasing health problem (15,16). The World Health Organization estimates that hypertension affects ≥25% of adults worldwide (17). It is predicted that in ≤20 years the percentage of the adult population with hypertension will increase by 60% (15). In developed countries, adequate BP control (<140/90 mmHg) among patients receiving antihypertensive treatment ranges between 30 and 50% while between 20 and 30% of patients are resistant to BP control (18,19).

The discrete etiology of hypertension is still not understood (20). However, it is understood to be a complex trait resulting from interactions between multiple genetic, environmental and epigenetic factors (21). Although the pathogenesis of hypertension is multifactorial, studies have shown that dysfunction of the endothelium lining blood vessels precedes the development of hypertension (22-24).

Impaired NO activity serves a primary role in endothelial dysfunction. Nitric oxide is a simple but pluripotent molecule, which is primarily synthesized in the vascular endothelium (25). Endogenous production of NO as an endothelium-derived vasorelaxation factor was first proposed in 1986 by Robert Furchgott and Louis Ignarro, and was confirmed in subsequent studies (26-28). Thus, NO was the first gaseous molecule accepted to be a signaling mediator (29). NO is generated from l-arginine by endothelial NO synthase (eNOS). eNOS enzyme metabolizes l-arginine to NO, which stimulates GC to form 3',5'-cyclic guanosine monophosphate (eGMP). eGMP causes vasodilatation of the vascular smooth muscle cells (30). Abnormalities in NO production and/or bioavailability are associated with

Table III. Summary of the characteristics of group A participants.

Characteristic	Mean	Standard deviation	Median	Minimum	Maximum
Age, years	51.78	11.33	51.50	24	70
Weight, kg	79.0	8.55	78.5	61	96
Height, cm	168.1	7.31	167	155	193
BMI, kg/m^2	23.68	2.24	23.55	20	27.1
Hb, g/dl	13.52	1.63	13.50	9.1	18.1
Glucose, mg/dl	100.4	28.53	95	75	278
Cholesterol, mg/dl	210.8	38.74	212	122	316
HDL, mg/dl	47.42	12.55	45	24	84
LDL, mg/dl	134.2	32.82	133	63	226
SGPT, U/l	31.14	16.54	27	12	126
gamma-GT, U/l	26.37	18.26	20	9	118
SBP, mmHg	152	15.32	150	142.7	158.9
DBP, mmHg	92.5	9.84	94.5	91.7	98.7

BMI, body mass index; Hb, hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SGPT, serum glutamic pyruvic transaminase; gamma-GT, gamma-glutamyl transpeptidase; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table IV. Summary of the characteristics of group B participants.

Characteristics	Mean	Standard deviation	Median	Minimum	Maximum
Age, years	57.06	13.03	63	21	70
Weight, kg	77.65	10.12	80	62	90
Height, cm	168.3	8.55	170	152	184
BMI, kg/m^2	22.96	2.31	23.55	20	26.4
Hb, g/dl	13.77	1.55	13.5	11	18
Glucose, mg/dl	116.4	55.18	98	78	353
Cholesterol, mg/dl	207.3	39.1	209.5	131	291
HDL, mg/dl	52.12	12.35	53.50	30	79
LDL, mg/dl	135.6	34.62	132.5	68	207
SGPT, U/l	29.74	11.08	27.5	11	60
gamma-GT, U/l	24.03	10.81	20	12	50
SBP, mmHg	170.5	17.33	169.5	160.2	178.9
DBP, mmHg	103.78	11.77	104	100.4	108.9

BMI, body mass index; Hb, hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SGPT, serum glutamic pyruvic transaminase; gamma-GT, gamma-glutamyl transpeptidase; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table V. Mean values of SBP and DBP for all participants in the study at the beginning and end of the study.

Type of BP	Mean at the beginning of the study, mmHg	Mean at the end of the study, mmHg	*t*-test P-value	Paired *t*-test P-value	Mann-Whitney test P-value
SBP	160.8	131.62	<0.001	<0.001	<0.001
DBP	100.3	80.14	<0.001	<0.001	<0.001

BP, blood pressure; SBP, systolic BP; DBP, diastolic BP.

hypertension (31,32). Understanding the role of NO in regulating BP has potential implications for improving the treatment of hypertension and reducing the risk of complications.

Table VI. Mean values of SBP and DBP at the beginning and end of the study for Group A.

Type of BP	Mean at time 1, mmHg	Mean at time 4, mmHg	*t*-test P-value	Paired *t*-test P-value	Mann-Whitney test P-value
SBP	152	131.22	<0.001	<0.001	<0.001
DBP	92.5	79.5	<0.001	<0.001	<0.001

BP, blood pressure; SBP, systolic BP; DBP, diastolic BP.

Table VII. Mean values of SBP and DBP at the beginning and end of the study for Group B.

Type of BP	Mean at time 1, mmHg	Mean at time 4, mmHg	*t*-test P-value	Paired *t*-test P-value	Mann-Whitney test P-value
SBP	170.5	131.92	<0.001	<0.001	<0.001
DBP	103.78	84.10	<0.001	<0.001	<0.001

BP, blood pressure; SBP, systolic BP; DBP, diastolic BP.

Table VIII. P-values for systolic blood pressure. Results are based on comparing A1 vs. A2 (group A), B1 vs. B2 (group B) and A1 + A2 vs. B1 + B2.

	P-value		
Parameter	Group A	Group B	All data
Time effect	<0.001	<0.001	<0.001
Effect of Evelor	0.241	0.580	0.139
Interaction between time and Evelor	0.481	0.998	0.850

Table IX. P-values for diastolic blood pressure. Results are based on comparing A1 vs. A2 (group A), B1 vs. B2 (group B) and A1 + A2 vs. B1 + B2.

	P-value		
Parameter	Group A	Group B	All data
Time effect	<0.001	<0.001	<0.001
Effect of Evelor	0.354	0.715	0.896
Interaction between time and Evelor	0.533	0.718	0.942

Table X. P-values for hemoglobin. Results are based on comparing A1 vs. A2 (group A), B1 vs. B2 (group B) and A1 + A2 vs. B1 + B2.

	P-value		
Parameter	Group A	Group B	All data
Time effect	0.636	0.227	0.203
Effect of Evelor	0.985	0.928	0.862
Interaction between time and Evelor	0.878	0.874	0.764

Table XI. P-values for glucose. Results are based on comparing A1 vs. A2 (group A), B1 vs. B2 (group B) and A1 + A2 vs. B1 + B2.

	P-value		
Parameter	Group A	Group B	All data
Time effect	0.706	0.562	0.976
Effect of Evelor	0.381	0.154	0.121
Interaction between time and Evelor	0.824	0.699	0.634

Previous studies have shown that short-term calorie restriction decreases BP in hypertensive rats and that the subsequent positive vascular adaptations involved increases NO bioavailability (33,34). However, calorie restriction requires significant patient compliance, which may be difficult to achieve. The utilization of small molecules to activate similar signal transduction pathways as calorie restriction could provide a potential therapeutic approach for hypertension (34).

The natural polyphenolic molecule RESV is an interesting candidate for the treatment of hypertension, as it mimics numerous molecular and biological effects of calorie restriction. RESV is found in high levels in red wine and to a lesser extent in a wide range of food products, including fruit, tea, coffee, cocoa and olive oil. RESV has multiple effects, including several positive vascular adaptations, such as causing reduced oxidative damage and improved hyperemic

Table XII. P-values for cholesterol. Results are based on comparing A1 vs. A2 (group A), B1 vs. B2 (group B) and A1 + A2 vs. B1 + B2.

	P-value		
Parameter	Group A	Group B	All data
Time effect	0.126	0.662	0.170
Effect of Evelor	0.662	0.373	0.318
Interaction between time and Evelor	0.734	0.585	0.832

Table XIII. P-values for high-density lipoprotein. Results are based on comparing A1 vs. A2 (group A), B1 vs. B2 (group B) and A1 + A2 vs. B1 + B2.

	P-value		
Parameter	Group A	Group B	All data
Time effect	0.365	0.645	0.338
Effect of Evelor	0.395	0.404	0.232
Interaction between time and Evelor	0.550	0.593	0.446

Table XIV. P-values for low-density lipoprotein. Results are based on comparing A1 vs. A2 (group A), B1 vs. B2 (group B) and A1 + A2 vs. B1 + B2.

	P-value		
Parameter	Group A	Group B	All data
Time effect	0.138	0.484	0.132
Effect of Evelor	0.669	0.226	0.218
Interaction between time and Evelor	0.857	0.623	0.772

Table XV. P-values for serum glutamate-pyruvate transaminase. Results are based on comparing A1 vs. A2 (group A), B1 vs. B2 (group B) and A1 + A2 vs. B1 + B2.

	P-value		
Parameter	Group A	Group B	All data
Time effect	0.513	0.961	0.645
Effect of Evelor	0.891	0.378	0.701
Interaction between time and Evelor	0.547	0.204	0.176

Table XVI. P-values for gamma-glutamyl transferase. Results are based on comparing A1 vs. A2 (group A), B1 vs. B2 (group B) and A1 + A2 vs. B1 + B2.

	P-value		
Parameter	Group A	Group B	All data
Time effect	0.290	0.844	0.687
Effect of Evelor	0.735	0.440	0.822
Interaction between time and Evelor	0.929	0.207	0.275

Table XVII. The percentage change in concentration levels of SGPT in patients treated, and not treated, with Evelor.

Statistic	SGPT percentage change in patients prior to and following Dapril plus Evelor treatment	SGPT percentage change in patients prior to and following Dapril treatment alone
Mean	-0.197	0.046
Standard deviation	0.193	0.351
P-value (from *t*-test)	<0.001	0.330

SGPT, serum glutamate-pyruvate transaminase.

Table XVIII. The percentage change in concentration levels of gamma-GT in patients treated, and not treated, with Evelor.

Statistic	Gamma-GT percentage change in patients prior to and following Dapril plus Evelor treatment	Gamma-GT percentage change in patients prior to and following Dapril treatment alone
Mean	-0.204	0.311
Standard deviation	0.212	1.297
P-value (from *t*-test)	<0.001	0.080

Gamma-GT, gamma-glutamyl transferase.

vasodilation, which correlate with activation of eNOS. RESV activates adenosine monophosphate-activated protein kinase (AMPK), which directly phosphorylates eNOS, increasing NO production (35). Alternatively, NO can activate AMPK, placing eNOS upstream of AMPK (36). In addition, RESV reduces oxidative damage to the heart, reduces cardiac left ventricular hypertrophy and inhibits pro-hypertrophic signaling pathways (33,34).

Based on the known ability of RESV to improve vascular function, the aim of the present study was to evaluate the effects of RESV on BP in patients with hypertension. This was determined by comparing the change in BP prior to and following standard antihypertensive treatment plus RESV,

compared with a control group receiving standard antihypertensive treatment alone. DBP and SBP were significantly reduced with the addition of RESV (P<0.001). In addition, RESV was shown to significantly decrease the levels of the liver enzymes SGPT and gamma-GT (P<0.001).

In conclusion, the results of the present study demonstrate that the addition of RESV to standard antihypertensive treatment decreases and efficiently controls BP. This indicates that the addition of RESV to standard antihypertensive therapy is sufficient to reduce BP to normal levels, without the need for additional antihypertensive drugs, which is common in many patients. In addition, RESV was shown to significantly decrease the levels of the liver enzymes SGPT and gamma-GT (P<0.001), suggesting that RESV prevents liver damage. Additional studies are needed to further evaluate the effects of RESV in liver function.

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