

Hemodynamic effects of aqueous extract of *Artemisia campestris* in adult men

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ABSTRACT

Arterial hypertension is a worldwide health problem with multiple origins. Its management remains difficult, particularly because of the pathology dependence on human lifestyle. Several ethno pharmaceutical are used to treat hypertension. Herein we investigated, for the first time, the effect of the water-boiled extract of *Artemisia campestris* on Human hemodynamic system. To do so, the blood pressure parameters of two groups of adult volunteers (smokers and non-smokers) were recorded before and each 15 minutes after drinking 20 ml of the boiled extract (20g of dried leaves / 1 L of water). The diastolic pressure and heart rate significantly diminished following the treatment, in both smoker and non-smoker men. In exception to a punctual reduction at 45 minutes in non- smokers, the systolic pressure did not significantly change. The classification of subjects in accordance to their hypertension statute at each time-point of recording, showed an important reduction of the stage 2 in smoking men, following the consumption of the extract. It is concluded that the water-boiled extract of *Artemisia campestris* could tip over arterial hypertension, especially in smokers. It is suggested that the mechanism of such effect involves epinephrine synthesis or binding to its receptor inhibition.

INTRODUCTION

Arterial Hypertension (HTA) is a multifactorial pathophysiology with global prevalence of 7.5 million patients, and causes serious health and socio-economic problems, especially when it associates to other diseases such as hyperglycemia, hyperlipidemia, and renal pathologies (Hall, 2003, Willmot *et al.*, 2004). The origin of HTA is almost dependent on Human lifestyle, fact that complicated its management (WHO report, 2012). Recently, great concern is brought back to ethno-pharmacy and natural products because of their valuable use to treat many diseases, and as tools for new drugs development (Mohanty *et al.*, 2012). *Artemisia* plants (Asteracea) that occupy large geographical extent are traditionally used for diverse endpoints. They are used as anti-helminthes, antidepressant, antispasmodic, diuretic, hypoglycemic, anti-cancer, and against many other diseases, by several populations around the world (Ashraf *et al.*, 2010, Tardio *et al.*, 2006). Recently, their Artimisinin extract attracted much interest for its potent anti-malarial activity

(De Ridder *et al.*, 2008). According to the work of Mansi and Lahham (2008), *Artemisia* extracts seems to have no real toxic features (Mansi and Lahham, 2008). However there is still much debate about their effects on the cardiovascular system and blood pressure. *A. capillaris* purified extract, the scoparone, induces heart rate and coronary flow increase (Yamahara *et al.*, 1989, Yamahara and Kobayashi, 1989); whereas extracts from *A. Persia* lead to heart rate and systolic pressure decrease (Esmaeili *et al.*, 2009, 2012). In rural and nomad desert's populations the water-boiled extract of *Artemisia campestris*, is customary used as anti-venin and to treat several pathogenic infections, but its real mode of action remains unknown. Herein, we propose to evaluate the effect of such extract on the hemodynamic system in Human.

SUBJECTS AND METHODS

Study Subjects

Adult men who were not previously medicated for hypertension or other related diseases (diabetes, hyperlipidemia, and previous cardiac events) have been recruited in this study. They confirmed being habituated to use the extract as anti-infection. At the initial measurement

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(at sitting position and without any treatment) of their arterial blood pressure, they were informed about their hypertensive statute (with a featured hypertension, or not) and asked if they would like to continue the experimentation. Finally only 14 volunteers have been enrolled in the study (8 non smokers and 6 smokers). All of volunteers had signed their contentment to participate at the experiment. Their overall age and body- mass index have been registered (Table 1). All of subjects are of the same ethnicity; and have roughly similar lifestyle. To achieve the diagnosis of their hypertensive statute, their BPs' parameters have been measured for three successive days, before the beginning of the experiment. The degree of variation of each parameter was calculated as the percentage of difference from the control point.

Table. 1: characterization of the recruited volunteers.

Group	N	Age (years)	BMI (kg/m ²)
Non-smokers	8	39.37 ± 1.68	21.93 ± 3.20
Smokers	6	42.83 ± 3.22	24.55 ± 0.79
Overall	14	40.85 ± 1.68	23.05 ± 1.84

The age and the body mass index (BMI) were statistically comparable between the studied groups.

Biological Material

Artemisia campestris (Asteracea) leaves were collected from Matmata mountains (Southern- East of Tunisia) in Marsh-April 2012, and were dried and conserved until use. At the day of the Trial, 20 g of the dried leaves were boiled for 10 minutes in 1 L of drinking water, and filtrated. The extract was orally administered after cooling. The administered dose is about ¼ of which traditionally used as anti-venin.

Conduct of the trial

At the expected day of the trial, the blood pressure components [Systolic (PS) and diastolic pressures (PD); and the pulse frequency (FC)] of each person were measured, after 30 minutes- period of quiescence. Thereafter, each subject orally took 20 ml of the water-boiled extract of *Artemisia campestris*. Subsequently, the studied parameters were recorded (3 fold at each time point) using an electronic tensiometer (AEG BMG 4906. Elektro-technische Vetriebsges.mb HindustrieringOst 40. 47906 Kempen) each 15 minutes, at the same resting conditions (at sitting position).

The mean arterial blood pressure was also calculated. The experiment began at 8H00 and finished with a five total timing-records. The mean of the three measurements was considered as the individual value for each time- point. The trial was carried out in a temperature acclimated room (at 23°C). The experimental protocol was in accordance with laws and policies governing authorities of our country, and was approved by a local ethic committee founded at the Medicine Faculty of Sfax – Tunisia.

Statistical analysis

The obtained results were firstly analyzed to check the possible correlation of all the recorded parameters via a

multivariate test. Thereafter, they have been subjected either to pair-wise Student's test or Wilcoxon one, in order to compare between the control point and different measurements following the treatment. Comparison between smoker and non smoker groups have been achieved using LSD test. The statistical analyses were performed using the SPSS program 0.11 for windows.

RESULTS

Evolution of the hemodynamic parameters:

In exception of the overall mean heart frequency (FC) which significantly decreased following the treatment (Spearman Rho= - 0.242, $p = 0.044$), means of the other investigated blood pressure (BP) parameters did not present significant chronologic correlation (Figure 1).

However, most of the studied parameters significantly dropped at 30 and 45 minutes after drinking the water-boiled extract of *A. campestris*. For example, the diastolic pressure was significantly reduced in both smokers and non- smokers group at 45 minutes (72.43±3.15 and 70.1±3.93) mmHg, respectively) in comparison to 15 minutes (82.25±5.16 and 78.41±2.48 mmHg) at $p = 0.028$ and 0.012 , respectively. Similar significant down-leveling was observed for the systolic pressure at 45 minutes (119.23±8.07 mmHg) in comparison to 30 minutes (130.25±8.81 mmHg) in non smokers, but not in smoker subjects. Also, the pulse frequency (FC) was consistently decreased in non smokers following the treatment, at 30 (66.88±4.9 bits/min), 45 (66.39±5.1 bits/min), and 60 minutes (65.5±4.8 bits/min), in comparison to the control point (74.3±4.8 bits/min); and transiently in smoker group at 60 (64.9 ±0.99 bits/min) in comparison to 45 min (68.76±0.85 bits/min).

The variation's degree of blood pressure parameters

Drinking the water-boiled extract of *A. campestris* induced significant diminishing of the diastolic (PD), systolic (PS) pressures, and pulse frequency variation, mainly at 30 and 45 minutes, in non smokers group, without affecting their mean blood pressure (MBP). PD and PS variations significantly change in smoker group, too.

However, this latter group exhibited significant variation degree of their mean blood pressure at 30 minutes after the treatment, in comparison to which of the control time point. The overall volunteers' PD and FC modifications were significant at 45 and 30 minutes when compared to controls, respectively. The recorded degrees of variation were of negative sign; and ponder for hypotensive effect of the administered extract.

Besides the recorded blood pressure parameters, at baseline, the adult volunteers have been classified into normotensive, pre-hypertensive and hypertensive. 60 minutes after *A. extract solution*' uptake, the percent of men with hypertension was decreased from 50 to 33.33 % in cigarette smoking group (table.3). While it is an immediate response, this fact consolidates the approach of the potential of *Artemisia* extract to offset hypertension.

Table. 2 : comparison of the variations' percents of the diastolic (PD), systolic (PS), and mean blood (MBP) pressures, and the cardiac frequency (FC) following water-boiled extract of *A. campestris* in healthy men.

	Time	PD	PS	MBP	FC
NON SMOKERS	00	00 ± 00	00± 00	00± 00	00± 00 (c,d)
	15	7.98± 4.6 (d)	3.08± 4.17	5.42± 3.64	-3.4± 4.52 (c)
	30	4.88± 5.61	4.15± 3.93 (d)	1.23± 4.8	-8.73± 4.21 (a,b)
	45	-3.25± 4.95 (b)	-4.2± 4.62 (c)	-1.2± 3.9	-8.53± 4.75 (a)
	60	2.58± 4.23	0.35± 3.66	-0.42± 3.84	-5.81± 6.69
SMOKERS	00	00± 00d	00± 00 (c)	00± 00 (c)	00± 00
	15	-0.5± 4.5 (d)	-9.36± 6.27	-4.78± 5.08	-2.76± 2.01
	30	-4.63± 2.6	-7.88± 2.74 (a)	-6.08± 2.28 (a)	-1.8± 2.48
	45	-6.59± 3.02 (a,b)	-4.12± 3.28	-5.43± 2.95	-0.29± 1.95
	60	-1.69± 2.86	-2.59± 2.92	-2.1± 2.54	-5.11± 3.31
OVERALL	00	00± 00	00± 00	00± 00	00± 00 (c)
	15	4.35± 3.35 (d)	-2.25± 3.84	1.05± 3.21	-3.12± 2.64
	30	0.80± 3.35d	-1.01± 2.95	-1.90± 2.99	-5.76± 2.71 (a)
	45	-4.68± 3.04 (b,c,e)	-4.16± 2.89	-3.01± 2.54	-5.00± 2.97
	60	0.75± 2.68d	-0.91± 2.38	-1.14± 1.10	-5.51± 3.95

(non parametric test of Wilcoxon (apparié) a, b, c, d, and e represent significant differences in comparison to control (00), 15, 30, 45, and 60 minutes after the water-boiled *A.* extract consumption, respectively.

Table. 3: percent of hypertension gradation before and after drinking the water-boiled extract of *A. campestris* by adult men.

	Hypertension grade	Normotensive	Pre-hypertensive	Hypertensive
	Systolic pressure	< 120 mmHg	120 ≤ PS < 140 mmHg	140 mmHg ≤ PS
	Diastolic pressure	PD < 80 mmHg	80 ≤ P D < 90 mmHg	90 mmHg ≤ PD
At baseline	Smokers	33.33 (2/6)	16.66 (1/6)	50 (3/6)
	Non smokers	37.5 (3/8)	50 (4/8)	12.5 (1/8)
60 min after the treatment	Smokers	16.66 (1/6)	50 (3/6)	33.33 (2/6)
	Non smokers	50 (4/8)	37.5 (3/8)	12.5 (1/8)

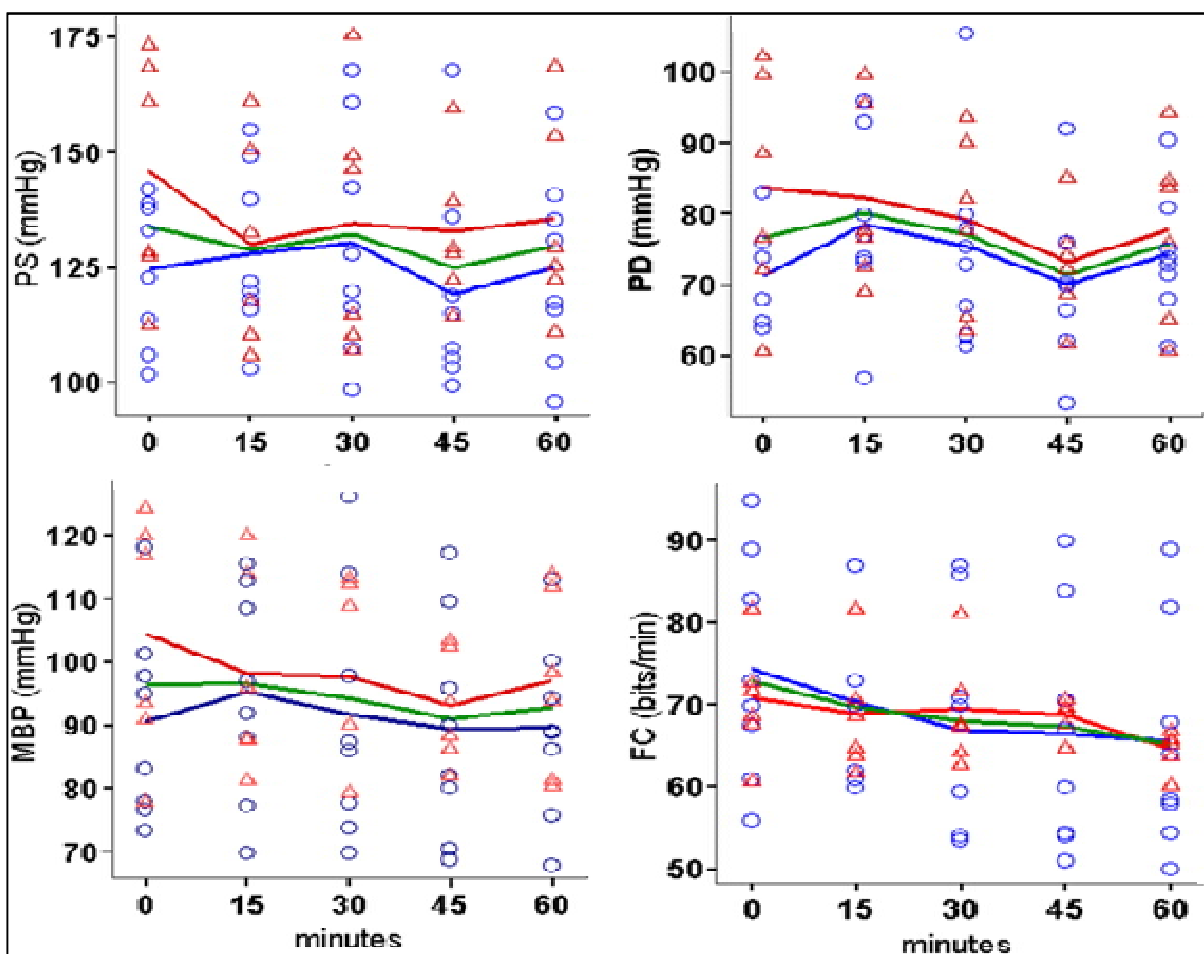


Fig 1 : Variation of the systolic (PS), diastolic (PD) and mean arterial pressures (MBP); and cardiac frequency (FC), before (0 minutes) and after 20 ml of the water-boiled extract of *Artemisia campestris* consumption by smoking (Red line); non- smoking groups (Blue line), and their overall means (Green lines).

DISCUSSION

Several plants are used in traditional medicine in different ways, by many populations. However, there is still great work in need to understand their mode of actions and to determine their safety and effectiveness in wound healing the disease. These objectives constitute the basis of pharmacognosy that is a determinant pace for new drugs wangling. In this context, we evaluated the effect of the water-boiled extract of *Artemisia campestris*, which is used as antivenin and anti-infection, on the hemodynamic system. Previous experimental and clinical studies showed unpredictable effects of *Artemisia* shrub extracts that might emanate from its important intra and inter specific variability, which in turn influences their extracts bioactive chemical content (Salido *et al.*, 2004). Our results, present for the first time the effect of the water-boiled extract of *A. campestris* on Human hemodynamic system. The used extract induced significant and consistent decrease of the diastolic pressure and heart rate. Whoever, the systolic pressure's fall transiently occurred. This was in agreement with their degree of variation with a negative sign. These findings clearly demonstrate that *Artemisia campestris* aqueous extract exerts a potent anti-hypertensive effect in the studied sample of population. In a murine experimental model, Esmaeili *et al.* (2009, 2012) found that *A. Persia* extract efficaciously reversed the epinephrine induced- hypertension more than the conventional anti-hypertensive drug, the enalapril that inhibits the angiotensin-converting enzyme endocrine activity.

The role of epinephrine, also known as adrenaline, in regulating the cardiovascular system is mostly established. This neuromediator induces heart rate and both diastolic and systolic pressure increase in Humans (Leenen *et al.*, 2007). Thus, the biological activity of *A. campestris* extract could originate from the induced inhibition of the cardiovascular response to epinephrine, and the enhanced one to acetylcholine (Tigno *et al.*, 2000), that ultimately contributes to vascular smooth muscle relaxation (Aziz *et al.*, 2012). Furthermore, vasodilatation has been observed in pulmonary tissues following the inhalation of the Chinese moxa that contains volatilized substances of *Artemisia* plants (Cheng *et al.*, 2011, Zhao *et al.*, 2010). Applying moxa to Humans did induce a heart rate decrease and general body depression (Zhao *et al.*, 2010, Kim *et al.*, 2010). The mechanism involving epinephrine could be explained by the inhibition of the monoamine oxidase, a key enzyme for its bio-synthesis, by several chemical contained in the extract (Lee *et al.*, 2000). Extracts from *A. anomala* exhibited a competitive binding to adrenergic receptors (Luedtke *et al.*, 2003) that inhibit the α_1 - adrenoceptor agonists- induced contraction of aorta (Mojarad *et al.*, 2005) suggesting a possible vasodilator effect mediated by such interactions. The responsiveness to epinephrine was recently demonstrated to importantly change in adult HTA-patients (Leenen *et al.*, 2007). Else, the endogenous secretion of adrenaline is enhanced by cigarette smoking (Houben *et al.*, 1981, Watts and Bragg, 1956); fact that might explain the observed differences between the smoker and non smoker men.

CONCLUSION

Our findings highlight the potential of the water-boiled extract of *Artemisia campestris* to offset hypertension, probably through the reduction of the heart frequency and the arterial diastolic pressure. This effect is seemingly differed by cigarettes smokings. The mode of action of this extract is suggested to involve the inhibition of the epinephrine synthesis and / or its effect on the cardiovascular system. Further investigations to highlight its real mechanism and mode of action are envisaged.

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