

A New Grape Seed Extract Pharma Standard Supplement (ECOVITIS™) Prevents and Controls Borderline Hypertension and Endothelial Dysfunction

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Abstract

This registry evaluates the effect of ECOVITIS™ (grape seeds extract) in borderline hypertension (also evaluating endothelial-mediated vasodilatation). The main targets of the registry were the normalization of blood pressure and of an altered endothelial function (EF); 3 groups of 15 subjects used: Standard Management (SM) (GROUP 1); GROUP 2: SM+ECOVITIS™ (150 mg/day); GROUP 3: SM+ECOVITIS™ (300 mg/day).

Results. The groups were comparable. Tolerability/safety were optimal. Blood tests, urines and ECG were normal at 4 and 12 weeks. BMI showed, minimal variations (<26) in 3 months. Blood pressure (systolic, diastolic) and heart rate indicate a progressive improvement in Group 3 with better values at 4 and 12 weeks ($p<0.05$). The lower dose improved ($p<0.05$) blood pressure and heart rate better than SM. Lipids and oxidative stress were improved better with the high dose ($p<0.05$). The lower dose resulted better than SM ($p<0.05$). Other metabolic parameters (blood sugar and glycosylated hemoglobin) followed the same patterns (Group 3 resulted better than the other two groups) ($p<0.05$). Laser Doppler measurements (skin flux) and strain gauge plethysmography measured an improvement in post-occlusive flow (EF) at the level of the arm ($p<0.65$). This was confirmed by artery ultrasound measurements showing a larger increase in size in the brachial artery after occlusion with ECOVITIS™ (subjects in Group 3 had the best results ($p<0.025$); the lower dose (Group 2) was superior to SM ($p<0.05$). Tc PO2 increased more in group 3 ($p<0.05$); PCO2 was decreased. Results in the lower dose group were better ($p<0.05$) than results in the SM patients.

In conclusion, this pilot registry shows that ECOVITIS™ is safe, well tolerated and may control and improve blood pressure and EF in borderline subjects. More studies may be needed for a longer period of time.

Keywords: Antihypertensives, Prevention, Blood Pressure, Hypertension, Risk Factors, Prehypertension, Cardiovascular Diseases, Hypercholesterolemia, Lifestyle, Cholesterol

Introduction

Grape seed extracts formulations as PS (Pharmaceutical-Standard) supplement derive from whole grape seeds (GS); this original product has a great concentration of vitamin E, active flavonoids, linoleic acid and phenolic proanthocyanidins (known as OPCs or oligomeric procyanidins) [1-3]. Extracts of grape seeds, different according to their origin, transformed into PS supplements include, in different quantities, polyphenols with an important antioxidant

activity. An important polyphenol contained in grape seeds is resveratrol, which is under chronic evaluation for its possible cardiovascular, antiaging and still questionable anticancer effects. Other preliminary research on disease models include management of vascular skin ulcers and wounds as OPCs-derivates induce the production of vascular endothelial growth factor and accelerated healing. In bone physiology, grape seed whole extracts and formulations made into PS supplements appear to enhance density

and strength of bones (but most work is only in animal studies). OPCs may also, theoretically, have antiviral and antibacterial activity to be confirmed in human models in clinical conditions [1-3]. A recent registry has shown the efficacy of a grape seed PS supplement in normalizing in a short period of time blood pressure in borderline, otherwise healthy, hypertensive subjects. One study in patients with coronary disease and clinically significant cardiac risk factors found that four weeks of grape seed supplementation caused improvements in endothelial function (EF) with a clinical meaning to be better assessed in longer studies.

A meta-analysis of grape seed supplementation (including different products and dosages) confirms that grape seed significantly lowers (borderline) systolic blood pressure and decreases heart rate with a minimal – possibly useful - effects on plasma lipids. The analysis included different patients managed with different supplements and has the limitations of a metanalysis).

Grape seed supplements (generally in capsules or tablets) usually contain 50 to 200 mg (or even more) of product. Because of the possible – theoretical - action of proanthocyanidins on decreasing platelet adhesion, grape seed PS supplement may - very theoretically - act on coagulation physiology or on bleeding in some patients by generally increasing clotting time.

Interactions studies (i.e., with antiplatelet agents or anticoagulants, with thyroid replacement therapy or diabetic medication) and different possible interferences (i.e., with antibiotics) are still in progress (particularly for ECOVITIS™).

Grape seed PS supplements are also aromatase inhibitors and may suppress the conversion of testosterone to estradiol; however, this effect may be very limited, difficult to quantify, it may require high loads and, possibly, long periods of supplementary management.

For most GSs, the suggested dose as a PS supplement is around 300-1000 mg/day. However, this dose may need adjustments according to the clinical or preclinical situation, on the basis of the single product formulation and considering clinical evaluations and targets.

ECOVITIS™, a new PS grape seeds product (Bonollo Nutraceuticals, Mestrino, Padova, Italy) may have beneficial effects on cardiovascular prevention (both arterial and veins) and it is currently under evaluation.

The aim of this registry was the evaluation of the effect of supplementary management with ECOVITIS™ in subjects with borderline hypertension (also evaluating endothelial-mediated vasodilatation).

Subjects, Methods

Subjects: otherwise healthy, borderline hypertensive subjects with associated alteration in endothelial function (EF) were included. A minimal, borderline hyperlipidemia, and hyperglycemia, without significant arterial alterations (plaques, IMT thickening) or coronary disease were present [1].

Pressure measurements: all measurements and the definitions of borderline hypertension are in agreement with the AHA guidelines [4, 5].

High blood pressure should be managed earlier with lifestyle changes and in some patients with medication – at 130/80 mmHg rather than 140/90 – based on ACC and AHA guidelines for the detection, prevention, management and treatment of high blood pressure. The guidelines lower the definition of high blood pressure to account for complications that can occur at lower numbers and to allow for earlier intervention. The new definition results in nearly half of the U.S. adult population (46 %) having high blood pressure, with the greatest impact expected among younger people. Additionally, the prevalence of high blood pressure is expected to triple among men under age 45, and double among women under 45, the guideline authors note. However, only a small increase is expected in the number of adults requiring antihypertensive medication. To avoid complications and costs the administration of medications could be controlled in earlier cases and some PS supplements may be used.

Dosage: 2 levels of daily dosages were used for this supplementation: 150 mg e 300 mg of ECOVITIS™ (1 capsule is equivalent to 150 mg). The main targets of the registry were defined as the normalization of blood pressure and of an altered EF (restored to normal values).

The 3 groups (15 subjects each one) used:

-Standard Management (SM) (GROUP 1); (age 44.6;3; females 8); no drop outs.

-GROUP 2; ECOVITIS™ 150 mg/day + SM (43.5;2.6; f 8); no drop outs.

-GROUP 3; ECOVITIS™ 300 mg/day + SM (44.1;3.2; f 7); no drop outs.

Period of supplementation: the initial registry lasted 4 weeks; when efficacy on lowering blood pressure and safety/tolerability (no side effects) were shown the registry, was extended to 3 months. The higher-dose ECOVITIS™ group, in comparison with SM were included in this 3-months extension.

The basic parameters evaluated in the registry and the target measurements are shown in Table 1. After the first month of supplementation, considering the efficacy seen in the first month, in agreement with the patients, the registry was extended.

Table 1: Target tests and predictive analytics (24 weeks). * = P<0.05 BEST RESULT (ANOVA).

TESTS		Inclusion	1W	2W	4W	12W	24WEEKS PREDICTIVE ANALYTICS
1 BMI	ALL	<26				<26 ns	
2 BIPr	GR3mx	143;3	143.3	142;2	143.2	128;6*	127;4 mmHg
	GR3mn	91;3	91;2	90;2	89;2	84;3*	83.3;2.1
	GR2mx	144;3	140;3	140;2	138;3	138;2	136;2
	GR2mn	92;2	90;3	90;2	88;4	86;3	85;2
	SMmx	144;2	139;3	140.4	138;4	138;3.2	136;4
	SMmn	92;3	92;2	91;1	91;2	89.3;2	89;3
3 Heart Rate	GR3	76;3.3	73;2	72;2	71;2	71;3.2*	70;2
	GR2	75;2	74;3	74;2	73;2	73;3	72;5
	SM	75;2	76;3	75;2	75;2	75;2.2	74;3
4.1 LIP mg/dL	GR3TC	211;8	201;5	200;3	189;5	189;4*	188;2.2
	HDL	52;4	55;3	57;2	58;3	63;6*	67;3
	Trig	178;6	154;6	155;4	149;2	147;8*	144;4
	GR2TC	212;6	210;4	208;4	202;3	191;5	188;4
	HDL	53;2	53;1	55;3	55;3	59;2	60.3
	Trig	179;6	170;5	168;4	166;4	162;4	158;3
	SMTc	216;6	211;6	205;6	208;5	204;6	205;3
	HDL	53;2	53;3	54;4	55;3	56;3	55;3
Trigl	181;7	178;3	177;4	179;4	180;6	174;4	
4.2 Ox STR	GR3	395;13	-	-	-	334;11*	331;8 CARR UNITS
	GR2	390;11	-	-	-	366;11	360;6
	SM	383;12	-	-	-	375;14	376;9
5 SUGAR	GR3	108;5.3	100;2	102;2	99;3	101;2.2	101;2
	GR2	107;2	102;3	104;2	103;2	104;3	103;2
	SM	107;3	106;4	105;2	108;3	104;0.3	106;3.2
6GLYC Hb	GR3	7.8;0.6	-	-	-	7.4;0.8*	7.3;0.4
	GR2	7.8;2	-	-	-	7.5;1.1*	7.4;1
	SM	7.7;1	-	-	-	7.7;0.4	7.6;0.6
7 LDF MICR	GR3	0.66;0.2	-	-	-	1.24;0.1*	1.39;0.1
	GR2	0.61;0.2	-	-	-	0.98;0.2	1.1;0.1
	SM	0.62;0.1	-	-	-	0.83;0.2	0.84;0.2
8 S.GAUGE	GR3	+14.3;2.3%	-	-	-	+18.8;2.2%*	19;3.3 Flow in ml/min
	GR2	+14;1%	-	-	-	+17.3;1	+18;1
	SM	+13.8;3%	-	--	-	+16;2%	+16;2.3
9 O2-CO2	GR3	48;2.2 O2	-	-	-	52;2.4*	53;2.5
		28.4;2 CO2	-	-	-	27.2;2,3	27;2.1
	GR2	47.4;2 O2	-	-	-	49;2	50;2
		29;0.8 CO2	-	-	-	28;0.7	28.4;0.2
	SM	48;3 O2	-	-	-	49;3.2	49;2
		28;2 CO2				28;1.3	28;2.3

10 US	GR3	+6.6%;1	-	-	-	12.63;2%*	13;3.1% ULTRASOUND:
	GR2	+6.3;0.	-	-	-	0:0.7	8.3;0.2 BRACHIAL ART. INCREASE
	SM	+5;1.1%	-	-	-	7.3;1.2%	7.1;2%
11 RETINA % sy com	GR3	4;1.1%	-	-	-	9.2;2%*	10;2.1*
	GR2	4.2;0.5	-	-	-	7.2;0.5	8;0.8
	SM	4.2;1.2%	-	-	-	5;1.4%	5.3;1
BLOOD		normal	-	-	-	normal	normal
URINES		normal	-	-	-	normal	normal
SAFETY		normal	-	-	-	optimal	
TOLERABILITY			-	-	-	-	
EKG		normal	-	-	-		
LIP=LIPIDS; TC TOTAL CHOLESTEROL; TRI=TRGLYCERIDES; Hb GLYC; GLYCOSILATED HEMOGLOBIN; OX STR=OXIDATIVE STRESS; LDF (LASER DOPPLER) SKIN FLUX; MICR=MICROCIRCULATION; SG=STRAIN GAUGE PLETHYSMOGRAPHY (arm) O2 AND CO2=TRANSCUTANEOUS O2, TCO2; US=ULTRASOUND; RETINA: RETINAL ARTERY FLOW; DIASTOLIC COMPONENT % (AVERAGE).							

Standard Management included *control of calories and reduction in carbohydrates/sugars, elimination of NaCl, regular exercise (at least 20 minutes, 3 times/week), reduction in use of products with caffeine, sugar and soda drinks, regular rest hours.*

Supplement studies. This supplement registry (and the subsequent extension study) were conducted as supplement registry study [1-3].

Statistical analysis A number of at least 10 subjects for each group (SM and SM+supplementation) was considered necessary to evaluate differences in target parameters over 12 weeks of management. All results and data were considered as non-parametric; the Mann-Whitney U-test and the ANOVA were used for symptoms or complaints. A predictive analysis was performed at the end of the study based on the observed data and results [6-10].

Safety and Tolerability were re-evaluated every week. Subjects were in constant contact with the physician observing the registry. The vascular system was screened with ultrasound to exclude vascular lesions. All subjects were within normal limits for age. Thyroid functional tests and parameters were within normal values.

Target tests were made/evaluated at inclusion (time 0) and repeated at 1, 2, 4, 12 and 24 weeks. Blood (routine) test and urine were normal at inclusion. EKG was also normal at inclusion. Subjects had no cardiovascular symptoms in the past.

Measurements:

1 BMI was at inclusion <26 in all subjects.

2 Blood pressure was borderline, not-permanently increased (with repeated daily self-measurements): borderline hypertension (BH) without other symptoms were defined according to the Merck

Manual and to the American Heart Association Guidelines [4, 5].

Target measurement 3 was heart rate [4].

Target 4 included metabolic measurements: lipids (minimal borderline, elevation) were target 4.1; study target 4.2 was oxidative stress (in Carr Units) [11]. Targets measurement 5 (fasting sugar) and 6 (glycosylated Hb) completed the metabolic panel.

Target measurements 7 included microcirculation measurements (laser Doppler as resting flux at the hand and flux after hyperemia) and strain-gauge evaluation of an increased flow after occlusion of the brachial artery with a suprasystolic cuff, for 3 minutes (EF) [8, 12]. Reactive hyperemia (the percent increase of the basic, resting flow) was considered to be associated to EF.

Measurement target 10 included brachial artery ultrasound (high resolution Preirus-Hitachi scanner, 14 Mhz linear Probe) to evaluate the increase in diameter of the artery after suprasystolic occlusion and in the post-occlusion period (of the brachial artery) dilatation [6, 7, 13]. The measurement target 11 included retinal flow and flow velocity (retinal arteries); it was measured with a high-resolution, trans-palpebral probe, as previously defined, focusing at the diastolic component; this component indicates vasodilatation (or vasoconstriction) in the retinal arterial system [14-18]. The diastolic component tends to be reduced or abolished in hypertensive patients with significant vasospasm. Recent studies show the importance of retinal flow evaluation in hypertension and in different types of microangiopathy. Improvements in technology make this test reliable, reproducible and completely non-invasive.

Finally, measurement target 12 included the evaluation of the fat mass (Fat Loss Monitor, Omron, USA) in these subjects the evaluation of the coagulation and platelets were also included.

Results

The 3 groups were comparable. Tolerability/safety were optimal. No subject had to stop supplementation. Blood tests, urines, EKG were normal at 4 and 12 weeks. BMI showed, minimal non-significant variations (< 26) in all subjects in 3 months. Therefore, the variations in physiologic measurements were not determined by a variation in weight.

Table 1 shows the main target parameters.

MAIN COMPARISON:

BP (systolic, diastolic) indicate a progressive improvement in Group 3 in comparison with the other two groups, with better values at 4 and 12 weeks ($p < 0.05$) (Fig. 1).

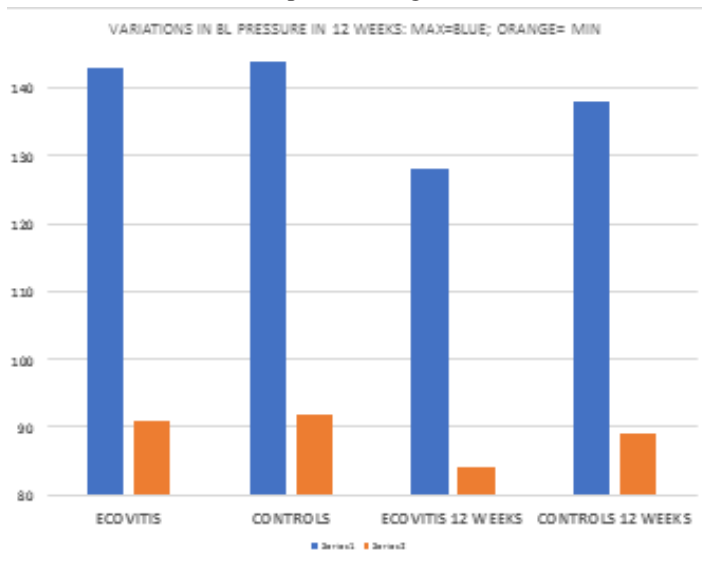


Figure 1: Variations in blood pressure

The lower dose also improved ($p < 0.05$) blood pressure and heart rate better than SM. Lipids and oxidative stress were all significantly improved better with the higher dose ($p < 0.05$). The lower dose resulted better than SM ($p < 0.05$).

The metabolic parameters (fasting blood sugar and glycosylated hemoglobin) also followed the same patterns (with G3 resulting better than in the other two groups) ($p < 0.05$).

Both laser Doppler measurements (resting skin flux) and strain gauge plethysmography measured an improvement in post-occlusive flow at the distal perfusional level (hand) and at the level of the arm ($p < 0.05$) indicating improvements in EF. This was confirmed by the artery ultrasound measurements showing a larger increase in size in the brachial artery after occlusion. Subjects in Group 3 had the best results ($p < 0.025$) with the lower dose (Group 2) also being superior to SM ($p < 0.05$). Tc PO₂ increased more in group 3 ($p < 0.05$); PCO₂ was decreased - as an indication of a better perfusion with ECOVITIS™. Results in the low dose group were better ($p < 0.05$) than results in the SM patients.

Retinal flow showed a better improvement (increase in the diastolic component) at retinal level (the measurements are an average of Doppler flow velocities in the two eyes) in the high dose group

($p < 0.05$). Results in the low dose group were better ($p < 0.05$) than in the SM group. Finally, (Table 2) Fat Mass was improved better with the high dose ($p < 0.05$). Results with the low dose were better than in the SM group. No changes in coagulation parameters were observed in the 3 groups.

Table 2: EXTRA MEASUREMENTS

		Inclusion	12 WEEKS	24 WEEKS
12 FAT MASS	GR3	22.2;0.12	21.1;0.6*	20.5;0.3*
	GR2	22;0.5	22.1;0.2	22.2;0.3
	SM	22.3;0.3	22.2;0.4	22;1.7
Normal values (age 49-59): 23-33 Females: 11-21 Males				

Conclusions

Early detection, evaluation and management of essential hypertension and of associated risk factors may stop or reverse progression of atherosclerosis and prevent most complications. Borderline hypertension may be noninvasively evaluated [19] with self-monitoring, home measurements and, if possible, with 24- 48 hours monitoring to get the best visualization of the problem, its pattern and severity in coincidence with environmental factors [18]. The first approach in hypertension medicine could be a change in lifestyle, a better perception and self-management; this step may also rely on non-drug management including PS supplements. If supplements are not effective, or satisfactory the next step would be to try initial drug treatment. The option is becoming more interesting as new studies emerge on the management of borderline, initial hypertension with specific PS supplements. These standardized, natural supplements, recognized as safe - in most patients - allow to avoid drugs or to delay their chronic use as they may produce side effects and complications in time (that would be associated to more costs).

The management of cardiovascular risk factors and a 'soft' management - while working on risk factor and lifestyle - could be an appealing solution to early, borderline hypertension without complications. Predictive analysis in these subjects shows a continuation of the progressive improvement projected at 24 weeks [10].

In this study all tests - before 10 am - were conducted in a controlled environment (22°C). A variable environment, without a possibility for patients to stabilize, may alter most microcirculatory and physiological results. This multiple-parametric (or measurements) model indicates several modes of action of ECOVITIS™ (including its important activity on oxidative stress and on metabolic parameters).

This grape seed extract includes proanthocyanidins prepared with an advanced technological system and with specifically analytical characterizations [19-21]. ECOVITIS™ is prepared using selected non-contaminated seeds obtained from Northeast Italian wineries and with an extractive aqueous-infusion and tangential-flow filtration with membranes with varying degrees of selective porosity. The full and in-depth analytical characterization

has been achieved by using an innovative procedure integrating information from Gel Permeation Chromatography (GPC) and Mass Spectrometry (MS). ECOVITIS™ is basically characterized by a low monomeric catechins content and a high concentration of oligo-polymeric proanthocyanidins with a well-defined molecular weight-related profile [21].

A preliminary study – in progress – indicates that ECOVITIS™ does not change coagulation in subjects under anticoagulants or antiplatelet agents. Also, this product does not change the metabolic needs in subjects using thyroid substitutes or oral medications for diabetes (Belcaro, Cox et al. Data on File, Study in progress, 2021)

In *conclusion*, this pilot registry shows that ECOVITIS™ is safe, well tolerated and may control and improve blood pressure and EF in borderline, otherwise healthy, compliant subjects. More studies may be needed for a longer period of time, in a less selected population, considering also the costs of management (as this product can be used – under medical supervision – without prescription and side effects may be absent).

References

1. Belcaro G (2017) PS Supplements Clinical applications. Singapore: Imperial College Press-World Scientific Publications.
2. Cesarone MR, Belcaro G (2020) Supplementi Pharma Standard: informatore, Ediz Minerva Medica, Turin 2020 Informatore.
3. Cesarone MR, Belcaro G (2019) La medicina alternativa-complementare e la medicina dei supplementi. Ediz Minerva Medica, Turin.
4. Porter R, Kaplan J, Lynn R, Reddy M (2019) The Merck Manual of diagnosis and Therapy. Kenilworth, NJ: Merck Sharp&Dohme Co, Inc; Whitewater, NJ.
5. New ACC/AHA High Blood Pressure Guidelines Lower Definition of Hypertension. <https://www.acc.org/latest-in-cardiology/articles/2017/11/08/11/47/mon-5pm-bp-guideline-aha-2017>.
6. Hu S, Belcaro G, Cornelli U, Luzzi R, Cesarone M, et al. (2014) Effects of Pycnogenol on endothelial dysfunction in borderline hypertensive, hyperlipidemic, and hyperglycemic individuals: the borderline study. *Int Angiol* 34: 43-52.
7. Enseleit F, Sudano I, Périat D, Winnik S, Wolfrum M, et al. (2012) Effects of Pycnogenol on endothelial function in patients with stable coronary artery disease: a double-blind, randomized, placebo-controlled, crossover study. *Eur Heart J* 33: 1589-1597.
8. Maxwell C (1987) Clinical research for all. Cambridge, UK: Cambridge Med Publications.
9. Cox DR (1992) Planning of experiments. New York, NY: J Wiley & Sons 320.
10. Siegel E (2013) Predictive analytics. J Wiley & Sons inc, Hoboken, New Jersey.
11. Cesarone MR, Belcaro G, Carratelli M, Cornelli U, De Sanctis MT, et al. (1999) A simple test to monitor oxidative stress. *Int Angiol* 18: 127-130.
12. Belcaro G, Bollinger A, Hoffman U, Nicolaidis AN (2006) Laser Doppler. Med Orion, London.
13. Belcaro GV (2018) The Angiology Bible, World Scientific Publications, Imperial College Press, London.
14. Cesarone MR, Laurora G, Steigerwalt R, Belcaro G (1992) Retinal duplex scanning in cerebrovascular disease and hypertension. *Vasa* 21: 163-166.
15. Steigerwalt RD Jr, Belcaro GV, Laurora G, Cesarone MR, De Sanctis MT, et al. (1998) Ocular and orbital blood flow in patients with essential hypertension treated with trandolapril. *Retina* 18: 539-545.
16. Gizzi C, Torino-Rodriguez P, Belcaro G, Hu S, Hosoi M, et al. (2017) Mirtogenol supplementation in association with dorzolamide-timolol or latanoprost improves the retinal microcirculation in asymptomatic patients with increased ocular pressure. *Eur Rev Med Pharmacol Sci* 21: 4720-4725.
17. Steigerwalt RD Jr, Laurora G, Belcaro GV, Cesarone MR, De Sanctis MT, et al. (2001) Ocular and retrobulbar blood flow in ocular hypertensives treated with topical timolol, betaxolol and carteolol. *J Ocul Pharmacol Ther* 17: 537-544.
18. Cesarone MR, Incandela L, Ledda A, De Sanctis MT, Steigerwalt R, et al. (2000) Pressure and microcirculatory effects of treatment with lercanidipine in hypertensive patients and in vascular patients with hypertension. *Angiology* 51: S53-S63.
19. Belcaro G, Ippolito E, Dugall M, Hosoi M, Cornelli U, et al. (2015) Pycnogenol® and Centella asiatica in the management of asymptomatic atherosclerosis progression. *Int Angiol* 34: 150-157.
20. Cesarone MR, De Sanctis M, Laurora G, Ambrosoli L, Marelli C, et al. (1994) Effects of trandolapril on 24-h ambulatory blood pressure in patients with mild-to-moderate essential hypertension. *J Cardiovasc Pharmacol* 23: S65-S72.
21. Morazzoni P, Vanzani P, Santinello S, Gucciardi A, Miotto G, et al. Antioxidants 2021,10,418. <https://doi.org/10.3390/antiox10030418>

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