The effects of a persimmon leaf oral supplement (Persimonal®) on cardiovascular health: a randomized, double-blinded, placebo-controlled study

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Abstract

Introduction: The present randomized, double-blinded, placebo-controlled study investigated the effects of Persimonal®, a persimmon leaf oral supplement on cardiovascular health.

Methods and materials: Eighty-six (86) subjects, male and female aged 40-75 years of age inclusive, with borderline hypertension and/or borderline high total cholesterol or high LDL, were enrolled onto the study and seventy-three (73) subjects completed the study. Qualified subjects returned to the testing facility for baseline (Day 0). Following review of qualification, the test product, diary, and instructions for use were dispensed according to the randomization for the study. Subjects returned for visits on Days 7, 30, 60, 90, 120, 150, and 180. Subjects had the same procedures completed depending on which group they were included in (blood pressure, blood draw or both). On Day 180, all subjects had a blood pressure check and blood drawn for a lipid profile for safety.

Results: Systolic and diastolic BP analysis indicated subjects assigned treatment with Persimonal® had statistically significant reductions in mean blood pressure values compared to baseline values at all study assessment timepoints for systolic BP and diastolic BP, except for day 07 in this last parameter. Between treatment analysis indicated statistically significant differences in systolic and diastolic blood pressure values favoring Persimonal®. The lipid profiles of the subjects randomized to treatment with Persimonal® showed a statistically significant reduction in the mean LDL and in the mean total cholesterol values compared to mean baseline values at Days 07, 60, 90 and 120 for LDL and Days 07, 30 and 120 for total cholesterol.

Conclusion: The results of the study provide data supporting the view that Persimonal® may be administered to patients as a potential cardiovascular dietary supplement. Further research will elucidate additional benefits from this multifunctional source.

Key Words: *Persimmon Leaf Extract, Persimonal, Cardiovascular health, Blood pressure, Cholesterol.*

Introduction

Persimonal® is a new multifunctional advanced botanical extract of highly therapeutic bioactive compounds of flavonoids, polyphenols, tannins, terpenoids, gallic acid, and carotenoids, which are naturally sourced from leaves of *Diospyros kaki* Thumb. (Persimmon leaves).

These polyphenolic compounds are known to be anti-oxidative, anti-inflammatory, anti-carcinogenic, anti-mutagenic, and cardioprotective, boosting the immune system and nourishing the cells with a daily intake of this highly nutritious supplement to maintain a healthy cardiovascular system (HAN *et al*., 2002).

Persimmon (*Diospyros kaki* Thumb.) is a traditional medicinal plant, widely cultivated in China, Japan, and South Korea and has been commonly used in folk medicine in East Asia, owing to its different pharmacological activities; mainly antihypertensive (KAWAKAMI *et al*., 2010), antioxidant (SUN *et al*., 2011), and vasorelaxant effects (KAWAKAMI *et al*., 2011).

Persimmon fruits possess high levels of dietary fiber, vitamin C, catechin and gallocatechin whereas Persimmon Leaf Extract mainly consists of caffeine, chlorophyll, flavonoids (including

therapeutic constituents, astragalin, kaempferol, quercetin), organic acids, phenolic compounds, tannins, and vitamins (LEE *et al*., 2006). As a folk medicine, Persimmon Leaf Extract and whole persimmon leaf have widely used to treat hypertensive disease and apoplexy syndrome in Asia (BAE *et al*., 2015).

Although, from the research perspective, there is convincing evidence that Persimmon Leaf Extract ingestion may improve cardiovascular conditions, and, based on the findings that Persimmon biomarkers are absorbed in their molecular form, accumulating in different tissues, it might be reasonable to investigate a new multifunctional Persimmon Leaf Extract as a nutritional supplement. Thus, the aim of this single-center investigation is to extend these earlier findings with Persimonal®.

Methods and materials

Study design

This was a randomized, double-blind, placebo-controlled study that utilized blood pressure monitoring and/or blood cholesterol assessments to demonstrate the potential of a nutritional supplement to aid in cardiovascular health improvement when used daily for approximately 180 days. The subjects as well as the Principal Investigator were blinded to whether the subject received active test article or placebo.

Inclusion criteria
Male or female, aged 40-75 years of age
Subject has borderline hypertension and/or borderline total cholesterol, or borderline LDL levels as determined by the consulting physician. If values are over the maximum for the study, staff are asked to refer the subject to their PCP
Subject can either be newly diagnosed and on no medication for the condition or on medication for a previous diagnosis (stable on the same medication for the last 3 months) and still have borderline hypertension, total cholesterol, or LDL levels
Subject has provided written informed consent
Subject has come to Visit 1 fasting for 9-12 hours
Subject can comply with study product requirements and attending all visits
Female subjects of child-bearing potential agree to use an adequate method of birth control which would include, 1) Systemic birth control (subjects must have been taking the same type of birth control for at least 3 months prior to entering the study and must not change type of birth control during the study); 2) Condom with spermicide; 3) IUD; 4) Abstinence. Females not of child-bearing potential (hysterectomy, bilateral tubal ligation, or no menses for more than 12 months) do not need to agree to use birth control

Exclusion criteria
Female subject who is pregnant, nursing, or planning to become pregnant (by verbal response only)
Females who have given birth within the past year
Subject has participated in another supplement study in the past 30 days
Subject is under treatment for known health issues which may include, but not be limited to: Asthma, Diabetes, Insomnia, Autism, Vertigo, Thyroid Issues, Migraines, Bi- Polar Disorder or episodes of Mania, Depression, Cancer or history of Cancer, Heart Disease or undergoing any form of hormone therapy
History of malignant disease
Known sensitivity/allergy to the test article, similar materials, or their constituents
Current use of recreational drugs
Principal Investigator deems the subject an unsuitable candidate for this study

Prohibitions and restrictions
Subject agrees to not start any new medications or herbal supplements without discussing first with study staff
Subject agrees to remain on a stable diet (i.e., no dietary changes from the last 30 days)
Subject who is in the high cholesterol/high LDL group agrees to come to every visit fasting for at least 9 hours prior to their visit for blood draw. Subjects may drink plenty of water to stay hydrated but must refrain from eating or drinking anything other than water prior to every visit

Selection of subjects

Subjects had to satisfy the following inclusion and none of the exclusion criteria and had to accept the prohibitions and restrictions to be enrolled onto the study. The suitability of each subject to participate was confirmed prior to their acceptance onto the study by completion and review of a study specific pre-study questionnaire along with the results of the baseline blood pressure assessment and baseline Cholesterol blood work results.

Subject withdrawal

The participation of a subject in this study was discontinued for any of the following reasons:

- the subject wished to withdraw from study participation.
- if, in the opinion of the Investigator, it was in the best interest of the subject.
- suspected adverse effects from the test article.
- inter-current illness.
- violation of the prohibitions and restrictions.
- development of an exclusion criteria.

Subjects were free to withdraw at any time and needed not give a reason, however, every reasonable attempt was made to ascertain such reasons. The data for those subjects who were withdrawn was included in the final clinical data but was excluded from final data analysis. Subjects were not followed up with after their withdrawal from the study, except in the case of a serious adverse event. Withdrawn subjects were not replaced.

One hundred and thirty-eight (138) male and female subjects were consented and screened for study eligibility. Eighty-six (86) qualified subjects were enrolled on to the study and assigned test product. Seventy-three (73) subjects completed the study. The following tables are a summary of the demographics for subjects who were enrolled into each of the treatment groups for the study.

Table 1. Demographic summary

Borderline Hypertension Group – 1			
	All subjects	Active	Placebo
Age			
N	29	16	13
Mean	55.6	52.6	59.2
Standard Deviation	10.2	8.4	11.2
Median	55.0	50.0	60.0
Range	40.0 to 74.0	40.0 to 69.0	40.0 to 74.0
Race – N (%)			
White	22 (75.9)	13 (81.3)	9 (69.2)
Black	5 (17.2)	2 (12.5)	3 (23.1)
Bi-racial	2 (6.9)	1 (6.3)	1 (7.7)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Gender – N (%)			
Female	21 (72.4)	13 (81.3)	8 (61.5)
Male	8 (27.6)	3 (18.8)	5 (38.5)

High Cholesterol Group – 2			
	All subjects	Active	Placebo
Age			
N	4	2	2
Mean	53.5	57.0	50.0
Standard Deviation	5.7	4.2	5.7
Median	54.0	57.0	50.0
Range	46.0 to 60.0	54.0 to 60.0	46.0 to 54.0
Race – N (%)			
White	4 (100)	2 (100)	2 (100)
Black	0 (0.0)	0 (0.0)	0 (0.0)
Bi-racial	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Gender – N (%)			
Female	4 (100)	2 (100)	2 (100)
Male	0 (0.0)	0 (0.0)	0 (0.0)
Borderline Hypertension and High Cholesterol Group – 3			
	All subjects	Active	Placebo
Age			
N	53	37	16
Mean	52.6	52.2	53.6
Standard Deviation	9.1	9.2	9.1
Median	51.0	51.0	50.0
Range	38.0 to 73.0	38.0 to 73.0	40.0 to 69.0
Race – N (%)			
White	51 (96.2)	35 (94.6)	16 (100)
Black	1 (1.9)	1 (2.7)	0 (0.0)
Bi-racial	0 (0.0)	0 (0.0)	0 (0.0)
Asian	1 (1.9)	1 (2.7)	0 (0.0)
Gender – N (%)			
Female	42 (79.2)	30 (81.1)	12 (75.0)
Male	11 (20.8)	7 (18.9)	4 (25.0)

Test article

The test articles utilized in this study were Persimonal® Persimmon Leaf Extract (Lot# PLE-191201) and Placebo (Lot# PLE-191202). Both were provided in identical plain packaging and marked with the lot number only (located on the underside of each container dispensed to subjects) that identified treatment assigned so that both the subjects and the PI were blinded to treatment.

Subjects were instructed to take 2 capsules daily, containing 150mg each, with water or juice, preferably at the same time of day each day. The subjects were asked to take the test product with a meal and asked to return to each visit with their study product and diary for compliance assessments. Subjects assigned to the high Cholesterol or high LDL group were also instructed to arrive at each subsequent visit fasting for at least 9 hours prior to arrive at the testing center.

Study procedures

Visit 1 – Screening

Subjects attended the test center for screening and completed the informed consent form (ICF). Subjects were asked to provide their medical history and any concomitant medications being taken. They were screened for eligibility (inclusion/exclusion criteria) to be on the study, sitting blood pressure was taken, and a blood draw for lipid profile assessment was collected. Following assessments, subjects were dismissed. The blood pressures captured, and the blood lipid panel results collected at visit 1 were the baseline values used for the study.

The consulting physician reviewed the screening information collected (including blood pressure and blood lipid profile panel results) and indicated which subjects qualified for study enrollment. Subjects who qualified for both the hypertension and cholesterol group comprised the third group. Subjects were contacted by the testing facility to notify them if they qualified for study enrollment. Subjects who qualified were given an appointment time and instructions for their next visit.

Subjects who did not qualify due to blood pressure results that were too high or lipid profile results that were in excess of the consulting physician's recommendation were notified by study staff and were encouraged to discuss their results with their Primary Care Physician (PCP). Subjects who were disqualified were allowed to request a copy of their screening results so that they could share the results with their PCP.

Visit 2 – Enrollment

Qualifying subjects returned to the test center at their scheduled time. Subjects were queried for any changes to their health or medication and eligibility with inclusion/exclusion criteria was confirmed. Subjects were then assigned into one of three groups – those with borderline hypertension; those with high total cholesterol or LDL levels, or subjects who had both borderline hypertension and high cholesterol/high LDL. Subjects were issued the test product (Persimonal® Persimmon Leaf Extract or Placebo) in numerical bottle number order as they qualified for study enrollment as well as issued with written instructions on when and how to take the test product, and a diary to document use was also provided. Subjects were given a return appointment for their next visit and instructions to arrive at that visit fasting if they were in the groups requiring blood draw.

Visits 3 to 8 - (Days 7 (± 2 days), 30, 60, 90, 120, and 150 (± 5 days)

Subjects returned to the test center with their assigned test product and diary and were queried for any changes in their health or medications. Subject's product and diary were collected and reviewed for compliance. If necessary, subjects were issued new test product per their treatment assignment and were given a new diary to complete as appropriate. Subjects underwent either a blood pressure check or blood draw or both depending on what group they were assigned and were given an appointment time for their next visit. If subjects were found to be non-compliant with test article use, they were counselled on the proper use of the test supplements. If continued compliance was an issue (barring any side effect experienced) the subject was discontinued from the study.

Visit 9 - (Day 180 (± 5 days)

Final Visit: Subjects returned to the test center with their product and diary and were queried for any changes in their health or medications. Subject's test product and diary were collected and

reviewed for compliance. Subjects underwent either a final a blood pressure check and/or a blood draw. After all assessments were completed, the subject's participation in the study was considered complete.

Blood Pressure Assessments

Subjects were asked to sit in a chair and rest for five minutes prior to any blood pressure measurement being taken. The arm that the blood pressure measurement was taken at visit 1 was documented in the source. At each subsequent visit, blood pressure was taken from the same arm and in the same way as the first visit. Blood pressure was taken with an automatic blood pressure monitoring device. Once the blood pressure was confirmed for each subject at screening, the medical consultant used the following guidance for approval of a subject as having borderline hypertension and was allowed to continue in the study: 120/80 < Subject's BP ≤ 140/90.

If the systolic and diastolic blood pressure readings at any time met the following, the subjects blood pressure should have been re-taken. If the readings recorded were confirmed, the medical consultant was contacted, and an assessment of the subject's safety was made. If appropriate, the subject was stopped from further study participation. The subjects were referred to their Primary Care Provider for follow-up: Systolic: Less than or equal to 90 mmHg/Diastolic less than or equal to 60 mmHg; or Systolic: Greater than 140 mmHg/ Diastolic greater than 90 mmHg.

If BP was 180/110 (for either systolic or diastolic) or higher, the subject may have been experiencing a hypertensive crisis. If this was the case, the subject was referred for immediate medical attention.

Laboratory Assessments (Blood Draws)

Subjects were asked to fast for 9-12 hours prior to every blood draw (no food or drinks except for water). It was important to remind subjects to still drink plenty of water during the fasting period to prevent dehydration. If the subject came to a visit without fasting the required 9-12 hours, the visit was to have been rescheduled within the visit window of that specific visit.

A standard lipid profile (including total cholesterol, triglycerides, HDL, LDL, cholesterol/ HDL ratio calculated, and non-HDL Cholesterol calculated) was completed at each required visit. The medical consultant reviewed the lipid panel results for each subject at screening and used the following guidance for approval of a subject as having high cholesterol or high LDL based on the lipid panel results as follows: Total Cholesterol between 5 mmol/L and 6 mmol/L; LDL between 3 mmol/L and 4 mmol/L.

For all subsequent lipid panel results, any levels observed above the initial baseline results at the completion of the study were reviewed by the medical consultant and if warranted, the subject was referred to their Primary Care Physician for follow-up.

Method of statistical analysis

The source data are the LDL, Total Cholesterol and Systolic and Diastolic blood pressure readings. There are 3 treatment groups, within each treatment group subjects were assigned to either Treatment (Persimonal® Persimmon Leaf Extract Lot# PLE-191201) or Placebo (Lot #PLE-191202).

Separate analyses were conducted separately for the following three groups:

Borderline Hypertension Group – 1	Systolic and Diastolic blood pressure readings were taken at Baseline and post-treatment at Days 7, 30, 60, 90, 120, 150 and 180. This group did not have LDL or Total Cholesterol assessments.
High Cholesterol Group – 2	LDL and Total Cholesterol Assessments were taken at Baseline and post-treatment at Days 7, 30, 60, 90, 120, 150 and 180. Blood pressure readings were done at Baseline and 180 days as a Safety check only, data was not entered nor listed.
Borderline Hypertension and High Cholesterol Group – 3	LDL and Total Cholesterol Assessments and Systolic and Diastolic blood pressure readings were taken at Baseline and post-treatment at Days 7, 30, 60, 90, 120, 150 and 180.

The post-treatment changes from baseline were analyzed within-treatment using Student's t-test for paired data and between-treatment using analysis of covariance with the baseline measurement as the covariate.

All statistical tests of hypothesis employed a level of significance of 0.05 and no adjustments were made for the number of tests performed. The number of subjects that were enrolled in group 2 was not sufficient to perform statistical analysis within the treated vs placebo group.

Table 2. Systolic Blood Pressure: Significant within-treatment t-test p-values are noted with an asterisk (*). Significant between-treatment ANCOVA p-values are noted with two asterisks (**).

Treatment	Evaluation	N	Treatment Mean	Mean Difference from Baseline	Within-Treatment t-test p-value	Percent Change Mean [1]	Percent Change Subject [2]	Number Improved	Percent Improved	Difference Between Treatments	Between-Treatment ANCOVA p-value
Persimonal®	Baseline	16	149.63								
	Day 7	16	142.44	-7.19	0.0016*	-4.8%	-4.7%	14	87.5%	-3.88	0.3220
	Day 30	16	126.38	-13.25	<0.0001*	-8.9%	-8.8%	15	93.8%	-3.40	>0.5000
	Day 60	16	134.63	-15.00	0.0012*	-10.0%	-9.6%	14	87.5%	-7.62	>0.5000
	Day 90	16	129.94	-19.69	<0.0001*	-13.2%	-12.9%	15	93.8%	-13.23	0.0095**
	Day 120	16	131.75	-17.88	<0.0001*	-11.9%	-11.5%	14	87.5%	-10.95	0.0556
	Day 150	16	129.44	-20.19	<0.0001*	-13.5%	-13.1%	15	93.8%	-14.34	0.0326**
	Day 180	16	130.13	-19.50	<0.0001*	-13.0%	-12.7%	15	93.8%	-16.73	0.0043**
Placebo	Baseline	13	141.38								
	Day 7	13	138.08	-3.31	0.0246*	-2.3%	-2.3%	11	84.6%		
	Day 30	13	131.54	-9.85	0.0009*	-7.0%	-6.8%	13	100.0%		
	Day 60	13	134.00	-7.38	0.0105*	-5.2%	-5.0%	11	84.6%		
	Day 90	13	134.92	-6.46	0.0211*	-4.6%	-4.2%	11	84.6%		
	Day 120	13	134.46	-6.92	0.0162*	-4.9%	-4.6%	11	84.6%		
	Day 150	13	135.54	-5.85	0.1654	-4.1%	-3.8%	8	61.5%		
	Day 180	13	138.62	-2.77	0.4139	-2.0%	-1.7%	8	61.5%		

** Significant change from baseline*
*** Significant change between treatments*

Table 3. Diastolic Blood Pressure: Significant within-treatment t-test p-values are noted with an asterisk (*). Significant between-treatment ANCOVA p-values are noted with two asterisks (**).

Treatment	Evaluation	N	Treatment Mean	Mean Difference from Baseline	Within-Treatment t-test p-value	Percent Change Mean [1]	Percent Change Subject [2]	Number Improved	Percent Improved	Difference Between Treatments	Between-Treatment ANCOVA p-value
Persimonal®	Baseline	16	93.81								
	Day 7	16	91.88	-1.94	0.1806	-2.1%	-1.9%	12	75.0%	0.37	0.1873
	Day 30	16	86.38	-7.44	<0.0001*	-7.9%	-7.8%	14	87.5%	-0.28	0.4118
	Day 60	16	85.81	-8.00	0.0032*	-8.5%	-8.1%	14	87.5%	-3.69	>0.5000
	Day 90	16	86.44	-7.38	0.0002*	-7.9%	-7.7%	14	87.5%	-4.30	0.2571
	Day 120	16	85.38	-8.44	<0.0001*	-9.0%	-8.7%	15	93.8%	-3.98	>0.5000
	Day 150	16	85.31	-8.50	0.0011*	-9.1%	-8.5%	14	87.5%	-5.50	>0.5000
	Day 180	16	86.94	-6.88	0.0002*	-7.3%	-7.0%	15	93.8%	-5.80	0.3169
Placebo	Baseline	13	88.54								
	Day 7	13	86.23	-2.31	0.3359	-2.6%	-2.0%	11	84.6%		
	Day 30	13	81.38	-7.15	0.0088*	-8.1%	-7.4%	12	92.3%		
	Day 60	13	84.23	-4.31	0.0882	-4.9%	-4.4%	10	76.9%		
	Day 90	13	85.46	-3.08	0.1174	-3.5%	-3.3%	8	61.5%		
	Day 120	13	84.08	-4.46	0.1300	-5.0%	-4.6%	10	76.9%		
	Day 150	13	85.54	-3.00	0.2512	-3.4%	-2.9%	6	46.2%		
	Day 180	13	87.46	-1.08	>0.5000	-1.2%	-0.6%	5	38.5%		

** Significant change from baseline*
*** Significant change between treatments*

Results and discussion

Borderline Hypertension Group – 1 Systolic

Systolic blood pressure analysis indicated subjects assigned treatment with Persimonal® Persimmon Leaf Extract had statistically significant reductions in mean Systolic blood pressure values compared to baseline values at all study assessment timepoints. Subjects assigned to the Placebo treatment had statistically significant reductions in mean Systolic blood pressure values compared to baseline values at Days 7, 30, 60, 90, and 120. Between treatment analysis indicated statistically significant differences in Systolic blood pressure values favoring Persimonal® Persimmon Leaf Extract at Days 90, 150 and 180.

Borderline Hypertension Group – 1 Diastolic

Diastolic blood pressure analysis indicated subjects assigned treatment with Persimonal® Persimmon Leaf Extract had statistically significant reductions in mean Diastolic blood pressure values compared to baseline values at Days 30, 60, 90, 120, 150, and 180. Subjects assigned to the Placebo treatment had statistically significant reductions in mean Diastolic blood pressure values compared to baseline values at Day 30. Between treatment analysis indicated no statistically significant differences in Diastolic blood pressure values.

High Cholesterol Group – 2 LDL

Due to the low number of subjects enrolled into this treatment group, no analysis was performed on this group.

High Cholesterol Group – 2 Total Cholesterol

Due to the low number of subjects enrolled into this treatment group, no analysis was performed on this group.

Borderline Hypertension and High Cholesterol Group – 3 Systolic

Borderline Hypertension and High Cholesterol Group – 3 Diastolic

Overall, there was no statistically significant changes in mean Systolic or Diastolic blood pressure for subjects assigned to Persimonal® Persimmon Leaf Extract treatment. Subjects assigned to the Placebo treatment had no statistically significant changes in mean Systolic blood pressure values compared to baseline but had statistically significant lower mean Diastolic blood pressure values at day 30 only when compared to baseline.

Table 4. LDL: Significant within-treatment t-test p-values are noted with an asterisk (*). Significant between-treatment ANCOVA p-values are noted with two asterisks (**).

Treatment	Evaluation	N	Treatment Mean	Mean Difference from Baseline	Within-Treatment t-test p-value	Percent Change Mean [1]	Percent Change Subject [2]	Number Improved	Percent Improved	Difference Between Treatments	Between-Treatment ANCOVA p-value
Persimonal®	Baseline	2	3.55								
	Day 7	2	3.70	0.15	>0.5000	4.2%	3.9%	1	50.0%		0.3784
	Day 30	2	3.70	0.15	0.2048	4.2%	4.2%	0	0.0%		Not done
	Day 60	1	4.50	0.80	Not done	22.5%	21.6%	0	0.0%		Not done
	Day 90	1	1.70	-2.00	Not done	-56.3%	-54.1%	1	100.0%		Not done
	Day 120	1	2.70	-1.00	Not done	-28.2%	-27.0%	1	100.0%		Not done
	Day 150	1	2.50	-1.20	Not done	-33.8%	-32.4%	1	100.0%		Not done
	Day 180	1	2.50	-1.20	Not done	-33.8%	-32.4%	1	100.0%		Not done
Placebo	Baseline	2	3.50								
	Day 7	1	4.05	0.55	0.0577	15.7%	15.7%	0	0.0%		
	Day 30	1	2.80	-0.40	Not done	-11.4%	-12.5%	1	100.0%		
	Day 60	1	2.40	-0.80	Not done	-22.9%	-25.0%	1	100.0%		
	Day 90	1	2.20	-1.00	Not done	-28.6%	-31.3%	1	100.0%		
	Day 120	1	2.70	-0.50	Not done	-14.3%	-15.6%	1	100.0%		
	Day 150	1	3.60	0.40	Not done	11.4%	12.5%	0	0.0%		
	Day 180	1	3.30	0.10	Not done	2.9%	3.1%	0	0.0%		

** Significant change from baseline*

*** Significant change between treatments*

Not done = test not done due to insufficient data (i.e. 1 subject)

Table 5. Total Cholesterol: Significant within-treatment t-test p-values are noted with an asterisk (*). Significant between-treatment ANCOVA p-values are noted with two asterisks (**).

Treatment	Evaluation	N	Treatment Mean	Mean Difference from Baseline	Within-Treatment t-test p-value	Percent Change Mean [1]	Percent Change Subject [2]	Number Improved	Percent Improved	Difference Between Treatments	Between-Treatment ANCOVA p-value
Persimonal®	Baseline	2	5.40								
	Day 7	2	5.70	0.30	Not done	5.6%	5.6%	0	0.0%	-0.05	>0.5000
	Day 30	2	5.45	0.05	0.5000	0.9%	0.9%	0	0.0%	0.35	Not done
	Day 60	1	6.40	0.70	Not done	13.0%	12.3%	0	0.0%		Not done
	Day 90	1	3.30	-2.40	Not done	-44.4%	-42.1%	1	100.0%		Not done
	Day 120	1	4.30	-1.40	Not done	-25.9%	-24.6%	1	100.0%		Not done
	Day 150	1	4.20	-1.50	Not done	-27.8%	-26.3%	1	100.0%		Not done
	Day 180	1	4.20	-1.50	Not done	-27.8%	-26.3%	1	100.0%		Not done
Placebo	Baseline	2	5.80								
	Day 7	1	6.15	0.35	0.2578	6.0%	6.1%	0	0.0%		
	Day 30	1	5.30	-0.30	Not done	-5.2%	-5.4%	1	100.0%		
	Day 60	1	5.10	-0.50	Not done	-8.6%	-8.9%	1	100.0%		
	Day 90	1	5.30	-0.30	Not done	-5.2%	-5.4%	1	100.0%		
	Day 120	1	5.10	-0.30	Not done	-8.6%	-8.9%	1	100.0%		
	Day 150	1	6.30	0.70	Not done	12.1%	12.5%	0	0.0%		
	Day 180	1	5.70	0.10	Not done	1.7%	1.8%	0	0.0%		

** Significant change from baseline*
*** Significant change between treatments*
Not done = test not done due to insufficient data (i.e. 1 subject)

Table 6. Systolic Blood Pressure: Significant within-treatment t-test p-values are noted with an asterisk (*). Significant between-treatment ANCOVA p-values are noted with two asterisks (**).

Treatment	Evaluation	N	Treatment Mean	Mean Difference from Baseline	Within-Treatment t-test p-value	Percent Change Mean [1]	Percent Change Subject [2]	Number Improved	Percent Improved	Difference Between Treatments	Between-Treatment ANCOVA p-value
Persimonal®	Baseline	37	132.22								
	Day 7	37	133.65	1.43	>0.5000	1.1%	2.4%	17	45.9%	3.36	0.2693
	Day 30	35	132.17	-1.06	>0.5000	-0.8%	0.4%	16	45.7%	6.23	0.0360**
	Day 60	35	130.00	-3.23	0.2393	-2.4%	-1.4%	20	57.1%	-7.09	0.2146
	Day 90	34	131.91	-1.12	>0.5000	-0.8%	0.3%	17	50.0%	-5.70	0.3944
	Day 120	35	132.26	-0.97	>0.5000	-0.7%	0.3%	17	48.6%	-10.72	0.0715
	Day 150	33	129.33	-1.94	>0.5000	-1.5%	-0.6%	18	54.5%	-10.34	0.1818
	Day 180	33	127.12	-4.15	0.1598	-3.1%	-2.2%	20	60.6%	-6.04	0.4201
Placebo	Baseline	16	128.63								
	Day 7	14	125.36	-1.93	>0.5000	-1.5%	-1.1%	7	50.0%		
	Day 30	14	120.00	-7.29	0.0501	-5.7%	-5.4%	11	78.6%		
	Day 60	14	131.14	3.86	0.1704	3.0%	3.4%	6	42.9%		
	Day 90	12	133.17	4.58	0.2007	3.6%	4.3%	4	33.3%		
	Day 120	12	138.33	9.75	0.0597	7.6%	8.2%	3	25.0%		
	Day 150	10	134.30	8.40	0.0780	6.5%	7.1%	2	20.0%		
	Day 180	9	128.78	1.89	>0.5000	1.5%	1.4%	4	44.4%		

** Significant change from baseline*
*** Significant change between treatments*

Between treatment comparison showed that the Placebo treatment group had statistically significant lower Diastolic blood pressure values compared to the active treatment at day 30.

This lack of effectiveness on blood pressure may be due to the sequence of study procedures. In most cases, blood pressure was taken first followed by blood draw. The anticipation of having a blood draw may have elevated the subject's blood pressure, however, it is unknown that this was actually the case.

Table 7. Diastolic Blood Pressure: Significant within-treatment t-test p-values are noted with an asterisk (*). Significant between-treatment ANCOVA p-values are noted with two asterisks (**).

Treatment	Evaluation	N	Treatment Mean	Mean Difference from Baseline	Within-Treatment t-test p-value	Percent Change Mean [1]	Percent Change Subject [2]	Number Improved	Percent Improved	Difference Between Treatments	Between-Treatment ANCOVA p-value
Persimonal®	Baseline	37	85.32								
	Day 7	37	86.24	0.92	>0.5000	1.1%	1.8%	19	51.4%	3.85	0.3425
	Day 30	35	83.77	-1.43	0.3816	-1.7%	-1.4%	22	62.9%	5.21	0.1074
	Day 60	35	86.23	1.03	>0.5000	1.2%	1.7%	16	45.7%	1.24	>0.5000
	Day 90	34	88.38	3.09	0.1204	3.6%	4.4%	14	41.2%	0.42	>0.5000
	Day 120	35	86.46	1.26	0.3713	1.5%	2.2%	15	42.9%	-2.24	0.2683
	Day 150	33	87.82	3.48	0.2158	4.1%	4.8%	16	48.5%	-2.02	>0.5000
	Day 180	33	86.18	1.85	0.2781	2.2%	2.7%	13	39.4%	-1.04	>0.5000
Placebo	Baseline	16	85.56								
	Day 7	14	83.21	-2.93	0.2631	-3.4%	-3.1%	8	57.1%		
	Day 30	14	79.50	-6.64	0.0346*	-7.8%	-7.3%	10	71.4%		
	Day 60	14	85.93	-0.21	>0.5000	-0,3%	0.0%	6	42.9%		
	Day 90	12	88.42	2.67	0.1211	3.1%	3.5%	3	25.0%		
	Day 120	12	89.25	3.50	0.0987	4.1%	4.4%	3	25.0%		
	Day 150	10	90.60	5.50	0.0968	6.4%	6.9%	3	30.0%		
	Day 180	9	88.78	2.89	0.3917	3.4%	3.4%	3	33.3%		

** Significant change from baseline*
*** Significant change between treatments*

Table 8. LDL: Significant within-treatment t-test p-values are noted with an asterisk (*). Significant between-treatment ANCOVA p-values are noted with two asterisks (**)

Treatment	Evaluation	N	Treatment Mean	Mean Difference from Baseline	Within-Treatment t-test p-value	Percent Change Mean [1]	Percent Change Subject [2]	Number Improved	Percent Improved	Difference Between Treatments	Between-Treatment ANCOVA p-value
Persimonal®	Baseline	36	3.63								
	Day 7	34	3.31	-0.33	0.0326*	-9.1%	-7.2%	23	67.6%	-0.14	>0.5000
	Day 30	30	3.45	-0.23	0.0538	-6.4%	-4.8%	16	53.3%	-0.05	>0.5000
	Day 60	29	3.34	-0.35	0.0485*	-9.7%	-7.6%	17	58.6%	-0.17	>0.5000
	Day 90	26	3.27	-0.32	0.0085*	-8.9%	-8.4%	18	69.2%	-0.04	>0.5000
	Day 120	24	3.46	-0.22	0.0114*	-6.1%	-5.6%	15	62.5%	0.09	0.4327
	Day 150	22	3.59	-0.13	0.2552	-3.6%	-3.2%	14	63.6%	-0.05	>0.5000
	Day 180	22	3.63	-0.08	>0.5000	-2.1%	-1.3%	12	54.5%	0.01	>0.5000
Placebo	Baseline	16	3.63								
	Day 7	13	3.42	-0.19	0.1257	-5.3%	-6.3%	7	53.8%		
	Day 30	14	3.39	-0.18	0.1947	-4.9%	-4.4%	5	35.7%		
	Day 60	14	3.39	-0.19	0.3318	-5.1%	-4.5%	7	50.0%		
	Day 90	13	3.23	-0.28	0.0655	-7.9%	-7.4%	9	69.2%		
	Day 120	9	3.22	-0.31	0.0221*	-8.6%	-8.7%	7	77.8%		
	Day 150	7	3.46	-0.09	>0.5000	-2.4%	-2.2%	4	57.1%		
	Day 180	7	3.46	-0.09	>0.5000	-2.4%	-2.1%	3	42.9%		

** Significant change from baseline*
*** Significant change between treatments*

Borderline Hypertension and High Cholesterol Group – 3 LDL

The lipid profiles of the subjects randomized to treatment with Persimonal® Persimmon Leaf Extract showed a statistically significant reduction in the mean LDL values compared to mean baseline values at the following timepoints: Day 7, Day 60, Day 90, and Day 120. Subjects randomized to treatment with the Placebo showed a statistically significant reduction in mean LDL values compared to baseline at Day 120. Between treatment analysis indicated no statistically significant differences between the two treatments at any timepoint.

Table 9. Total Cholesterol: Significant within-treatment t-test p-values are noted with an asterisk (*). Significant between-treatment ANCOVA p-values are noted with two asterisks (**).

Treatment	Evaluation	N	Treatment Mean	Mean Difference from Baseline	Within-Treatment t-test p-value	Percent Change Mean [1]	Percent Change Subject [2]	Number Improved	Percent Improved	Difference Between Treatments	Between-Treatment ANCOVA p-value
Persimonal®	Baseline	37	5.78								
	Day 7	35	5.44	-0.37	0.0371*	-6.3%	-5.2%	22	62.9%	-0.22	0.4121
	Day 30	31	5.62	-0.24	0.0409*	-4.1%	-3.3%	17	54.8%	-0.07	>0.5000
	Day 60	30	5.55	-0.32	0.1025	-5.6%	-4.2%	19	63.3%	-0.34	0.2995
	Day 90	27	5.54	-0.19	0.1123	-3.3%	-3.0%	16	59.3%	0.05	>0.5000
	Day 120	25	5.57	-0.21	0.0205*	-3.6%	-3.4%	18	72.0%	0.04	>0.5000
	Day 150	23	5.69	-0.16	0.2489	-2.7%	-2.5%	16	69.6%	-0.04	>0.5000
	Day 180	23	5.81	-0.03	>0.5000	-0.6%	-0.1%	12	52.2%	0.14	>0.5000
Placebo	Baseline	16	5.76								
	Day 7	13	5.63	-0.15	0.2894	-2.5%	-2.7%	6	46.2%		
	Day 30	14	5.57	-0.16	0.2136	-2.9%	-2.6%	8	57.1%		
	Day 60	14	5.75	0.01	>0.5000	0.2%	0.5%	6	42.9%		
	Day 90	13	5.46	-0.24	0.1085	-4.1%	-3.8%	8	61.5%		
	Day 120	9	5.49	-0.24	0.0191*	-4.2%	-4.2%	8	88.9%		
	Day 150	7	5.59	-0.11	0.4758	-2.0%	-1.9%	5	71.4%		
	Day 180	7	5.53	-0.17	0.4386	-3.0%	-2.6%	4	57.1%		

** Significant change from baseline*
*** Significant change between treatments*

Borderline Hypertension and High Cholesterol Group – 3 Total Cholesterol

The lipid profiles of the subjects randomized to treatment with Persimonal® Persimmon Leaf Extract showed a statistically significant reduction in the mean Total Cholesterol values compared to mean baseline values at the following timepoints: Day 7, Day 30, and Day 120. Subjects randomized to treatment with the Placebo showed a statistically significant reduction in mean LDL values compared to baseline at Day 120. Between treatment analysis indicated no statistically significant differences between the two treatments at any timepoint.

Conclusion

The purpose of this study was to define whether administration of Persimonal™ daily would improve the cardiovascular system in subjects who were experiencing borderline hypertension, high total cholesterol, or high LDL levels or both high blood press and high total cholesterol and/or high LDL. The design of the clinical trial was appropriate to reveal that Persimmon Leaf Extract as a nutritional supplement ingested over 180 days was safe and efficacious in improving cardiovascular health indicators. The results of the study provide data supporting the view that Persimonal® may be administered to patients as a potential cardiovascular dietary supplement. Further research will elucidate additional benefits from this multifunctional source.

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