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Perilla seed oil as an adjunctive treatment with statins improves lipid profiles in elderly patients: A post hoc data analysis

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ABSTRACT

Background: Dyslipidemia is characterized by abnormal lipid concentrations in the bloodstream, heightening the risk of atherosclerosis. While statins are primarily prescribed to treat dyslipidemia, not all patients benefit from them for various reasons, such as intolerance, myopathy, and hepatotoxicity. *Perilla frutescens* (L.) Britton, traditionally grown in East Asia, has been used for various therapeutic purposes. The seed oil of this plant is prosperous in omega-3 polyunsaturated fatty acids. Previous research found the efficacy of perilla **(***P. frutescens***)** seed oil in reducing cholesterol in patients with dementia. Our study aimed to determine if the lipid-lowering effects of *P. frutescens* seed oil occur on their own or alongside statin treatments by conducting a retrospective analysis of existing data to assess its efficacy in improving lipid profiles among the elderly.

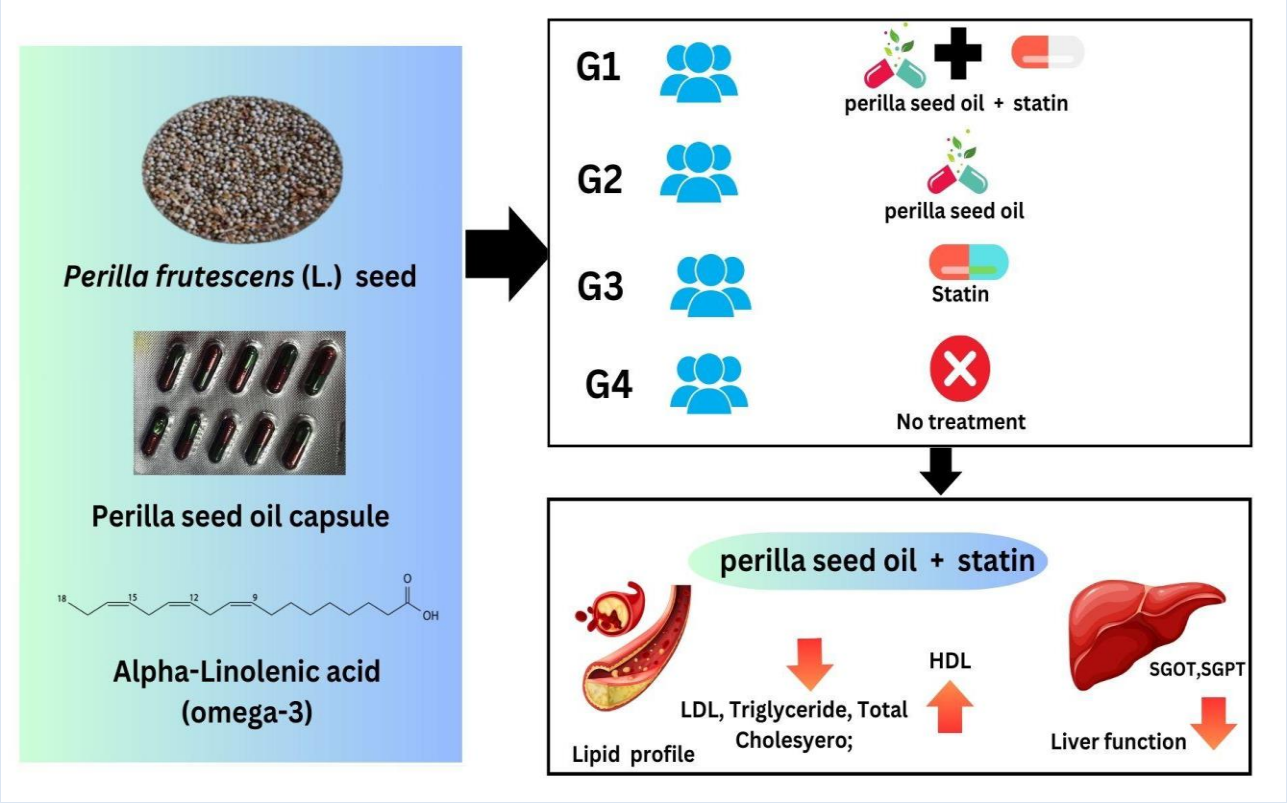
Objective: This study aimed to understand if *P. frutescens* seed oil inherently possesses lipid-lowering properties or if these effects are amplified when combined with statins.

Methods: A retrospective post hoc analysis was performed on 182 geriatric patients previously involved in a dementia study. These patients were categorized into four groups: those administered both *P. frutescens* seed oil and a statin (G1), only *P. frutescens* seed oil (G2), only a statin (G3), and neither (G4). The outcomes evaluated post-intervention included lipid profiles, liver and renal functions, complete blood count, and neutrophils to lymphocytes and platelets (N/LP) ratio.

Results: Patients in G1 exhibited the most pronounced reductions in total cholesterol and LDL-C levels, suggesting a potential synergistic effect when *P. frutescens* seed oil is combined with statins. Liver enzyme levels remained stable across all groups, suggesting the hepatic safety of *P. frutescens* seed oil even when co-administered with statins.

Conclusion: *P. frutescens* seed oil, particularly when used alongside statins, exhibits the potential to improve lipid profiles and may also offer liver protection. However, extended studies are necessary to understand its therapeutic significance in cardiovascular disease management fully.

Keywords: *Perilla frutescens*, omega-3, statins, lipid profile**,** elderly, hepatoprotection, functional food, bioactive compound



INTRODUCTION

Dyslipidemia is characterized by aberrant lipid concentrations in the circulatory system, which may include elevated levels of low-density lipoprotein cholesterol (LDL-C), diminished levels of high-density lipoprotein cholesterol (HDL-C), and heightened triglyceride (TG) concentrations. Such imbalances are associated with the onset of atherosclerosis [1]. Statins are the predominant pharmacological agents prescribed for dyslipidemia due to their efficacy in considerably mitigating the risk associated with atherosclerosis [2]). The therapeutic mechanism of these stains involves the reduction of total cholesterol, LDL-C, and TG concentrations and elevation of HDL-C [3]. Clinicians frequently employ LDL-C concentrations to determine the appropriate statin treatment intensity. Patients exhibiting a heightened risk for atherosclerosis require more stringent LDL-C thresholds compared to those with

lower associated risks [4]. However, it is noteworthy that a segment of patients might require supplementary pharmacological interventions to achieve their LDL-C targets [5]. Additionally certain patients might exhibit intolerance to statins, manifested in side effects such as myopathy and hepatotoxicity [6]. Consequently, it is imperative to understand that statins might not universally satisfy all dyslipidemia patients' needs.

Perilla frutescens (L.) Britton, a member of the Lamiacene family (Also knonw as "Ngakeemon" in Thai) an herbal plant traditionally cultivated in East Asian nations like Japan, Korea, China, Laos, and Thailan [7]. Functional foods refer to natural or processed foods containing of biologically active compounds in effective but non-toxic amounts which offer health benefits by using certain biomarkers verified by clinical research to support better health, minimize the risk of chronic/viral diseases and cope with the symptoms [8]. *P. frutescens* is a functional food containing bioactive compounds that can benefit human health such as essential oils, fatty acids, flavonoids and triterpenes, phenolic compounds/polyphenols. The biological activities of *P.frutescens* range from anti-inflammatory, antibacterial, antifungal, antidepressant, anticancer, anti-obesity, antioxidant, anti-osteoporosis, anti-ulcer to lowering the cognitive and mental decline caused by aging [9].. A salient feature of *P. frutescens* is its seed oil, which is a rich reservoir of omega-3 polyunsaturated fatty acids, boasting an alpha-linolenic acid. This specific fatty acid acts as a precursor to eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA), which are known for their myriad health advantages ([10]. Previous investigations on the efficacy of *P. frutescens* seed oil as a supplementary treatment in elderly participants with mild to moderate dementia highlighted its potential to diminish total cholesterol and LDL-C concentrations [11]. We aimed to determine whether the lipid-lowering properties of *P. frutescens* seed oil are inherent or if they manifest in conjunction with statin treatments. To this end, we executed a retrospective, post hoc analysis of existing data, with the overarching goal of investigating the potential of *P. frutescens* seed oil to ameliorate lipid profiles in geriatric populations.

MATERIALS AND METHODS

Design and study group: A retrospective post hoc data analysis was conducted on the medical records of 182 patients previously involved in a study examining the efficacy of ***P. frutescens*** seed oil for elderly patients with mild to moderate dementia. This previous study was executed at Thammasat University Hospital between January 2014 and December 2017 [11]. It is registered with the Thai Clinical Trials Registry under registration number 142/2556.

Patients eligible for inclusion were outpatients of the Internal Medicine Department at Thammasat University Hospital. The diagnosis was established by a physician using the International Classification of Diseases, 10th edition (ICD10) codes. Eligible patients aged between 50-90 years had scores ranging from 10-23 on the Thai Mental State Examination (TMSE) or 7-20 on the Thai Montreal Cognitive Assessment (MoCA-Thai). They were diagnosed with mild to moderate dementia as per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and they could recognize obects, and communicate within certain parameters. All participants gave written informed consent for their participation in the study.

Intervention program: Of the 182 eligible patients, participants were segregated into four distinct groups:

- Group 1 (G1): participants were administered both ***P. frutescens*** seed oil (two capsules thrice daily before meals, totaling three grams/day) and a statin for a period of six months.
- Group 2 (G2): participants were given only the ***P. frutescens*** seed oil at the previously prescribed dose for six months.

- Group 3 (G3): participants administered only a statin.
- Group 4 (G4): participants receiving neither *P. frutescens* seed oil nor statin.

Follow-up: Regarding post-intervention, the participants in four groups underwent two follow-up visits in month 3 and month 6. Each visit measured various clinical parameters including lipid profiles (total cholesterol, triglyceride, HDL-C, LDL-C, LDL/HDL ratio), liver function levels (SGOT, SGPT), renal function levels (BUN, creatinine, and eGFR), complete blood count (CBC) attributes like red blood cell count (RBC), hematocrit (Hct), and white blood cell count (WBC), and the neutrophils to lymphocytes and platelets (N/LP) ratio. Any adverse events during the intervention were systematically recorded.

Ethical Compliance: The faculty of medicine's human research ethics committee at Thammasat University approved this study validated under EC number MTU-EC-OO-0-260/64.

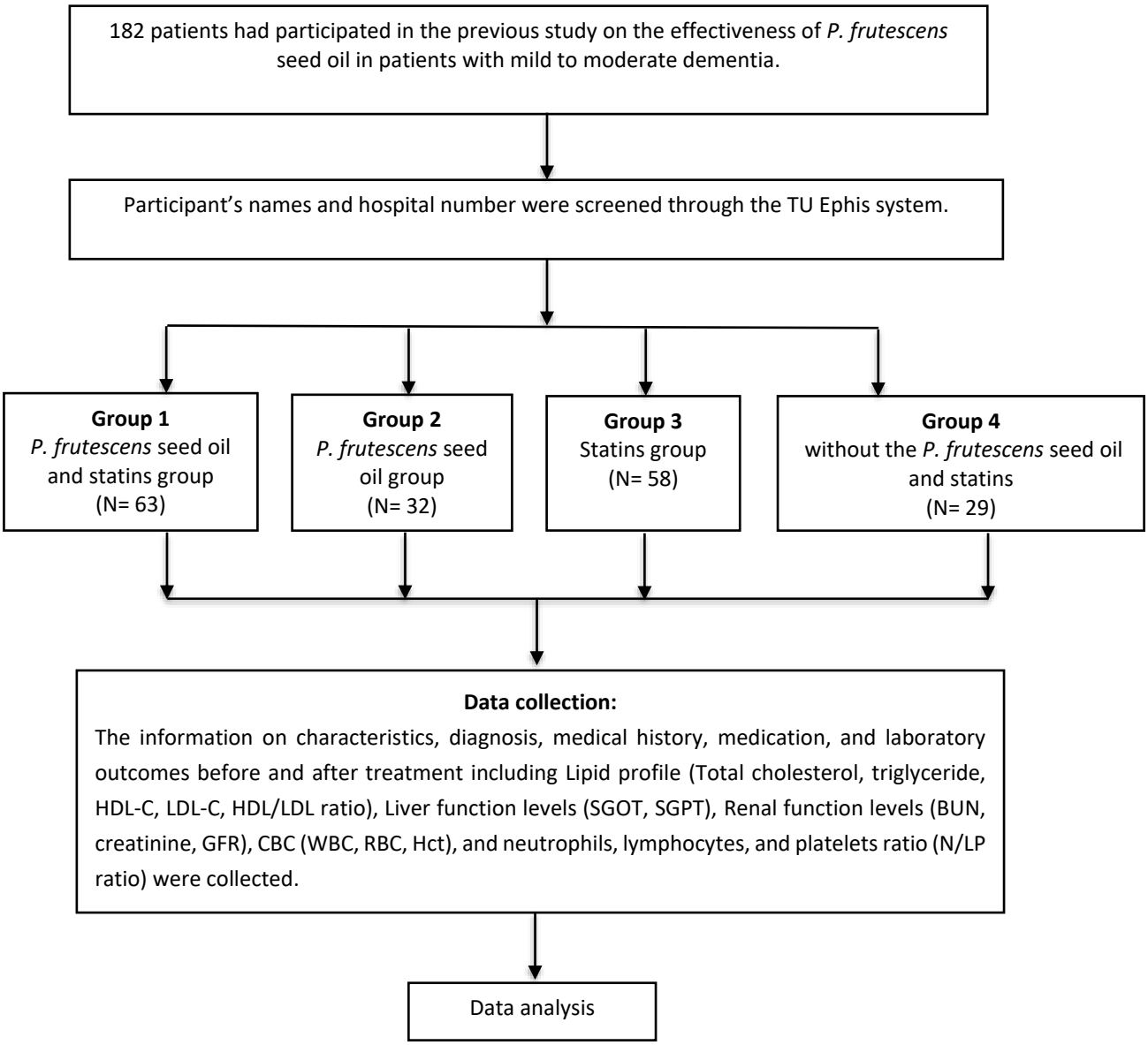


Figure. 1 The research process flowchart

Data Collection: Participant data, retrieved from Thammasat University Hospital's electronic database as per ICD10 specifications, encompassed demographic details, diagnoses, medical histories, medications, and both pre-intervention and post-intervention laboratory results. The results included the lipid profile, liver and renal function levels, CBC parameters, and the N/LP ratio over sixth months.

Statistical Analysis: Baseline characteristics and laboratory outcomes were assessed using descriptive statistics - percentage, mean, standard deviation (SD), and standard error of the mean (SEM). The laboratory results were statistically analyzed employing paired t-tests and one-way ANOVA. All statistical computations were performed using SPSS software, with a p-value threshold of <0.05 deemed statistically significant in one-way ANOVA.

RESULTS

Participants: In this study, 182 participants were categorized into four groups: G1 (n=63, 34.61%), G2 (n=32, 17.58%), G3 (n=58, 31.86%), and G4 (n=29, 15.93%). Demographic information, medical history and laboratory details were presented in Table 1.

Table 1. Demographic and clinical characteristics of participants

Laboratory	G1 N= 63 (34.61%)	G2 N=32 (17.58%)	G3 N= 58 (31.86%)	G4 N= 29 (15.93%)	p-value
Gender					
Male (N=81, 44.50%)	33 (52.38%)	11 (34.37%)	24 (41.37%)	13 (44.82%)	-
Female (N=101, 55.49%)	30 (47.61%)	21 (65.62%)	34 (58.62%)	16 (55.17%)	-
Age, mean ±SD	76.87±8.87	76.5±8.96	74.13±8.29	77.13±9.96	-
Smoking (N=30, 16.48%)	9 (0.01%)	2 (6.25%)	16 (27.58%)	3 (10.34%)	-
Alcohol (N=34, 18.68%)	11 (17.46%)	2 (6.25%)	16 (27.58%)	5 (17.24%)	-
Underlying disease (N=109, 59.89%)	35 (55.55%)	8 (25%)	43 (74%)	23 (79.31%)	-
Lipid profile (mean ±SE)					
Total cholesterol <200 mg/dL	163.58±6.03	196.60±8.37	178.64±6.84	172.44±7.04	0.50
Triglyceride <150 mg/dL	115.77±8.63	124.53±10.11	114.08±7.18	139.51±17.22	0.18
HDL-C F >40 mg/dL M >50 mg/dL	55.41±2.08	58.35±3.21	56.77±2.00	50.59±2.93	0.98
LDL-C <100 mg/dL	89.01±4.56	115.39±6.94	100.98±5.57	96.25±5.25	0.36
LDL/HDL ratio <3.5	1.74±.11	2.09±.14	1.95±0.14	2.02±0.13	0.09
Blood sugar					
FBS	111.27±4.62	113.19±8.16	111.14±3.21	113.24±5.47	0.67

Laboratory	G1 N= 63 (34.61%)	G2 N=32 (17.58%)	G3 N= 58 (31.86%)	G4 N= 29 (15.93%)	p-value
70-100 mg/dL					
HbA1c 4.8-6.0% High value>6.5 %	7.76±1.61	5.86±0.15	6.15±0.11	6.14±0.25	0.16
Liver function levels					
SGOT 0-35 IU/L	25.74±0.94	26.16±2.04	29.000±1.44	29.80±2.03	0.26
SGPT 0-48 IU/L	32.30±1.48	33.66±3.90	33.50±2.47	31.49±6.42	0.11
Renal function levels					
BUN 10-20 mg/dL	15.77±0.92	14.71±0.96	14.34±0.63	17.02±1.41	0.35
Creatinine 0.6-1.2 mg/dL	1.04±0.03	0.94±0.06	1.02±0.04	1.15±0.07	0.82
GFR 125 ml./s	68.87±2.64	72.02±3.70	70.43±2.82	58.48±3.96	0.90
CBC					
WBC 4-11 x 10^3 cell/mm^3	6.91±0.25	6.49±0.46	8.03±1.20	6.90±0.49	0.67
RBC 4.5-6.0 x 10^6 cell/mm^3	4.32±0.07	4.13±0.10	4.37±0.07	4.38±0.14	0.43
Hct Male 40-54 mg/dL Female 37-47 mg/dL	37.30±0.61	35.40±0.82	37.78±0.46	37.45±0.96	0.30
N/LP ratio <4.86	1.23±0.12	1.54±0.32	1.15±0.06	1.32±0.28	0.02*

P-value to compare between groups by one-way ANOVA. *P-value <0.05 was considered statistically significant.

Upon comparison of baseline data with the results in month six (Table 2), lipid profiles in G1, G2, and G3 showed a decline. In G1, Perilla seed oil and statins improved certain parameters including total cholesterol, LDL-C levels, and the LDL/HDL ratio statistically significantly. Total cholesterol decreased from 163.93 mg/dL to 151.68 mg/dL (p<0.01). LDL-C levels dropped from 88.88 mg/dL to 77.34 mg/dL (p<0.02). The LDL/HDL ratio significantly reduced from 1.73 to 0.24 (p<0.01).

Additionally, there was a trend toward increased HDL-C values in G1, G2, and G4. The SGOT values in G1 and G2 decreased (p<0.22 and 0.29) but the SGOT levels in G3 and G4 increased (p<0.32 and 0.36). A downward trend in SGPT values was observed in G1, G2, and G4 with G1 showing a significant decrease from 32.50 IU/L to 28.09 IU/L (p<0.01). Conversely, G3 displayed elevated mean SGPT values. BUN values declined in G1 but surged in G2, G3, and G4. Creatinine levels decreased in G1, G3,

and G4, with G4 showing a notable decrease from 1.15 mg/dL to 1.07 mg/dL (p<0.01). The N/LP ratio in G2 and G4 declined, while it augmented in G1 and G3, with G3 presenting a significant increase from 1.13 to 1.47 (p<0.02).

In the analysis of the mean laboratory results of patients across four groups between baseline and month 6, G4 (without statin and *P. frutescens* seed oil) as the control group (Table 3). Total cholesterol values between G4 and G1 in month 6 (mean difference=29.93, p<0.02). G1, G2, and G3 presented lower triglyceride values than G4 in month 6. LDL-C values between G4 and G1 were significantly varied in month 6 (mean difference=22.75, p<0.01). HDL-C values in G1, G2, and G3 were higher than those in G4 in month 6. The difference in the LDL/HDL ratio between G4 and G1 was significant in month 6 (mean difference=0.50±0.16, p<0.02).

Table 2: Lipid level and laboratory test compared within groups at baseline to month 6

parameters	Mean±SE		baseline to month 6	p-value
	baseline	month 6	Mean±SE (95% CI)	
Total cholesterol				
G1	163.93±6.12	151.68±4.31	12.24±4.60 (3.03, 21.45)	0.00*
G2	196.60±8.37	197.60±8.19	-1.00±1.74 (-4.57, 2.57)	0.28
G3	178.64±6.84	171.03±6.42	7.61±5.37 (-3.15, 18.38)	0.08
G4	172.44±7.04	181.14±8.63	-8.70±6.85 (-22.80, 5.39)	0.10
Triglyceride				
G1	115.77±8.63	113.48±9.39	2.29±7.31 (-12.33, 16.91)	0.38
G2	124.53±10.11	121.28±11.36	3.25±5.75 (-8.55, 15.05)	0.28
G3	114.08±7.18	114.35±7.02	-0.26±4.56 (-9.41, 8.88)	0.47
G4	139.51±17.22	127.70±17.56	11.81±4.82 (1.90, 21.72)	0.01*
LDL-C				
G1	88.88±4.57	77.34±3.01	11.54±3.93 (3.68, 19.40)	0.00*
G2	115.39±6.94	114.53±6.79	0.85±1.86 (-2.97, 4.68)	0.32
G3	100.98±5.57	94.24±5.11	6.74±4.62 (-2.51, 15.99)	0.07
G4	96.25±5.25	100.22±6.20	-3.96±4.73 (-13.69, 5.76)	0.20
HDL-C				
G1	55.62±2.09	56.62±2.43	-1.00±1.19 (-3.39, 1.39)	0.20
G2	58.35±3.21	58.78±3.38	-0.42±1.96 (-4.46, 3.61)	0.41
G3	56.77±2.00	55.06±1.93	1.70±0.87 (-0.03, 3.45)	0.02*
G4	50.59±2.93	52.74±2.78	-2.14±1.07 (-4.36, 0.06)	0.02*
LDL/HDL ratio				
G1	1.73±0.11	1.49±0.08	0.24±0.08 (0.07, 0.40)	0.00*
G2	2.09±0.14	2.08±0.14	0.01±0.07 (-0.13, 0.17)	0.41

parameters	Mean±SE		baseline to month 6	p-value
	baseline	month 6	Mean±SE (95% CI)	
G3	1.95±0.14	1.85±0.12	0.09±0.08 (-0.08, 0.27)	0.14
G4	2.02±0.13	2.00±0.14	0.01±0.11 (-0.21, 0.25)	0.43
SGOT				
G1	25.93±0.94	25.36±0.89	0.56±0.75 (-0.95, 2.08)	0.22
G2	26.16±2.04	25.56±1.45	0.59±1.08 (-1.62, 2.81)	0.29
G3	28.91±1.44	29.70±2.02	-0.79±1.74 (-4.29, 2.71)	0.32
G4	25.86±2.69	26.63±2.83	-0.76±2.25 (-5.39, 3.87)	0.36
SGPT				
G1	32.50±1.51	28.09±1.58	4.41±1.19 (2.02, 6.81)	0.00*
G2	33.66±3.90	29.06±2.79	4.59±3.26 (-2.05, 11.24)	0.08
G3	33.41±2.47	34.08±3.08	-0.67±2.49 (-5.67, 4.33)	0.39
G4	30.29±6.24	28.75±3.46	1.53±3.99 (-6.65, 9.73)	0.35
Creatinine				
G1	1.04±0.02	1.00±0.02	0.03±0.01 (0.00, 0.05)	0.01*
G2	0.94±0.06	0.94±0.06	-0.00±0.03 (-0.07, 0.07)	0.49
G3	1.02±0.04	1.01±0.04	0.01±0.02 (-0.03, 0.06)	0.28
G4	1.15±0.07	1.07±0.07	0.08±0.03 (0.00, 0.15)	0.01*
RBC				
G1	4.32±0.07	4.32±0.07	-0.00±0.03 (-0.07, 0.05)	0.41
G2	4.13±0.10	4.16±0.09	-0.02±0.04 (-0.11, 0.05)	0.25
G3	4.37±0.07	4.39±0.07	-0.01±0.02 (-0.07, 0.04)	0.28
G4	4.38±0.14	4.27±0.14	0.10 ±0.06 (-0.01, 0.23)	0.04*
N/LP ratio				
G1	1.23±0.12	1.41±0.12	-0.18±0.13 (-0.45, 0.08)	0.09
G2	1.83±0.41	1.66±0.37	0.16±0.55 (-0.97, 1.30)	0.38
G3	1.13±0.06	1.47±0.15	-0.33±0.17 (-0.67, 0.00)	0.02*
G4	1.29±0.28	1.03±0.11	0.26±0.30 (-0.35, 0.88)	0.19
HbA1c				
G1	7.76±1.61	7.79±1.61	-0.03±0.06 (-0.17, 0.10)	0.30
G2	5.86±0.15	5.74±0.09	0.11±0.12 (-0.13, 0.36)	0.17
G3	6.15±0.11	6.25±0.15	-0.10±0.07 (-0.25, 0.04)	0.08
G4	6.14±0.02	5.91±0.16	0.22±0.11 (-0.00, 0.45)	0.02*

The *P*-value was determined by paired t-test. **P*-value <0.05 was considered statistically significant.

Table 3: Lipid level and laboratory tests between groups at baseline and month 6

Parameters	Baseline				Month 6			
(i-j)	Mean ± SE i	Mean ± SE j	Mean diff ± SE (i-j)	*P*	Mean ± SE i	Mean ± SE j	Mean diff ± SE (i-j)	*P*
Total cholesterol								
G4-G1	172.44±7.04	163.58±6.03	8.86±9.27	0.91	181.14±8.63	151.20±4.27	29.93±9.63	0.02*
G4-G2	172.44±7.04	196.60±8.37	-24.16±10.94	0.17	181.14±8.63	197.60±8.19	-16.45±11.90	0.66
G4-G3	172.44±7.04	178.64±6.84	-6.20±9.82	0.98	181.14±8.63	171.03±6.42	10.11±10.76	0.92
Triglyceride								
G4-G1	139.51±17.22	115.77±8.63	23.74±19.26	0.76	127.70±17.56	113.32±9.41	14.38±19.93	0.97
G4-G2	139.51±17.22	124.53±10.11	14.98±19.97	0.97	127.70±17.56	121.28±11.36	6.41±20.92	1.00
G4-G3	139.51±17.22	114.08±7.18	25.43±18.66	0.68	127.70±17.56	114.35±7.02	13.35±18.92	0.97
LDL-C								
G4-G1	96.25±5.25	89.01±4.56	7.24±6.95	0.87	100.22±6.20	77.47±3.00	22.75±6.89	0.01*
G4-G2	96.25±5.25	115.39±6.94	-19.13±8.71	0.17	100.22±6.20	114.53±6.79	-14.31±9.20	0.54
G4-G3	96.25±5.25	100.98±5.57	-4.72±7.66	0.99	100.22±6.20	94.24±5.11	5.98±8.04	0.97
HDL-C								
G4-G1	50.59±2.93	55.41±2.08	-4.82±3.60	0.69	52.74±2.78	56.41±2.43	-3.67±3.69	0.89
G4-G2	50.59±2.93	58.35±3.21	-7.76±4.35	0.38	52.74±2.78	58.78±3.38	-6.04±4.37	0.66
G4-G3	50.59±2.93	56.77±2.00	-6.18±3.55	0.41	52.74±2.78	55.06±1.93	-2.32±3.39	0.98
LDL/HDL ratio								
G4-G1	2.02±0.13	1.74±0.11	0.28±0.17	0.50	2.00±0.14	1.50±0.08	0.50±0.16	0.02*
G4-G2	2.02±0.13	2.09±0.14	-0.07±0.19	0.99	2.00±0.14	2.08±0.14	-0.07±0.20	0.99
G4-G3	2.02±0.13	1.95±0.14	0.07±0.19	0.99	2.00±0.14	1.85±0.12	0.14±0.19	0.97

P-value for comparison between groups was determined by one-way ANOVA. **P*-value <0.05 was considered statistically significant.

DISCUSSION

This study assessed the efficacy of *P. frutescens* seed oil in ameliorating lipid profiles among elderly patients with mild to moderate dementia. The data revealed that the participants in G1 co-administered with statins and *P. frutescens* seed oil demonstrated the most optimal lipid profiles. The co-administration of statins and *P. frutescens* seed oil emerged as the most potent intervention for total cholesterol and LDL-C reduction ($p<0.05$). The participants in G1 exhibited greater reductions in total cholesterol and LDL-C levels compared to G2 and G3. These empirical results suggest that *P. frutescens* seed oil could exert the lipid-lowering effects of statins. The implications of these findings advocate for the adjunctive use of *P. frutescens* seed oil alongside statins. However, the tangible clinical benefits in attenuating atherosclerosis require validation via extended, prospective studies.

Our findings aligned with prior research highlighting the cholesterol-lowering capabilities of *P. frutescens* seed oil in participants [11]. To our understanding, this research is pioneering in presenting *P. frutescens* seed oil's potential as an adjunct to statin therapy. Our study results on the co-administration of *P. frutescens* seed oil and statins to protect liver damage were consistent with previous studies that reported its health benefits of hepatoprotection. [12].

P. frutescens seed oil is distinguished for its rich content of plant-derived omega-3 fatty acids, predominantly alpha-linolenic acid [13]. Such fatty acids are deemed essential, necessitating dietary acquisition due to the body's inability to synthesize them [14]. Remarkably, alpha-linolenic acid from *P. frutescens* seed oil can metamorphose into elongated-chain omega-3 fatty acids like EPA and DHA, analogously found in fish oils [15]. Fish oil, a commendable source of omega-3s, is different from *P. frutescens* seed oil in its fatty acid profile. Fish oil is replete with EPA and DHA while *P. frutescens* seed oil a plentiful source of alpha-linolenic acid [16]. Both oils serve distinct dietary roles based on their fatty acid spectra. The bioactive compounds, particularly omega-3 in *P. frutescens* seed oil may possibly cause its lipid-lowering process [17]. Moreover, omega-3 has been shown to reduce total triglycerides and maintain HDL levels, as well as regulate systolic blood pressure. It also shifts the HDL particle distribution toward a cardioprotective profile in healthy older adults without dyslipidemia [18]. In postmenopausal women, omega-3 fatty acids have resulted in a significant reduction in triglyceride concentrations and a modest increase in HDL-C and LDL-C levels [19]. Additionally, omega-3 may significantly lower TG levels in younger children and those with hypertriglyceridemia [20]. Moreover, omega-3 may cause beneficial hypolipidemic effects by lowering TG levels in young children and those with hypertriglyceridemia [21].

The N/LP ratio, an inflammatory marker, suggests amplified inflammation when it is escalated [22]. Current literature indicates that statins, especially in higher dosages, can temper inflammation, as gauged by the N/LP ratio [23]. ***P. frutescens*** seed oil has also been speculated to possess anti-inflammatory attributes based on the N/LP ratio as the inflammatory index [24]. Nonetheless, post-treatment results in this study indicated that the administration of either *P. frutescens* seed oil or statins did not induce any observable alterations in the N/LP ratio.

As a functional food, *P. frutescens* seed oil encompasses bioactive compounds such as rosmarinic acid and flavonoids, recognized for their antioxidant and anti-inflammatory properties, potentially conducive to liver protection [25]. Additionally, omega-3 in the diet can reduce the risk of liver disease incidents and offer protection against alcoholic liver disease [12]. A previous study in 2017 reported that omega-3 exhibited anti-inflammatory effects compared to diclofenac. Omega-3 was found to function as a natural anti-inflammatory agent against osteoarthritis [13].

By attenuating oxidative stress and liver inflammation, the bioactive compounds in *P. frutescens* seed oil could be protective against hepatic damage and related disorders [26]. In our research, liver enzyme levels remained stable following *P.frutescens* seed oil administration, irrespective of concurrent statin usage, implying its hepatic safety.

The SGPT assay is correlated with muscle injury [27]. The common understanding is that Elevated SGPT with absent liver pathology suggests muscle tissue damage [28]. In this study, the co-administration of *P. frutescens* seed oil and statins caused a greater decrease in SGPT compared to statins alone. However, it remains skeptical to assert if *P. frutescens* seed oil mitigates statin-induced muscle damage based on the results of this study. Subsequent research should consider CPK as a more reliable biomarker for assessing the muscle-protective potential of *P. frutescens* seed oil and statin therapy.

This study has several limitations that warrant discussion. Firstly, one of the most notable limitations is the unequal distribution of patients across the study groups. This imbalance arose due to the retrospective nature of the study and posed challenges in ensuring representative sampling and unbiased comparisons. The uneven group sizes could potentially influence the study's outcomes, as the statistical power and the ability

to detect differences or similarities between groups might be affected.

Secondly, the lack of long-term follow-up for liver function tests is another limitation. The absence of long-term data restricts our understanding of the sustained effects or potential late-onset implications of the treatments under study.

Given these limitations, future research in this area should aim for a more balanced allocation of patients in study groups. Prospective designs, especially randomized controlled trials with larger and more evenly distributed sample sizes, are recommended to enhance the reliability and validity of findings. Additionally, incorporating long-term follow-up assessments would provide a more comprehensive understanding of the long-term impacts and safety profiles of the interventions. Moreover, research results can be developed or further studied by addressing *P. frutescens* seed oil as functional food to relieve dyslipidemia.

CONCLUSIONS

In summation, *P. frutescene* seed oil when considered as functional food containing bioactive compounds particularly omega 3 can be co-administered with statins and shows a promising treatment in enhancing lipid profiles and possibly in affording hepatic protection. While its intrinsic omega-3 content and beneficial molecules are noteworthy, comprehensive research, encompassing longitudinal studies, is requisite to unequivocally establish its therapeutic significance in cardiovascular disease and associated ailments.

Abbreviations: TC: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, EPA: Eicosatetraenoic acid, DHA: Docosahexaenoic acid, ICD10: International classification of diseases, 10th edition, TMSE: Thai Mental State Examination, MoCA-Thai: Thai Montreal Cognitive Assessment, DSM-IV: Diagnosis and statistical manual of mental disorders, Fourth Edition, SGOT: Serum glutamic oxaloacetic transaminase activity, SGPT: Serum glutamic pyruvate transaminase, BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, CBC: Complete blood count, RBC: Red blood cell count, Hct: Hematocrit, WBC: White blood cell count, N/LP ratio: Neutrophils, lymphocytes and platelet ratio.

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