ORIGINAL ARTICLE

Efficacy and Safety of *Prunus mume* and Choline in Patients with Nonalcoholic Fatty Liver Disease

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Abstract

Aim: The primary objectives of this study include evaluating changes in lipid profile and liver enzyme levels in nonalcoholic fatty liver disease (NAFLD) patients receiving *Prunus mume* and choline supplementation (Revolic).

Materials and methods: Two-hundred patients were recruited from the hepatology outpatient department of a public hospital between January and June 2023. Patients who had confirmed diagnosis of NAFLD, proven with ultrasound (US) followed by biopsy or US alone with age >18 years were included in this study. The study variables were fasting blood sugar, cholesterol levels, low-density lipoprotein (LDL), triglyceride, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase levels (GGT). All investigations were conducted and compared between baseline, 12 and 24 weeks following treatment.

Results: The mean age of all participants was 40.49 ± 10.59 years with 34 males and 166 females. The mean cholesterol levels were reduced to 179.86 ± 35.63 mg/dL from the mean baseline of 197.57 ± 42.52 mg/dL ($p = 0.001$). There was also a statistically significant difference found between baseline and posttreatment levels of LDL and triglyceride ($p < 0.001$). The ATL levels were also reduced from baseline 44.91 ± 32.40 U/L to 44.25 ± 30.66 and 41.06 ± 22.15 U/L between 12 and 24 weeks after treatment respectively. There was a statistically significant reduction in ATL, AST, and GGT levels from baseline with *p*-value < 0.001.

Conclusion: The combination of *P. mume* and choline (Revolic) gives promising results with a significant reduction in lipid profile and liver enzymes.

Clinical significance: The combination of *P. mume* and choline can be considered a reliable option for the management of NAFLD due to its efficacy and safety at 24 weeks after treatment as evident in the present study.

Keywords: Choline, Fatty liver, Lipid profile, Liver enzymes, Nonalcoholic liver diseases, *Prunus mume*.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a major public health concern globally, affecting a large population. It is characterized by the accumulation of excessive amounts of fat around the liver that impact its function significantly. It may cause problems like simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis.[1,2] It is highly correlated or associated with obesity, metabolic syndromes, and insulin resistance. Nonalcoholic fatty liver disease is considered as one of the leading causes of chronic liver disease.[3,4] The therapeutic strategies to manage and treat NAFLD need immediate attention due to the continuous rise of its prevalence.[5]

Recently, herbal medicines have gained a lot of attention as potential treatments for NAFLD due to promising results and safety profiles. The *prunus mume* plant (Chinese plum or Japanese apricot) has medicinal properties and has been used traditionally for various health purposes.[6] Similarly, choline is a nutrient that plays a vital role in liver function and lipid metabolism. Its therapeutic effects on NAFLD have been explored in different previous studies due to its involvement in fat metabolism, transport, and hepatoprotective properties. However, despite the potential benefits and safety profile of herbal medicine, there is a dearth of comprehensive studies, investigating their efficacy specifically in patients with NAFLD.[7,8]

To our knowledge, there is not even a single clinical study in the past that studied the combined therapeutic effect of *P. mume* and choline for the treatment of NAFLD.[9] Therefore, we aim to bridge this gap by reporting the efficacy and safety of *P. mume* and choline in patients with NAFLD, providing valuable and authentic findings regarding their potential as alternative treatment options.

The primary objectives of this study include evaluating changes in lipid profile and liver enzyme levels in NAFLD patients receiving *P. mume* and choline supplementation (Revolic). Furthermore, we will also report adverse effects to the treatment regimen.

Materials and Methods

Two-hundred patients were recruited from the Hepatology Outpatient Department of the Public Hospitals between January and June 2023. Patients who had confirmed diagnoses of NAFLD, proven with ultrasound (US) followed by biopsy or

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US alone with age >18 years and treated with *P. mume* and choline supplementation (Revolic) were included in this study. The disease's nonalcoholic origin was confirmed during a direct interview with the patient during the medical history assessment. Patients with known increased liver enzyme due to other reasons such as viral hepatitis (B or C), chronic hepatitis, cirrhosis, Wilson's disease, any metabolic disorder of the liver, or -1 antitrypsin deficiency or as were those who consumed alcohol and were taking hepatotoxic drugs were excluded from the study. The study protocols were designed according to the declaration of Helsinki and were approved by the institution review board of Jinnah Postgraduate Medical Centre (JPMC) (registration no. NO.F.2-81/2021-GENL/61365-A/JPMC). All patients were consented before data collection. The study was conducted ethically in accordance with the declaration of Helsinki.

General information (age, gender, family history, symptoms, diagnosis, comorbidities) of the patients was extracted from the departmental database. All patients underwent baseline investigations such as fasting blood sugar levels (FBS), cholesterol levels, low-density lipoprotein (LDL), triglyceride, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase levels (GGT). Patients were followed at least for 6 months after treatment. All investigations were repeated at 12 and 24 weeks of treatment and compared with baselines for analysis purposes.

The data was analyzed by using SPSS software 25 version. Descriptive statistics was used to summarize all the variables. The non-parametric repeated measure analysis of variance (ANOVA) Friedman's test was performed to evaluate the difference between pre- and posttreatment in liver enzymes (ALT, AST, GGT), FBS, cholesterol levels, triglycerides, and LDL. The p-value < 0.05 was considered as significant.

Results

The mean age of all participants was 40.49 ± 10.59 years with 34 males and 166 females. The most commonly reported symptoms were nausea, epigastric pain, burning sensation in limbs, hypochondriac pain, constipation, dyspepsia, abdominal pain, and vomiting. Diabetes and hypertension were the most prevalent comorbidity in this series (Table 1). All parameters including lipid profile (cholesterol level, LDL, triglycerides), FBS and liver enzymes (ALT, AST, GGT levels) were higher in all patients due to NAFLD as presented in Table 1. However, all parameters were at a normal level at 24 weeks posttreatment.

The mean cholesterol levels were reduced to 179.86 ± 35.63 mg/dL from the mean baseline of 197.57 ± dL with p-value < 0.001. There was also a statistically significant difference found between baseline and posttreatment levels (at 24 weeks) of LDL and triglyceride from 139.38 ± 57.80 mg/dL and 191.45 ± 83.42 mg/dL to 129.85 ± 47.60 mg/dL and 184.77 ± 77.32 mg/dL, respectively ($p < 0.001$). There was also a statistically significant reduction in FBS from baseline at each follow-up ($p = 0.01$).

Similarly, the liver enzymes (ALT, AST, and GGT levels) also showed declined levels at each follow-up (12 and 24 weeks). The ATL levels were also reduced from baseline 44.91 ± 32.40 U/L to 44.25 ± 30.66 and 41.06 ± 22.15 U/L at 12 and 24 weeks after treatment respectively. There was a statistically significant reduction in ATL levels from baseline with p-value < 0.001. The AST and GGT levels were also significantly decreased from baseline ($p < 0.001$). All the baseline comparisons with each follow-up (12 and 24 weeks) of treatment are mentioned in Table 2.

Table 1: Baseline characteristics of study participants

Baseline	*Mean ± SD (%)*
Age (in years)	40.49 ± 10.59
Gender	
Male	34 (17%)
Female	166 (83%)
Comorbidities ($n = 87$)	
Diabetes	15 (17%)
Hypertensive	31 (35%)
Chronic kidney diseases	6 (7%)
Cardiovascular diseases	2 (2%)
Diabetes + Hypertensive	32 (36%)
Diabetes + Chronic kidney diseases	2 (2%)
Hypertensive + Chronic kidney diseases	1 (1%)
FBS levels (mg/dL)	112.11 ± 48.08
Cholesterol levels (mg/dL)	197.57 ± 42.52
LDL levels (mg/dL)	139.38 ± 57.80
Triglycerides (mg/dL)	191.45 ± 83.42
ALT (U/L)	44.91 ± 32.40
AST (U/L)	60.58 ± 42.30
GGT (IU/L)	81.72 ± 50.68

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FBS, fasting blood sugar; GGT, gamma glutamyl transferase; IU/L, international unit per liter; LDL, low-density lipoprotein; mg/dL, milligrams per deciliter; mmol/mol, millimoles per mole; U/L, units per liter

Table 2: Comparison of all parameters from baseline, 12 and 24 weeks after treatment

Parameters Mean ± SD	*Baseline*	*12 weeks posttreatment*	*24 weeks posttreatment*	*p-value*
Cholesterol level	197.57 ± 42.52	191.72 ± 39.60	179.86 ± 35.63	<0.001
LDL level	139.38 ± 57.80	134.26 ± 52.90	129.85 ± 47.60	<0.001
Triglyceride level	191.45 ± 83.42	188.89 ± 78.76	184.77 ± 77.32	<0.001
FBS (m/dL)	112.11 ± 48.08	112.23 ± 47.99	111.06 ± 46.39	0.01
ALT level (U/dL)	44.91 ± 32.40	44.25 ± 30.66	41.06 ± 22.15	<0.001
AST level	60.58 ± 42.30	38.81 ± 14.67	37.87 ± 14.17	<0.001
GGT levels	81.72 ± 50.68	54.51 ± 27.36	49.77 ± 19.68	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FBS, fasting blood sugar; GGT, gamma glutamyl transferase; LDL, low-density lipoprotein; mg/dL, milligrams per deciliter; U/L, units per liter

Discussion

According to the findings of this study, all the parameters of lipid profile (cholesterol, LDL, and triglycerides levels) and Liver enzymes (ALT, AST, GGT) levels were significantly reduced from baseline at 12 and 24 weeks of treatment with *P. mume* and choline supplementations. None of the patients reported any posttreatment complications or adverse events.

Several Studies reported the benefits of *P. mume* extract and its hepatoprotective effects, not only in NAFLD but also in alcoholic liver injuries.[6,7,9–12] Pan JH et al.[10] investigated the impact of *P. mume* Sieb Et Zucc. Extract on the alcoholic liver injury at the cellular level. They found that *P. mume* has anti-oxidative properties that inhibit lipogenesis and suppress hepatic apoptosis. A similar study was performed on the effectiveness of fixed-dose combination (FDC) of *P. mume* extract with choline.[9] According to the findings, this FDC significantly reduces the weight and glucose level which is directly associated with NAFLD. However, the present study was done in the clinical setup and therefore, we did not evaluate the cellular changes associated with this extract like previous studies.

A randomized clinical trial was conducted to evaluate the efficacy of *P. mume* extract for liver protection.[11] The results showed a statistically significant difference between placebo and *P. mume* extract effects on liver function, with reduced levels of all liver enzymes (AST, ALT, GGT), and lipid profile was also modified positively from the baselines. In our study, we also reported a significant reduction in liver enzymes (AST, ALT, GGT) from baseline and modification in cholesterol, LDL, and triglycerides levels ($p = <0.001$). However, we used the combination of *P. mume* with choline in our study. The previous study also determined the anti-oxidant action of *P. mume* extract and reported decreased levels of oxidized glutathione, reduced/oxidized cysteine glycine, oxidized cysteine (intracellular pro-oxidant) and neopterin (inflammation biomarker). The primary objective of our study was to evaluate the effectiveness of the *P. mume* and choline combination specifically in NAFLD patients. Therefore, we did not analyze the anti-oxidant effects of this combination like above-mentioned study. The choline and its effect on liver function was studied on patients with total parenteral nutrition (TPN).[12] At 4 weeks, TPN with choline group showed decreased Hounsfield unit (HU) densities on computed tomography (CT) and also reduced significant levels of serum liver enzymes (ALT and AST) with *p*-value 0.01 and 0.05 respectively, when compared with placebo group. In our study, there was a slight difference between baseline and 12 weeks posttreatment in liver enzyme level and lipid profile. However, all study parameters improved significantly at 24 weeks of treatment from baseline values. These findings are consistent with the previous literature.[6–8,11,13]

There are certain limitations of this study. First of all, it is a case series and lacks a control group. Consequently, it is impossible to determine or compare the efficacy of *P. mume* and choline combination with other frequently used treatment options for NAFLD. Therefore, our findings may not be comparable to other treatment regimens, frequently used in clinical setups. Secondly, there was no radiological assessment (US) was done after treatment to determine the drug effect on US findings. Therefore, no subjective correlation was established with radiological investigations. Lastly, the small sample size and short follow-up reduced the internal validity of the study findings. Therefore, the results are not valid for a larger population. This study can serve as a framework and provide a starting point for future studies on similar topics. We recommend multi-center, experimental, and long follow-up clinical studies on the *P. mume* and choline combination (Revolic) to evaluate long-term benefits and complications associated with this treatment option for NAFLD patients.

Conclusion

The combination of *P. mume* and choline (Revolic) gives promising results with a significant reduction in lipid profile and liver enzymes. Therefore, it can be considered a reliable option for the management of NAFLD due to its efficacy and safety at 24 weeks after treatment. However, clinical and radiological correlations and longitudinal follow-up studies are necessary to precisely ascertain the rate of complications, efficacy, and safety of this combination.

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