Effects of *Mangifera indica* leaves improves blood lipids profile and biochemical indices in high-fat diet-induced hyperlipidaemia rats

Lijia Liu[1], Siwei Li[2], Lingling Liang[2], Yan Mao [1*]

[1] Faculty of Pharmacy, Guangxi University of Chinese Medicine, Nanning 530200, China.
[2] Guangxi Key Laboratory of Efficacy Study on Chinese Materia Medica, Nanning 530200, China.

Abstract. Dyslipidemia a chronic, metabolic syndrome characterized by elevated lipid profiles together with lipid peroxidation in individuals with atherosclerotic cardiovascular disease (CVD). Functional ingredients such as high phenolic content and potent antioxidant activity obtained from agricultural waste by-products or waste are of great interest. However, the hypolipidemic effects of the waste mango (*Mangifera indica* L.) leaves (MLE) have not been investigated. Here, the specific lipid-lowering and potential hepatoprotective mechanisms by which the gavage administration of MLE affects lipid metabolism and liver steatosis in rats fed on a high-fat diet (HFD) were evaluated. In rats treated with high level of MLE, a persistent suppressive effect on liver weight and body weight gain was discovered after 28-day intervention. Furthermore, body lipid index and reduced inflammatory reaction and liver function parameters in HFD control rats were markedly ameliorated by supplementation with high doses of MLE. In addition, histological and histomorphometric analyses here demonstrated that fat accumulation changed in HFD supplemented hyperlipidaemia rats, but normalized in MLE treatment groups. Further real-time quantitative reverse transcription polymerase chain reaction (RT-PCR) and western blot analyses were carried out to determine the mRNA and protein abundance of PPARα receptors and CYP7A1 in liver tissues of rats. These results indicate that MLE supplement have the promising lipid lowering effects in HFD-induced hyperlipidaemia rats based on positive ameliorations in the serum lipid profile and liver function parameters.

1 Introduction

Hyperlipidaemia is very often involved in dyslipidaemia, which have abnormalities in one or more parameter of the biochemical lipid triad [1]. It has previously been shown that excess intake of HFD can be at increased risk for abnormal lipid homeostasis [2]. In this context, the development and complications of this disease induced by consuming long-term HFD is direct related to a series of inflammation and lipid accumulation that affect and impair the disorder of lipid metabolism. Several laboratory studies point to the health-promoting effects of various active chemical ingredients from traditional herbal origin without side effects that are able to regulating the gene and protein expression levels linked to hyperlipidaemia [3]. Considering the effectiveness of the existing medications differ, the use of natural medicine for improving hyperlipidaemia would be of tremendous benefit [4]. Functional ingredients such as high phenolic content and potent antioxidant activity obtained from agricultural waste by-products or waste, such as barks and leaves, are of great interest. Although leaves of *Mangifera indica*, as a traditional herbal medicine, has a long history of usage since ancestral times in China and worldwide, but still unexploited properly and are usually discarded directly leading to great waste [5]. Also, the 1 million tons of *Mangifera indica* leaves, representing a promising source of active pharmaceutical ingredients, pruned from mango trees each year are not well utilized in effect, resulting in a significant waste of resources [6]. Whereas some rigorous pharmacological studies found that the use of *Mangifera indica* leaves extracts have variety of pharmacological activities making them suitable for human consumption, the underlying mechanisms remain unclearly established.

Despite growing scientific evidence pointing to the potential function of MLE on several biofunctional properties, researches have not yet been extensively conducted on the anti-lipid peroxidation role of MLE in hyperlipidaemia subjects [7, 8]. Prior to this research, we found that the ethanolic extracts of *Mangifera indica* leaves has a protective efficacy on acute liver injury induced by alcohol in mice, which may be related to its anti-lipid peroxidation [9]. Therefore, the purpose of the study was to investigate its action of MLE on the modulation of the mRNA and protein abundance of PPARα receptors and CYP7A1 markers associated with hyperlipidaemia rats fed with HFD diet.

* Corresponding author: 150182267@qq.com

2 Materials and methods

2.1 Preparation and analyses of MLE

The waste mango (*Mangifera indica* L.) leaves were obtained from Guangxi Subtropical Crops Research Institute (Nanning, China). The taxonomic identification was performed in the Guangxi Key Laboratory of Efficacy Study on Chinese Materia Medica (Nanning, China). The proper method for the ethanolic extracts of *Mangifera indica* leaves was described basing on our previous study [10]. Meanwhile, diluted samples of MLE were analyzed using an Acquity UPLC system (Waters) equipped with a tandem quadrupole mass spectrometry according to the literature with a previously published work [9]. HPLC analysis showed that the composition of MLE included mangifera, quercetin, protocatechuic acid and gallic acid has been reported previously [11].

2.2 Animals and diets

The use of laboratory rats was performed in our study following the Guidelines for Guangxi University of Chinese Medicine Institutional Animal Use and Care Committee (approval number, DW20210321-057). 48 male Wistar Albino rats aged 2 months and weighing 200 ± 10 g took part. Throughout the experimental period, standard laboratory settings were offered for laboratory rats rearing in the animal house at Guangxi University of Chinese Medicine (Nanning, China). The rats housed in the laboratory housing standard conditions were maintained at a room temperature of 22 ± 2°C and humidity of 50 ± 10%.

The healthy rats were received a standard pellet diet (carbohydrates 52 %, protein 25 % and fat 5 %, minerals, ash, moisture, and fibres) and water ad libitum for adaptation early in the experiment. After a 7-day acclimatization period, 8 rats, as the control groups (COM) were fed the ordinary food as before throughout the study, but 40 remainder rats were given HFD (w/w, 68.6% normal chow, 10 % lard, 1% cholesterol, 0.5% sodium cholate) for 14-day for the development of dyslipidemia in the course of making model. 2-week after HFD feeding, all 32 HFD-fed rats satisfied inclusion criteria of Hyperlipidaemia by serum lipid measurement were randomly distributed into 4 groups (eight rats per group): model rats (HFD), positive control rats (COL, colestyramine 0.2 g/kg body weight), low-dose rats (MLEL, 1 g/kg body weight) and high-dose rats (MLEH, 4 g/kg body weight). From the 21th day onwards, rats from the HFD, COL, MLEL, and MLEH groups in which the lipid abnormality process was already installed maintained the HFD. Treatment groups were intragastrically applied daily the corresponding dose of test sample dissolved in distilled water for 4-week at the same time. The body weight gained in all animals were monitored once a week until the end of the experiment.

At the end of the experiment, all animals were euthanized under anaesthesia for sample collection on 28th day after treatment.

2.3 Biochemical assessment

Automatic biochemical analyzer was performed to quantify the contents of plasma lipid profile (TC, TG, HDL and LDL). Commercially available multifunctional enzyme-reagent kits were used to determine the levels of alpha tumour necrosis factor (TNF-a), inter leukin (IL)-6 and interleukin (IL)-1b in serum. Total hepatic tissue of the rats submitted to the different treatments was collected and weighed and the relative masses of liver were recorded.

2.4 Histopathological analysis

To assess the histopathological alterations, the liver tissues samples suspended in 10% buffered formalin were processed histopathological study and stained with haematoxylin-eosin (H&E) after a 1-day of fixation period according to previously reported [12]. After dehydration, the structure of liver tissue was observed by microscope and photographed.

2.5 Western blot assay

The protein expression levels of Recombinant cytochrome P450 7A1 (CYP7A1) and Peroxisome proliferator-activated receptor alpha (PPARα) were assessed respectively by immunoblotting. The Western blotting was conducted as per the standard procedure [10]. The total content of proteins samples was separated and electrophoresed by 12% sodium dodecyl sulfate-polyacrylamide gel (SDS-PAGE) and then immediately transferred to polyvinylidene fluoride (PVDF) membranes, where incubated at 4 °C overnight with the primary antibodies against PPARα and CYP7A1. The cleaned membranes adequately reacted with ECL substrate, yielding the protein bands.

2.6 Quantitative PCR (qPCR) Assay

The hepatic tissues samples from each group were trimmed for analysis of the target gene expression level of CYP7A1 and PPARα by RT-PCR. Total mRNA was isolated using RNAzol followed as per the manufacturer's instruction (Invitrogen, Carlsbad, CA, USA). The primer sequences were as follows: CYP7A1, 5'-AGGCCGAGAAGGAGAAGCTGTTG-3' (Forward) and 5'-TGGCCACCTCTTTGCTGTGCTC-3' (reverse); PPARα, 5'-CCTCAGGGTACCACTACGGAGT-3' (Forward) and 5'-GCCGAATAGTTCGCCGAA-3' (reverse) [12].

2.7 Statistical analysis

All experimental data are given as mean ± standard deviation (SD) and statistical significance of the groups was compared using one-way ANOVA of software version 6.02. The $P < 0.05$ or 0.01 values indicates the statistically significant.

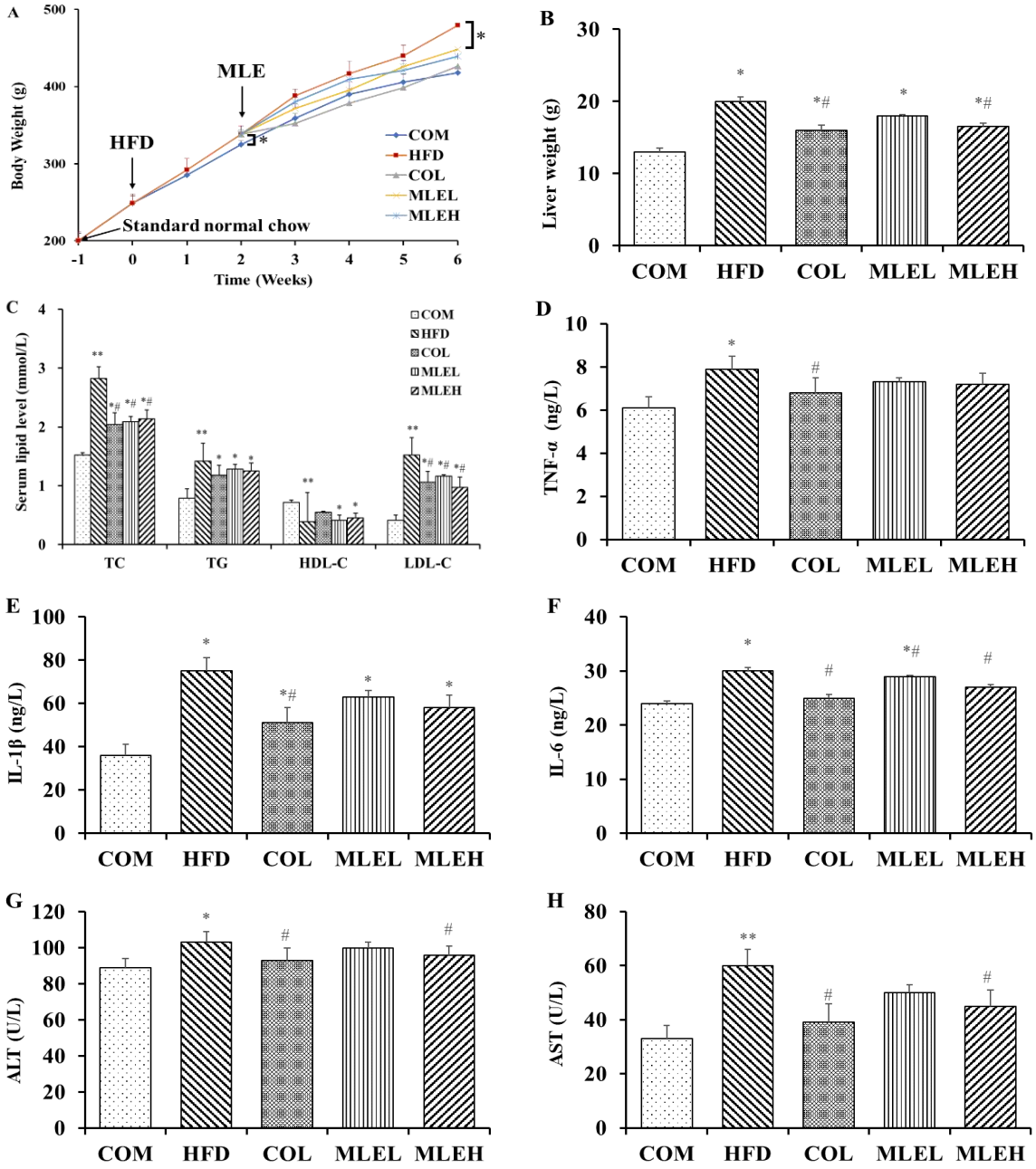

Fig. 1. MLE treatment improved serum lipid index and reduced inflammatory reaction and liver function parameters in HFD fed rats. (A) Body weight. (B) Liver weight. (C) Serum lipid levels. (D) Alpha tumour necrosis factor (TNF-α). (E) interleukin (IL)-β. (F) interleukin (IL)-b. (G) Alanine aminotransferase (ALT). (H) Aaspartate aminotransferase (AST). Values with different superscript letters are significantly different. *Differences are compared with CON group and # compared with T2DM group except CON group, $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$, $^{\#\#\#}p<0.001$, $^{\#\#}p<0.01$, $^{\#}p<0.05$.

3 Results

3.1 Effect of MLE on the body weight and liver weight

The body weight of HFD-induced rats is depicted presented in Fig 2A. The results showed that the gain weight of healthy rats (COM) decreased steadily throughout the experiment, while the HFD animals (HFD) gain significant body weight after the establishment of the hyperlipidemia model ($p<0.05$); this effect weight loss was ameliorated by the treatment with MLE. It has been clearly shown that rats in MLEH group were dramatically lighter than the HFD group in the final week ($p<0.05$) (Fig. 1A). In addition, the liver weight gain in all treatment's groups were higher than the normal control group, and similar outcomes to the group receiving HFD except administration of high doses MLE (Fig. 1B).

3.2 Effect of MLE on lipid profile

Fig. 1C presents diverse group's serum lipid level of TC, PL, FFA, and TG. The plasma lipid profiles showed that there was a significant decline ($p<0.01$, Fig. 1C) in HDL-

C level in hyperlipidaemia rats, while TC, TG, and LDL-C levels were shown to be significant higher ($p<0.01$, Fig. 1C) in the group receiving HFD ($p<0.01$, Fig. 1C), meaning that dyslipidemia was substantial. However, these parameters prominently declined ($p<0.05$, Fig. 1C) following MLE feeding on week six. More so, the high doses of MLE were remarkably decreased to a level comparable to that of the HFD rats ($p<0.05$, Fig. 1C), while HDL-C concentration was not altered significantly. Remarkably, rats treated with MLEH had similar outcomes to those treated with standard medication colestyramine.

There was a substantial ($p<0.05$, Fig. 1D) increase in the TNF-α level of hyperlipidaemia rats. Compared with the chow feeding, the MLE supplementation had no effect on TNF-α level (Fig. 1D). Besides, treatment with MLE resulted to a downward trend in (IL)-1β levels of HFD-induced hyperlipidaemia rats, however, the reduction was only dramatically ($p<0.05$, Fig. 1D) in colestyramine group on week six. On the contrary, compared to HFD group, the levels of interleukin (IL)-6 of the MLE-treated rats significantly reduced ($p<0.05$, Fig. 1E), whereas did not statistically differ from that of COM group.

3.3 Effect of MLE on liver function parameters

The variations in each study group's liver function parameters are displayed in Fig 2F and G. Compared to control rats, the MLE treatment regimens also lowered the activity of ALT level, which were statistically similar to the control rats, but higher than that of colestyramine-treated rats (Fig. 1F). Similar effects were noted in animals fed an HFD diet.

In addition, the AST level of all treatments markedly decreased ($p<0.05$, Fig. 1G) compared to the HFD rats, but similar to that of COM rats on week six. The outcomes highlight that the hepatocyte integrity and function in HFD-induced hyperlipidaemia rats would be restored by the intake of MLE.

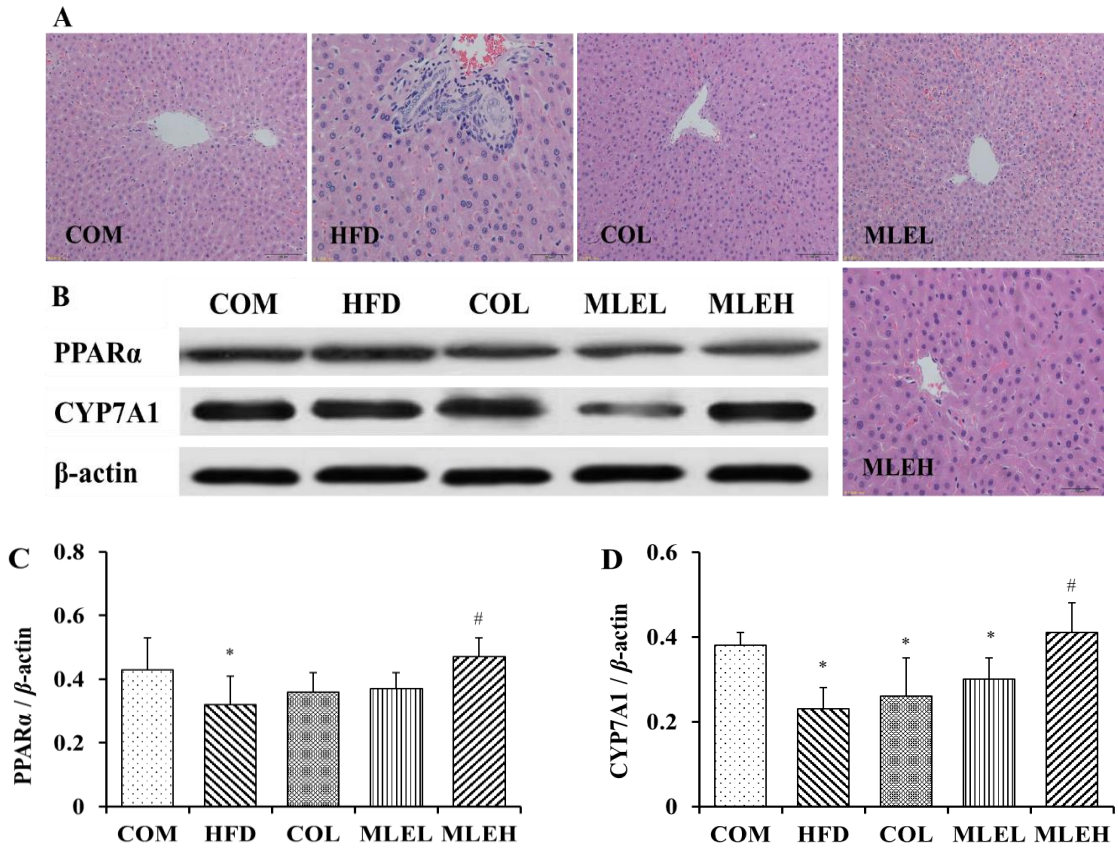

Fig. 2. MLE treatment improves lipid metabolism in HFD-fed rats. (A) Hepatic Histology with H&E. (B) Representative images of the western blotting for PPARα and CYP7A1. (C) Statistical analysis of PPARα. (D) Statistical analysis of CYP7A1. *Differences are compared with CON group and # compared with T2DM group except CON group, $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$, $^{\#\#\#}p<0.001$, $^{\#\#}p<0.01$, $^{\#}p<0.05$.

3.4 Histopathological observations

As shown in Fig. 2A, H&E Hepatic histopathology demonstrated severe hepatic steatosis, which were closely associated with hepatocytic lipid metabolism in hyperlipidaemia rats. This change leads to a growth in the accumulation of fat observed in the liver of HFD-induced hyperlipidaemia rats. On the other hand, MLE-treated hyperlipidaemia rats significantly ameliorated fat deposition and vacuolar degeneration, indicating that MLE treatment regime attenuated hepatic fatty droplets and lipid accumulation. These data indicate that the normal liver is damaged due to sustained HFD, and the improvement in liver function showed comparatively low lipid accumulation by administration of MLE.

3.5 Effect of MLE on PPARα and CYP7A1 protein expression

The two key proteins expression of PPARα and CYP7A1, related to lipid metabolism, is depicted in Fig. 2C and D. Immunofluorescence results showed that induction of hyperlipidaemia with HFD led to a remarkable reduction in the hepatic mRNA expression of PPARα and CYP7A1 compared with those in the COM rats, and which was prominently up-regulated and normalized by MLE intervention (Fig. 2C and D). The results of MLE-treated rats are similar to the negative control animals. These phenomena were significantly reversed in MLE treated animals.

4 Discussion

Mangifera indica L. leaves, as one the least-exploited plants, contain various natural pharmaceutical ingredients that contribute to alleviate inflammation and regulate lipid metabolism. In this context, the bioactive compounds potentially responsible for the lipid-lowering effect of *Mangifera indica* leaves may be because of the presence of mangiferin (xanthone-C-glycoside), which is the major effective constituents present in different extracts of *Mangifera indica* leaves [13]. To date, there is limited information on lipid-lowering effect n on the expression of lipid profile markers. Therefore, the objective of present study was to evaluate the anti-inflammatory and hypolipemic properties of MLE on the improvement of hyperlipidaemia rats fed with HFD.

To determine the hypolipidemic activity of MLE on HFD-induced hyperlipidaemia rats, models of lipid metabolism abnormality were established by continuous 2-weeks feeding of HFD. This study investigated the effects of MLE on BW, the level of blood lipid level, liver tissue morphology and liver function parameters in HFD-induced hyperlipidaemia rats. Body weight affects the onset and management of hyperlipidaemia [3]. It has been clearly shown that HFD induced hyperlipidaemia rats was proved to be a useful model for the development of CVD. After MLE intervention, the weight of rats decreased. It has also been reported that an elevation in blood lipid concentrations of total serum cholesterol is related to an indication of increased mobilization of body fats, while high plasma levels of TC and LDL with a low HDL is an indicator of dyslipidemia, meaning increased risk of atherosclerotic cardiovascular disease [14]. Overall, MLEH effectively improved the symptoms of weight loss and lipid abnormality in HFD rats.

An obesogenic HFD feeding for a long period can result in excessive formation of free radicals through peroxyacylation reaction, as well as lead to inflammation, hyperlipidaemia and fatty liver disease and so on [15]. TNF-α is positively correlated with dyslipidemia [16]. In addition, IL-1β is essential for preventing the infliction of cellular and tissue injury, and accelerates the release of pro-inflammatory cytokines [15]. In our study, rats treated with MLE were found to have markedly lowered in the levels of IL-6 and IL-1β, as proinflammatory factors, indicated decreases blood levels of TNF-α, IL-1βand IL-6. This reduction might be due to inhibit the occurrence and development of inflammation [7]. Previous studies indicate that mangifera can enhance or stimulate the elimination of cholesterol from the body, eventually reducing blood lipid concentrations [13]. In general, this effect was less pronounced only in standard medication colestyramine, but not MLE in our present study. Interestingly, the measured parameters above were noticeably reverted back to near-normal levels after intragastric administration of MLE.

A long-term HFD feeding contributes to a stress reaction, such as liver lipid accumulation and other phenomena, causing liver function impairment [12]. The liver is counted as the major organ for lipid metabolism [17]. The disturbance of lipometabolism caused by HFD significant increases in TC, LDL-C, TG, resulting in lipid accumulation and fatty degeneration of hepatocytes [18].

Results from recent studies have implicated that activation of Peroxisome proliferator-activated receptors associated with the regulation of lipid metabolism and alleviation of inflammation triggers hypolipidemic activities via acting on gene expression involved in lipid homeostasis [19]. There is emerging evidence that PPARα, a positive regulator of lipolysis connected with fatty acid oxidation and extracellular lipid metabolism, has ability to regulate the lipolysis of very low-density lipoprotein-triglycerides (VLDL-TG), thereby raising plasma HDL-C levels and decreasing the levels of LDL-C and TG [19, 20]. On the other hand, CYP7A1, as a key protein for the control of cholesterol transport in vivo, plays an important role in inhibition cholesterol synthesis and conversion of excess cholesterol to bile acids [21]. From our study and available reports, we propose a probable mechanism of MLE related to alleviate hyperlipidaemia in hyperlipidaemia rats. Indeed, real-time qRT-PCR and western blot analysis validated that gene and protein expression levels of PPARα and CYP7A1, which were related to lipid metabolism and inflammation, were effectively modulated in the MLE group compared with those in the HFD group. Accordingly, given the overexpression of PPARα and CYP7A1 in MLE treated rats, we hypothesized that MLE led to upregulation in hepatic CYP7A1 through activation of PPARα pathway in HFD-induced hyperlipidaemia rats and promoted the conversion of cholesterol into BA and its excretion to accelerate the clearance of circulating cholesterol.

5 Conclusion

This present study has demonstrated the anti-dyslipidemia effects of MLE in high-fat diet-induced hyperlipidaemia rats. Also, most of these actions were comparable to colestyramine. These data suggest that the high doses of MLE are capable of ameliorating the lipid levels of serum TC, TG, and LDL-C prominently, and alleviating liver injury and hepatic steatosis by regulating inflammation and lipid metabolism. These protective efficacies were supported additionally by raised gene and protein expression levels of PPARα and CYP7A1. Moreover, these antihyperlipidemic roles were comparable with those of colestyramine suggesting the importance and

possible clinical impact of MLE in patients with abnormal blood lipids (ABL). However, other detailed regulation mechanisms might be associated with mediating hypolipemic actions of MLE and need to be analysed further. Though further researches are required to prove our main results outcomes, and these results mentioned above show that supplemented with MLE can alter both the plasma lipid profiles and liver function parameters, and may be useful in prevention of hyperlipidemia.

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