

Effects of the Mixture of *Cichorium intybus* L. and *Cinnamomum zeylanicum* on Hepatic Enzymes Activity and Biochemical Parameters in Patients with Nonalcoholic Fatty Liver Disease

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Abstract

The prevalence of nonalcoholic fatty liver disease (NAFLD) as a metabolic disorder affecting the liver function is rapidly increasing and there is a need to develop new and more efficient treatment. This study was designed to evaluate the protective effect of *Cichorium intybus* L. and *Cinnamomum zeylanicum* mixture infusion (2.5 and 0.5 g/100mL and twice/day) on patients with NAFLD. This before-after clinical trial study was performed on 25 patients with NAFLD. They were administered the mixture of extract prepared in special bags twice a day for 30 days. Hepatic and metabolic markers of NAFLD like alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphates (ALP), fasting blood sugar (FBS), cholesterol (chol), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) in plasma and also, fatty liver ultrasonographic grading were determined before and after using the extracts. 30-day treatment with extracts in NAFLD patients resulted in a significant decrease in ALT and AST. FBS, TG and ALP were also decreased after administration of the extracts but not significantly. A significant linear correlation was found between age and ALP, and between gender and liver enzymes. It is concluded that the mixture of *Cichorium intybus* L. and *Cinnamomum zeylanicum* extracts has some benefits in NAFLD patients

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making them valuable for future investigations.

Keywords

Nonalcoholic Fatty Liver Disease, *Cichorium intybus* L., Cinnamon, Liver Enzymes, Biochemical Parameters

1. Background

As a result of obesity epidemic, non-alcoholic fatty liver disease (NAFLD) is going to be the most important liver disease in the near future. The clinical significance of NAFLD is derived mostly from its manifestation in metabolic disruption and in its possible progression to end-stage liver failure. Many pathological conditions have been associated with NAFLD, such as diabetes mellitus, hyperlipidemia, obesity, metabolic syndrome and cardiovascular diseases. Historically, the first therapeutic line of NAFLD was non-pharmacologic measures consisted of diet and lifestyle modification in order to weight loss and control of associated metabolic disorders. However, the issue was always enough important and concerning for medical scientist to find pharmacologic approach, and efficacy of many drugs such as metformin, thiazolidinediones, vitamin E, betaine, *N*-acetylcysteine, ursodeoxycolic acid (UDCA), and probucol has been investigated for treating NAFLD afflicting patients. Nevertheless, none had a demonstrating effective resolution of NAFLD, and finding a proper and effective therapy is under different trials [1]-[3].

On the other hand, there has always been a tendency among medical researchers to seek remedial agents among traditional sources. In this respect, lots of plant extracts have been evaluated for their effectiveness in metabolic disorders. *Cinnamomum zeylanicum* and *Cichorium intybus* L. (Chicory or Kasni) have a long history of therapeutic use in traditional medicine for various diseases particularly diabetes and hepatic problems. *Cinnamomum zeylanicum* has been repeatedly investigated for its promising role in alleviation of diabetes and metabolic syndrome through increasing insulin sensitivity [4]-[8]. Chicory seed extract has also been tested and shown to have improving effects on pancreatitis, diabetes presentations, insulin signaling, and NAFLD in experimental set-ups [9]-[13].

The aim of this study was to determine the capability of *Cichorium intybus* L. and Cinnamon mixture infusion (2.5 and 0.5 g/100mL and twice/day) on patients with NAFLD.

2. Material and Method

To meet the aim of this study, 25 patients with NAFLD diagnosis who referred to the tertiary centre GI Clinic of Zahedan University of Medical Sciences were studied in 2012. The study protocol was approved by Tehran University of Medical Sciences Ethics Committee. All included patients had no history of coronary artery disease, alcohol or alcoholic beverages consumption, insulin-dependent diabetes, bleeding diathesis, severe anemia, and cancer within the past 5 years. There were no use of anti-coagulants and cyclosporine and conditions likely to lead to death within 5 years. Any conditions of chronic liver disease such as viral, metabolic, hereditary and autoimmune were excluded by detailed history and appropriate tests. Trans-abdominal ultrasonography and ultrasonography fatty liver grading were used for diagnosis by an experienced sinologist in all subjects before and after trial. According to the Declaration of Helsinki, all participants were provided with specific written information about the aims of the study before consents were obtained. Prior to blood collection, each individual was extensively interviewed by a specialized physician who filled in a structured questionnaire about disease and habit diet. The included subjects were administered *Cichorium intybus* L. and Cinnamon mixture infusion (2.5 and 0.5 g/100mL, twice/day) for 30 days at 7.5 am and 2 pm every day. A supervisor carefully checked to make sure that the volunteers were taking infusion properly. Blood samples were collected from all subjects before using *Cichorium intybus* L. and Cinnamon infusion and 12 hours after the last dose of 30-day treatment with infusion.

2.1. Plant Material

Cinnamomum and *Cichorium intybus* L. were supplied by Arak Medicinal Plants Company and identified as

Cinnamon zeylanicum and *Cichorium intybus* L.

2.2. Infusion Preparation and Protocol

The subjects were instructed how to prepare the infusion by mixing a total of (2.5 and 0.5 g/100mL) *Cinnamon* and *Cichorium intybus* L. infusion in 100 mL 98°C water for 30 minutes (Katalinic et al., 2006). A qualified expert supervised the whole procedure.

2.3. Biochemical Analysis of Serum Parameters

All biochemical serum analysis including alanine aminotransferase (ALT), aspartateamino transferase (AST), alkaline phosphates (ALP), fasting blood glucose (FBS), cholesterol (CL), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were performed with Pars test kits in the same laboratory.

2.4. Statistical Analysis

Results are presented as mean \pm SD. Statistical analyses were conducted using SPSS software (version 18). The paired t-test and Wilcoxon Matched-Pairs Signed-Ranks Test analysis were applied to this study and associations between parameters were determined through Pearson correlation analysis. Value of $p < 0.05$ was considered statistically significant.

3. Results

The mean \pm SD values for age and BMI and sex percentage of subjects have been showed in **Table 1**. After using *Cinnamon* and *Cichorium intybus* L. infusion, ALT activity decreased significantly ($p = 0.003$). The before and after mean \pm SD were 51.20 ± 37.16 and 36 ± 21.43 , respectively. A decrease in AST activity was also observed after administration of the infusion (41.20 ± 23.87 before versus 29 ± 17.73 after, $p = 0.000$). A decrease ($p = 0.419$) in ALP activity was observed by using the infusion. The mean \pm SD before and after using were 201.40 ± 57.92 and 191.95 ± 80.11 . Moreover a decrease ($p = 0.065$) in FBS was observed by using the infusion. The mean \pm SD before and after using were 99.30 ± 12.90 and 96.80 ± 10.83 . Also a decrease in TG was observed after administration of the infusion (150.70 ± 82.60 before versus 138.80 ± 53.82 after, $p = 0.394$). On the other hand, a decrease ($p = 0.402$) in HDL was observed by using the infusion. The mean \pm SD before and after using infusion were 78.15 ± 129.49 and 53.55 ± 27.26 . However an increase in cholesterol was observed after administration of the infusion (173.72 ± 66.96 before versus 187.39 ± 37.90 after, $p = 0.346$) (**Table 2**).

Analysis by Wilcoxon Matched-Pairs Signed-Ranks Test showed a significant decrease in grade of sonographic examination ($p = 0.020$).

A significant linear correlation was found between age and ALP ($df = 1.24$, $F = 5.753$ and $p = 0.028$). However, linear correlation was found between gender and ALT ($df = 1.24$, $F = 6.380$ and $p = 0.021$) and gender and AST ($df = 1.24$, $F = 6.832$ and $p = 0.018$).

Table 1. Demographic data of study subjects.

Subjects	Age	Sex	BMI
Patients (n = 25)	43.55 ± 17.28	Male (45%), Female (55%)	27.59 ± 2.81

Table 2. The effect of aqueous extract of *Cinnamon* and *Cichorium intybus* L. on liver biochemical enzymes parameters.

Biochemical tests	Before	After	p value
FBS	99.30 ± 12.90	96.80 ± 10.83	0.065
TG	150.70 ± 82.60	138.80 ± 53.82	0.394
Chol	173.72 ± 66.96	187.39 ± 37.90	0.346
HDL	78.15 ± 129.49	53.55 ± 27.26	0.402
AST	41.20 ± 23.87	29.00 ± 17.73	0.000
ALT	51.20 ± 37.16	36.00 ± 21.43	0.003
ALP	201.40 ± 57.92	191.95 ± 80.11	0.419

4. Discussion

The present study evaluated the effect of extract of *Cinnamon* and *Cichorium intybus* L. on determinant parameters of hepatic function in NAFLD patients. Except HDL and cholesterol, the other factors including FBS, TG, AST, ALT, and ALP have been partially improved by infusion of the extracts, and interestingly the decrease in AST and ALT was significant.

As a complex metabolic disorder manifested in the liver, NAFLD not only can lead to fibrosis, cirrhosis, and liver-related death, but also is considered a serious risk factor for cardiovascular diseases and metabolic syndrome. NAFLD is etiologically accompanied with insulin resistance which makes disruption of the main parameters of glucose and lipid metabolism expectable. So, monitoring these parameters is logical and useful for evaluating progression and clinical symptoms of the disease.

By using *Cinnamon* and *Cichorium intybus* L. extracts in this study, no remarkable change was observed in FBS, TG, cholesterol, and HDL level of NAFLD patients. This can be explained as these parameters were in the normal range before starting the treatment and there was no expectation to have significant change.

The AST/ALT ratio was in the normal range (less than 1) giving no probability of liver damage due to cirrhosis, alcoholic hepatitis, and hepatocellular carcinoma. Furthermore, ALP was decreased after treatment with extracts but the change was not significant indicating that the extract had no or partial effect on bile duct obstruction if existed. Significant decrease in the level of serum transaminases ALT and AST, and grade of sonographic examination was the good point of this study, though effectiveness of *Cinnamon* and *Cichorium intybus* L. extracts in NAFLD patients should be more confirmed.

There are several *in vitro*, animals, and/or human studies implicating on protective effects of *cinnamon* extract on insulin resistance, type 2 diabetes and metabolic syndrome [6] [14]. *Cichorium intybus* L. has also been shown to ameliorate experimental diabetes and NAFLD in rats via modulating the expression of peroxisome proliferator-activated receptors (PPARs) and sterol regulatory element-binding protein-1 (SREBP-1) genes in hepatocytes. PPARs are nuclear fatty acid receptors with known role in lipid and carbohydrate homeostasis via activating fatty acid catabolism and are molecular target of related pharmacologic agents including lipid lowering fibrates and insulin sensitizing thiazolidinediones. SREBPs also include a family of membrane-bound transcription factors regulating cellular pathways involved in insulin response and lipid metabolism. In this respect, PPARs ligands and modulators of SREBPs show promising strategies for treatment of NAFLD [13]. *Cichorium intybus* L. has also been shown to enhance glucose uptake and improve insulin sensitivity through inhibiting protein tyrosine phosphatase 1B (PTP1B) in adipogenic insulin signaling cascade both *in vitro* and *in vivo* [9].

5. Conclusion

It would be concluded that the therapeutic potential of cinnamon that is the possible mechanism of this activity may be free radical-scavenging polyphenol compounds [15] [16] and *Cichorium intybus* L. due to hepatoprotective effect on esculetin and a phenolic compound. Cichotyboside, a guaianolide sesquiterpene glycoside [17] [18] resulted in improving NAFLD, however the extracts has worth to be more evaluated for treating NAFLD and related complications. The limitations of the study were the lack of evaluating liver tissue and also the lack of controlling diet and activity.

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Abbreviation

Nonalcoholic fatty liver disease (NAFLD)
Alanin aminotransferase (ALT)
Aspartate aminotransferase (AST)
Alkaline phosphates (ALP)
Fasting blood sugar (FBS)
Cholesterol (chol)
Triglycerides (TG)
High-density lipoprotein (HDL)
Low-density lipoprotein (LDL)
Ursodeoxycolic acid (UDCA)
Peroxisome proliferator-activated receptors (PPARs)
Sterol regulatory element-binding protein-1 (SREBP-1)
Protein tyrosine phosphatase 1B (PTP1B)