

Could phytoproducts be effective in the treatment of nonalcoholic steatohepatitis?

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Abstract

Background: Despite the fact that liver steatosis is a very frequent condition mainly due to alcohol consumption and metabolic syndrome, yet there is no consensus regarding appropriate therapy.

Aim and study design: Open label nonrandom study in order to assess efficiency of liver protective phytoproducts in patients with nonalcoholic steatohepatitis(NASH)

Patients and methods: 30 patients, 11 men and 19 women, mean age=49,23±12,92 years old, diagnosed by abdominal Duplex exam with mild to moderate liver steatosis, having slightly elevation of liver enzymes, undertook this study, after ruling out other causes of steatohepatitis(alcohol consumption or other toxic exposure, hepatitis viruses, endocrine conditions). Patients adjusted life style including diet with limitation of fat and carbohydrates food intake and also received a mixture of registered, over the counter phytoextracts (*Picrorhiza kurroa* 100mg, *Eclipta alba* 50mg, *Phyllanthus niruri* 50mg, *Tinospora cordifolia* 50mg, *Boerhaavia diffusa* 25mg, *Centella asiatica* 20mg, *Piper longum* 10mg /tablet) twice a day for 3 months.No drop-out cases were recorded.Ultrasound exam and liver biochemistry were also performed at the finish of the treatment and compared to previous data.

Results: Severity of steatosis index before therapy was 1,33±0,48 versus the same index after 3 months of treatment: 0,5±0,51, being very statistically significant ($p<0.0001$).Analyze of the evolution of liver enzymes also revealed a good outcome:53,30±6,86 IU/ml versus 41,76±3,58IU/ml($p<0,0001$).

Conclusions: Phytoproducts could improve liver steatosis and biochemical profile, at least in initially course of treatment of patients with mild to moderate NASH.

Keywords: nonalcoholic steatohepatitis(NASH), therapy with phytoproducts

1. Introduction

Liver steatosis or fatty liver disease is a very frequent condition mostly seen in well developed countries, mainly due to alcohol consumption, obesity, diabetes mellitus, metabolic syndrome, viral hepatitis B and C or toxicity to various drugs.[1,2,3]

From clinical point of view nonalcoholic liver diseases (NAFLD) could manifest in a wide range

of presentations: as a simple "innocent" steatosis, nonalcoholic steatohepatitis (NASH), liver fibrosis and end stage liver disease with cirrhosis.[4,5,6]

Gold standard diagnosis remains the liver biopsy and the histopathologic diagnosis [6], but there are also a lot of noninvasive possibilities of diagnosis like fibromax test with scoring of steatosis and NASH index, ultrasonography with recently CAP (Controlled Attenuation Parameter), CT (computer-

tomography), MRI (magnetic resonance imaging) for the assessment of the severity of steatosis, fibroscan elastography and fibromax for the assessment of fibrosing score [7,8,9].

Ultrasonography is known to have a high sensitivity (60-100%) and relatively good specificity (77-95%) in the diagnosis of liver steatosis and due to the fact of its innocuity, low costs and high patient's compliance is still very widely used in clinical practice [10].

The most important therapeutical possibilities are : life style changes with exercise and diet with gradual weight reduction and avoidance of hepatotoxic agents, control of diabetes and hypertriglyceridemia, insulinsensitizer agents, supplements with vitamin E, antisteatotic and antioxidant agents with hepatoprotective effects, antibiotics and probiotics in order to restore the normal intestinal microbiome.[11]

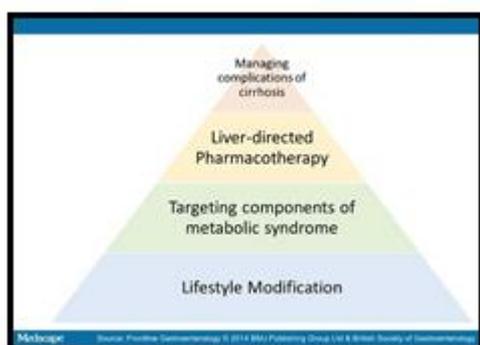


Figure 1. Management strategies in non-alcoholic fatty liver disease (NAFLD) [11]

Despite a lot of clinical research, in this area of great interest, no consensus therapy is currently available [12].

Phytotherapy as a part of alternative therapy with botanicals as bulk herbs, tinctures, capsules and tablets; includes herbs and other plant materials has a long history of research and use even in Europe.

Liver steatosis and some metabolic issues could be treated with botanicals, given as different type of drinking medicine, with increasing concentrations like teas, infusions and decoctions, after steeping fresh or dried herbs for a few minutes in water and formulations as extracts: herbs being extracted

with an organic solvent or tinctures were extraction was made with alcohol [13].

2. Aim and study design

The study we have performed was an open label nonrandom study in order to assess efficiency of some over the counter liver protective phytoproducts in patients with nonalcoholic steatohepatitis (NASH)

3. Patients and methods

30 patients, 11 men and 19 women, mean age = 49,23±12,92 years old were enrolled in this study after signing the informal content forms.

They were thoroughly clinical examined, with assessment of the body mass index (BMI), hepato and splenomegaly characteristics.

They have undertaken usually lab studies in order to evaluate liver disease: hemoleucogram, transaminases (ASAT, ALAT), gamma GT (GGT), total bilirubin, albumin, international normalized ratio (INR), fast glucose, total cholesterol, high density (HDL) and low density (LDL), cholesterol, trygliderides, feritine, creatinin, Hepatitis B virus surface antigen (antigenAg HBs), antibodies anti hepatitis C virus (Ab antiHCV), thyroid stimulating hormone (TSH), urine tests, feccal antigen for Helicobacter pylori infection.

The Duplex ultrasound examination was made with a high resolution GE device Logic 5 Expert, in 8 hours fasting patients, before and after completing the treatment.

The semiquantitative assessment of the severity of steatosis was made according to scoring of Tominaga at al. [14]: grade 0- no steatosis, grade 1- mild steatosis, grade 2-moderate steatosis and grade 3-severe steatosis.

The inclusion criteria were: mild to moderate diffuse liver steatosis diagnosed by abdominal Duplex exam and slightly elevation of liver enzymes, consistent with the diagnosis of NASH.

Other causes of steatohepatitis(alcohol consumption or other toxic exposure, hepatitis viruses, endocrine conditions, cortison or other potential steatotic drugs) were ruled out.

Patients adjusted life style including daily exercise, diet with limitation of saturated fat and carbohydrates and exceeding of fibers food intake.

They have also received a mixture of registered, over the counter indian phytoextracts: *Picrorhiza kurroa* 100 mg, *Eclipta alba* 50 mg, *Phyllanthus niruri* 50 mg, *Tinospora cordifolia* 50 mg, *Boerhaavia diffusa* 25 mg, *Centella asiatica* 20 mg, *Piper longum* 10 mg /tablet, twice a day for 3 months long. No drop-out cases were recorded.

Liver biochemistry tests were also performed before and at the finish of the treatment and compared to previous data .

The study was aproved by the local ethical comitee and patients and their families provided written informed consent. Statistical analysis was made using GraphPad software with the panel for continous data, with calculation of mean values and standard deviation, unpaired t test, p values with CI= 95%.

Table 1. Ultrasound assessment of the severity of diffuse liver steatosis [14]

Severity of steatosis - ultrasound scoring	Hyperechoic Bright liver(hepatic echotexture)	Posterior atenuation	Portal vessels and diaphragm visualisation
Mild(degree 1)	+	+	Normal
Moderate(degree 2)	++ between degree 1 and 3	++ between degree 1 and 3	Slightly blurred vessels
Severe(degree 3)	+++	+++	Blurred vessels and no visualisation of the diaphragm

Table 2. Basic patients data

Hb (gr%)	Ht(%)	L (count/ml)	ALT (ui/ml)	GGT (ui/ml)	Creat (mg/dl)	Chol (mg%)	Trigl (mg%)	Bil (mg%)	Fast glucose (mg%)	Alb (g/l)	TSH (µmol/ml)	BMI (kg/m ²)
12,26±0,64	45,95±0,91	7723±589	53,30±6,86	33,7±5,61	0,79±0,083	228±25,63	141±23,53	0,8±0,02	98±12,52	5,5±0,21	3,16±0,4	31,93±0,84

Legend: Hb = hemoglobin, Ht = hemathocrit, L = leucocytes, ALT = alanin-aminotransaminases, GGT = gamma glutamyl transpeptidase, creat = creatinin, Chol = cholesterol, HDL = high density of lipoproteins, LDL = low density of lipoproteins, Trigl = triglycerides, Bil = bilirubin, alb = albumin, TSH = thyroid stimulating hormon, BMI= body mass index.

4. Results

The starting, basic patients data are depicted in the table below(table 2)

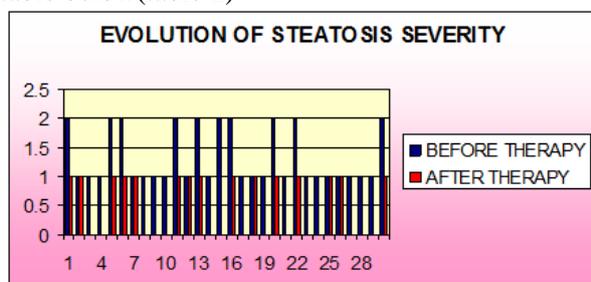


Figure 1. Evolution of the steatosis severity index related to the treatment

As seen in the figure below(figure 1) the severity of liver steatosis has significantly improved: index before therapy was 1,33±0,48 versus index after 3 months of treatment: 0,5±0,51, being very statistically significant (p<0.0001).

BMI also improved after therapy: 31,93 kg/m² ± 0,94 vs. 31,65 kg/m²±0,96, but in a low range, the difference being not statistically significant (p=0,277).

The ultrasound steatosis related features are depicted in figure 2: bright liver, posterior atenuation with decreasing of diaphragm definition.



Figure 2. Liver steatosis: ultrasound assessment

The liver tests have also significantly improved after first course of therapy.

The profile of the evolution of the liver enzymes revealed a good outcome, ALAT: $53,30 \pm 6,86$ IU/ml versus ALAT: $41,76 \pm 3,58$ IU/ml ($p < 0,0001$).

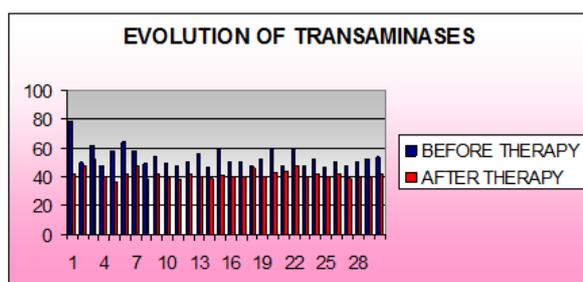


Figure 4. The profile of the liver enzymes

5. Discussions

Suggestions regarding treatment in NAFLD highlight the importance of life style change, targeting the metabolic syndrome if present, liver directed pharmacotherapy and management of complications in end stage liver disease.

Regarding pharmacotherapy, the majority of studies are focussed on insulinsensitizers, vitamin E supplements, but no consensus therapy is yet available as guidelines [15,16,17].

Several asian studies emphasize the importance of some phytochemicals in the treatment of fatty liver including some aspects of the underlying metabolic disorders.

In a study investigating the antioxidant and antifibrotic activity, 85 patients with NASH with or without HCV coinfection were treated for 6 months with of a complex sylubin-vitamin E therapy, showing a good outcome with

improvement of liver enzymes profiles and some fibrosing biomarkers [18].

In a relatively recent published study conducted in Korea some researchers attempted to find some formula for the treatment of metabolic syndrome and fatty liver in mice, by preparing a mixture of dietary components including grape extract, green tea extract and L-carnitine with good results [19].

Orraly administrated pycnogenol(PYC), a natural extract from a Pinus species, may serve to prevent NASH-induced liver damages, in a high fat diet rat model, concluded a chinese study , also published in Phytotherapy Research by L Mei et al [20].

The beneficial effect of dietary supplements is sustained by a lot of studies, majority of them being observational or rat model studies, demonstrating the good outcome regarding the metabolic issues and alleviation of liver steatosis, after consuming coconut flakes, spirulina, grape or pomegranate juice or flowers [21,22,23,24].

From such of an outnumbered different studies it is really very difficult to reach to a conclusion or to attempt to compare one to another, in order to make a stratification of their relevancy.

Despite the multitude of clinical trials with different agents, researchers have failed to identify effective treatments for patients with NASH, because of the great heterogeneity due to particularities of the clinical trials design and very different regimens of treating.

Probably we need to better understand the concept of NAFLD and its underlying pathogenic pathways in order to find a correct cure.

Our data shown that a particular combination of life style modification in association with a mixture of some over the counter, indian herbal remedies could equally decrease the severity of fat liver infiltration.

Despite encouraging results, present study has his own multiple limitations, being addressed only to a low range scale of steatohepatitis, comprising not a large cohort of patients and assessment of the liver steatosis by imagistic semiquantitative method.

6. Conclusions

Phytoproducts associated to life style changes could be an alternative option for the treatment of the fatty liver.

Our study showed an improvement of liver steatosis and biochemical profile, at least in initially course of treatment of patients with mild to moderate NASH.

Compliance with Ethics Requirements. Authors declare that they respect the journal's ethics requirements. Authors declare that they have no conflict of interest and all procedures involving human / or animal subjects (if exist) respect the specific regulation and standards.

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