

REVIEW

DERLEME

Efficacy of Herbal Remedies in The Treatment of Nonalcoholic Fatty Liver Disease/Hepatic Steatosis in Human and Animals

Bülent ELİTOK*

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S U M M A R Y

Nonalcoholic fatty liver disease (NAFLD) is a condition in which excess fat accumulates in the liver of a patient without a history of alcohol abuse. Nonalcoholic fatty liver disease (NAFLD) is characterized by a wide range of liver damage spanning steatosis, nonalcoholic steatohepatitis (NASH), cryptogenic liver cirrhosis, and even to hepatocellular carcinoma. The pathogenesis of NASH is multifactorial, with insulin resistance and increased fatty acid are possibly important factors in the accumulation of hepatocellular fat, and oxidative stress, lipid peroxidation, mitochondrial dysfunction, and dysregulation of various cytokines are important causes of hepatocellular injury in steatotic liver. Herbal remedies have long been used in treating liver inflammation and other symptoms associated with fatty liver disease, although more clinical research evidence may be necessary to determine these supplements' true effectiveness and mechanisms of action. In this review, we tried to describe the characteristics and current treatments of NAFLD and provide opportunities for developing new therapeutic management approaches, with particular emphasis on development of animal studies.

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İnsan ve Hayvanlarda Nonalkolik Yağlı Karaciğer Hastalığı/Hepatik Steatozis Tedavisinde Bitkisel İlaçların Etkinliği

ÖZET

Alkol alımı ile ilgili olmayan yağlı karaciğer hastalıkları (NAFLD) geçmişte alkol kullanmamış hastaların karaciğerlerinde aşırı yağ birikmesi durumunu ifade eder. NAFLD, alkol alımı ile ilgili olmayan steatohepatit (NASH), kriptojenik karaciğer sirozu ve hepatoselüler karsinoma varan yaygın karaciğer hücre yıkımı hasarını ifade eder. NASH'ın patogenezi multifaktöriyel olup, muhtemel en önemli faktörler; insülin rezistansı ve artan yağ asidi nedeniyle karaciğer hücrelerinde yağ birikimi, oksidanlara bağlı stres, lipid peroksidasyon, mitokondrial fonksiyon bozukluğu ve değişen oranlardaki sitokinlerin regülasyon bozuklukları steatotik karaciğerde hepatoselüler hasarın en önemli sebepleridir. Etki mekanizmalarının ve gerçek etkilerinin daha çok bilimsel araştırmalarla kanıtlanmasına gerek duyulmasına rağmen, bitkisel ilaçlar karaciğer yangıları ve karaciğer yağlanması ile ilişkili diğer semptomların tedavilerinde uzun süreden beri kullanılmaktadırlar. Bu derlemede, hayvan çalışmalarının geliştirilmesinin gerekliliği üzerine kısmen vurgu yapmakla birlikte, NAFLD'nin bitkisel ilaçlarla tedavisindeki özellikleri mevcut durumu ve yeni terapötik yaklaşımların geliştirilmesi için fırsatlar sağlamaya çalıştık.

Key Words

Fatty Liver Disease
Herbal Treatment
Nonalcoholic

Anahtar Kelimeler

Yağlı Karaciğer Hastalığı
Bitkisel Tedavi
Nonalkolik

Afyon Kocatepe University
Faculty of Veterinary Medicine
Department of Internal Medicine
Afyonkarahisar / TURKEY

* Corresponding author

Email: elitok1969@hotmail.com

Phone: +90 (553) 969 52 89

INTRODUCTION

The most frequent liver disorder in metabolic syndrome is nonalcoholic fatty liver disease. Its pathogenesis is complex, multifactorial process, characterized by insulin resistance and involves endocrine system. Nonalcoholic fatty liver disease (NAFLD) is increasingly recognized clinico-pathological condition that may progress to end-stage liver disease. The pathological picture resembles alcohol-induced liver injury, but occurs in patients who avoid alcohol abuse (Angulo and Lindor 2002). NAFLD is classified into simple steatosis and nonalcoholic steatohepatitis (NASH) (Takahashi et al 2012). In NASH, not only steatosis but also intralobular inflammation and hepatocellular ballooning are present, often accompanied by progressive fibrosis (Takahashi and Fukusato 2008). Long-standing NASH may progress to liver cirrhosis, and hepatocellular carcinoma (HCC) may be an outcome (Powell et al 1990, Harrison et al 2003, Cohen et al 2011).

NAFLD has been increasing worldwide over recent decades in line with the increased prevalence of obesity, type 2 diabetes, and hyperlipidemia. NAFLD/ NASH is currently regarded as the most common chronic liver disease worldwide. It is estimated that about 20% of all adults have NAFLD and 2%-3% of adults have NASH (Neuschwander-Tetri 2005). NAFLD affects 10–24% of the general population from different countries. The prevalence of NAFLD, however, increases significantly to 57.5–74% in obese individuals (Ballentani et al 2000, Luyckx et al 1998). NAFLD affects 2.6% 10 of children and this figure increases to 22.5–52.8%12 in the obese child population (Franzese et al 1997).

Studies of NAFLD/NASH have limitations in human materials, because the occurrence and progression of NAFLD/NASH requires a long period of several decades and ethical limitations exist in administering drugs to patients or collecting liver tissues from patients. Animal models of NAFLD/NASH give crucial information, not only in elucidating the pathogenesis of NAFLD/NASH but also in examining therapeutic effects of various agents. These animal models need to reflect correctly both histopathology and pathophysiology of human NAFLD/NASH (Takahashi et al 2012). Recently, several review articles on animal models of NAFLD/NASH have been published (Takahashi et al 2012, Schattenberg and Galle 2010, Hebbard and George 2011). It is hoped that animal models which more closely reflect the histopathology and pathophysiology of human NASH will be

developed in the future, and information on pathogenesis and treatment of NASH will increase by using these models (Angulo and Lindor 2011, Takahashi et al 2012).

Herbal remedies have long been used in treating liver inflammation and other symptoms associated with fatty liver disease, although more clinical research evidence may be necessary to determine these supplements' true effectiveness and mechanisms of action. In a study the mechanism of liver injury induced by carbon tetrachloride (CCl₄) in rats with non-alcoholic fatty liver disease (NAFLD), and the therapeutic effects of the extract mixture of Dangyao (*Swertia pseudochinensis* Hara) and Shuifeiji (*Silybum marianum* Gaertn) on NAFLD rats. The results of the study show that the mixture of Dangyao and Shuifeiji extracts could decrease the susceptibility and degree of liver injury induced by hepatotoxin in rats with NAFLD. Balance regulation of pro- and anti-oxidative stress factors are involved in the mechanism (Mao et al 2012). In the other study, to evaluate the probable effect of the crude extract of *Silybum marianum*, with high polyphenolic content on experimental nonalcoholic steatohepatitis has been observed that *Silybum* crude extract has beneficial effects on NASH are mainly due to its antioxidant and anti-inflammatory properties (Aghazadeh et al 2011).

Luper (1998) reported that *Picrorhiza kurroa*, though less well researched than *Silybum*, appears to have similar applications and mechanisms of action. When compared with *Silybum*, the hepatoprotective effect of *Picrorhiza* was found to be similar, or in many cases, superior to the effect of *Silybum*.

In Phyllis A. Balch's book "Prescription for Nutrition Healing," (Balch 2010) stated that artichoke, turmeric, ligustrum, milk thistle, burdock, dandelion, fumitory and black radish may be among the most helpful supplements for this health problem. In this review, we determined a lot of researches about the possible effects of herbal treatments on NAFLD/NASH in animal models.

Lugası et al (2005) and Schrader (1956) claim that; although the exact mechanism of biologically active compounds in black radish, on the lipid metabolism and lipid peroxidation, is not clear yet, a beneficial effect of the drug was evident in alimentary hyperlipidaemia.

Park et al (2010) estimated the inhibitory effect of two polysaccharides from *Taraxacum officinale* (TOP) on CCl₄-induced oxidative stress and inflammation in Sprague-Dawley rats. They suggest that TOPs have a

hepatoprotective effect by modulating inflammatory responses and ameliorating oxidative stress. In the other work, it was estimated that the inhibitory effect of two polysaccharides from *Taraxacum officinale* (TOP) on CCl₄-induced oxidative stress and inflammation in Sprague-Dawley rats. Histopathological observation further revealed that CCl₄-induced moderate levels of inflammatory cell infiltration, centrilobular fatty change, apoptosis, and necrosis. However, TOPs pretreatment markedly decreased AST and ALT activities as well as hepatic lesions. TOPs pretreatment also reversed other hepatitis-associated symptoms, including GSH depletion, inhibited anti-oxidative enzyme activities, up-regulation of NF-kappaB and increased expression in regulation of inflammatory mediators, such as inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2, tumor necrosis factor (TNF)-alpha, and interleukin (IL)-1beta. These authors suggest that TOPs have a hepatoprotective effect by modulating inflammatory responses and ameliorating oxidative stress.

Insulin resistance occurs in almost all patients with non-alcoholic fatty liver disease (NAFLD), and mitochondrial dysfunction likely plays a pivotal role in the progression of fatty liver to non-alcoholic steatohepatitis (Tseng et al 2011, Takahashi and Fukusato 2008). Curcumin is a compound derived from the spice turmeric, a spice that is a potent antioxidant, anti-carcinogenic, and anti-hepatotoxic agent. Although the efficacy and safety of these herbal medicines need to be evaluated in multicenter large-scale clinical trials, Chinese medicine is promising and effective for preventing and treating NAFLD disease (Kuo et al 2012, Dong et al 2012). In a study related with the effects of Qushi Huayu Decoction (QSHYD) (Li et al 2009), a compound traditional Chinese herbal medicine, in prevention and treatment of non-alcoholic fatty liver disease (NAFLD) in rats observed that QSHYD could affect the ADP-FFA pathway by increasing the content of serum ADP, which may be one of its important mechanism in preventing and treating NAFLD in rats (Dong et al 2012).

Evidences from randomized controlled trials (RCTs) for the efficiency of traditional Chinese medicine (TCM) on the treatment of nonalcoholic fatty liver disease (NAFLD) were conflicting (Shi et al 2012, Xu and Hu 2003, Yang et al 2011). Studies were searched on PubMed and China National Knowledge Infrastructure from January 1995 to June 2010. RCTs comparing either TCM formulations alone or in combination with placebo, ursodeoxycholic acid, insulin sensitizers, lipid-lowering drugs, or antioxidants were included. The category of most usually used herbs in the treatment

of NAFLD was also calculated. Five thousand nine hundred and four patients from 62 RCTs were included for meta-analysis and 25,661 patients from 419 clinical studies were for TCM formulation analysis. Comparing with western medicines mentioned above, TCM had a better effect on the normalization of alanine aminotransferase and disappearance of radiological steatosis in the treatment of NAFLD. Furthermore, 246 kinds of Chinese herbs were included in our present study, with an average of 10 herbs (range 1-31) in each formulation. Hawthorn Fruit (321 times in 17,670 patients) was the most often used herb in the treatment of NAFLD. In conclusion, TCM has modest benefit to the treatment of NAFLD (Shi et al 2012).

In the other study (Yang et al 2011), obese individuals with a large belly, red face, thick and yellow coated tongue, constipation, and avoidance of heat are thought accumulates of evil internal heat, and they are also treated with purgatives such as Ta-Cheng-Chi-Tang (TCCT), Xiao-Chen-Chi-Tang (XCCT), and Tiao-Wei-Chen-Chi-Tang (TWCCT) by TCM doctors. The results of the study showed that XCCT and TWCCT might exert beneficial effects in the treatment of hyperlipidemia.

Yang et al (Yang et al 2012), in their study related to investigate the therapeutic effects of Ping-tang Recipe (PTR) on high-fat diet (HFD)-induced insulin resistance and non-alcoholic fatty liver disease (NAFLD), and to elucidate the underlying mechanisms suggested that PTR improves insulin resistance and reverse hepatic steatosis in the rat model of HFD-induced obesity through promotion of lipolysis and reduction of lipogenesis, which involves the AMPK signaling pathway, thus representing a new therapeutic intervention for obesity related insulin resistance and NAFLD.

The Kampo formula keishibukuryogan (KBG, Guizhifulingwan) is frequently used in traditional Japanese and Chinese medicine to treat several symptoms, manifests anti-inflammatory and scavenging effects. While it is unlikely that Kampo formulas may substitute the current nutritional approaches to the metabolic syndrome, future studies should address the possibility of an additive effect, through possible anti-inflammatory mechanisms (Fujimoto et al 2010).

CONCLUSION

Botanicals have been used traditionally by herbalists and indigenous healers worldwide for the prevention and treatment of liver disease. In this

century, clinical research has confirmed the efficacy of several plants in the treatment of liver disease. Basic scientific research has uncovered the mechanisms by which some plants afford their therapeutic effects. *Silybum marianum* (milk thistle) has been shown to have clinical applications in the treatment of toxic hepatitis, fatty liver, cirrhosis, ischemic injury, radiation toxicity, and viral hepatitis via its antioxidative, anti-lipid peroxidative, antifibrotic, anti-inflammatory, immunomodulating, and liver regenerating effects.

REFERENCES

- Aghazadeh S. Amini R. Yazdanparast R. Ghaffari SH. 2011.** Anti-apoptotic and anti-inflammatory effects of *Silybum marianum* in treatment of experimental steatohepatitis. *Exp Toxicol Pathol.* 63(6):569-74.
- Angulo P. Lindor KD. 2002.** Non-alcoholic fatty liver disease. *Journal of Gastroenterology and Hepatology.* 17:186–S190.
- Angulo P. Lindor KD. 2011.** Treatment of non-alcoholic fatty liver: present and emerging therapies. *Sem. Liver Dis.* 21: 81–8.
- Balch AP. 2010.** Prescription for Nutritional Healing. 4 th edition. Avery Trade; 5 Rev Upd edition, USA
- Ballentani S. Saccoccio G. Masutti F. 2000.** Prevalence of and risk factors for hepatic steatosis in northern Italy. *Ann. Intern. Med.* 132: 112–7.
- Cohen JC. Horton JD. Hobbs HH. 2011.** Human fatty liver disease: old questions and new insights. *Science.* 332: 1519-1523
- Dong H. Lu FE. Zhao L. 2012.** Chinese herbal medicine in the treatment of nonalcoholic fatty liver disease. *Chin J Integr Med.* 18(2):152-60.
- Franzese A. Vajro P. Argenziano A. 1997.** Liver involvement in obese children. Ultrasonography and liver enzyme levels at diagnosis and during follow-up in an Italian population. *Dig. Dis. Sci.* 42: 1438–2.
- Fujimoto M. Tsuneyama K. Kinoshita H. Goto H. Takano Y. Selmi C. Keen CL. Gershwin ME. Shimada Y. 2010.** The traditional Japanese formula keishibukuryogan reduces liver injury and inflammation in patients with nonalcoholic fatty liver disease. *Ann N Y Acad Sci.* 1190:151-8.
- Harrison SA. Torgerson S. Hayashi PH. 2003.** The natural history of nonalcoholic fatty liver disease: a clinical histopathological study. *Am J Gastroenterol.* 98: 2042-2047.
- Hebbard L. George J. 2011.** Animal models of nonalcoholic fatty liver disease. *Nat Rev Gastroenterol Hepatol.* 8: 35-44
- Kuo JJ. Chang HH. Tsai TH. Lee TY. 2012.** Curcumin ameliorates mitochondrial dysfunction associated with inhibition of gluconeogenesis in free fatty acid-mediated hepatic lipoapoptosis. *Int J Mol Med.* 30(3):643-9.
- Li HS. Feng Q. Xu LL. Chen SD. Li XM. Hu YY. 2009.** Effects of Qushi Huayu Decoction in prevention and treatment of fatty liver in rats based on adiponectin-free fatty acid pathway. *Zhong Xi Yi Jie He Xue Bao.* 7(6):546-51.
- Lugasi A. Blazovics A. Hagymasi K. Kocsis I. Kery A. 2005.** Antioxidant effect of squeezed juice from black radish (*Raphanus sativus L. var niger*) in alimentary hyperlipidaemia in rats. *Phytother Res.* 19(7):587-91.
- Luper S. 1998.** A review of plants used in the treatment of liver disease: part 1. *Altern Med Rev.* 3(6):410-21.
- Luyckx FH. Desai C. Thiry A. 1998.** Liver abnormalities in severely obese subjects. effect of drastic weight loss after gastroplasty. *Int. J. Obes.* 22: 222–6.
- Mao ZM. Song HY. Yang LL. Liu T. Li DF. Zheng PY. Liu P. Ji G. 2012.** Effects of the mixture of *Swertia pseudochinensis* Hara and *Silybum marianum* Gaertn extracts on CCl(4)-induced liver injury in rats with non-alcoholic fatty liver disease. *Zhong Xi Yi Jie He Xue Bao.* 10(2):193-9.
- Neuschwander-Tetri BA. 2005.** Nonalcoholic steatohepatitis and the metabolic syndrome. *Am J Med Sci.* 330: 326-335.
- Park CM. Youn HJ. Chang HK. Song YS. 2010.** TOP1 and 2, polysaccharides from *Taraxacum officinale*, attenuate CCl(4)-induced hepatic damage through the modulation of NF-kappaB and its regulatory

mediators. *Food Chem Toxicol.* 48(5):1255-61.

Powell EE. Cooksley WG. Hanson R. Searle J. Halliday JW. Powell LW. 1990. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. *Hepatology.* 11(1):74-80.

Schattenberg JM. Galle PR. 2010. Animal models of non-alcoholic teatohepatitis: of mice and man. *Dig Dis.* 28: 247-254.

Schrader R. 1956. Black radish in the treatment of liver and bile duct diseases. *Hippokrates.* 27(17):561-3.

Shi KQ. Fan YC. Liu WY. Li LF. Chen YP. Zheng MH. 2012. Traditional Chinese medicines benefit to nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Mol Biol Rep.* 39, (10): 9715-9722.

Takahashi Y. Fukusato T. 2008. Pathology of nonalcoholic steatohepatitis. In: *Current Research in Hepatology 2.* Trivandrum: Research Media. 99-112.

Takahashi Y. Soejima Y. Fukusato T. 2012. Animal models of nonalcoholic fatty liver disease/ nonalcoholic steatohepatitis. *World J Gastroenterol.* 18(19): 2300-2308.

Tseng SH. Chien TY. Chen JR. Lin IH. Wang CC. 2011. Hypolipidemic effects of three purgative decoctions. *Evid Based Complement Alternat Med.* 2011:249-254.

Xu LM. Hu YY. 2003. Studies on treatment of fatty liver with traditional Chinese medicine. *Zhong Xi Yi Jie He Xue Bao.* 1(2):138-41.

Yang LL. Wang M. Liu T. Song HY. Li DF. Zheng PY. Liu P. Ji G. 2011. Effects of Chinese herbal medicine Jiangzhi Granule on expressions of liver X receptor α and sterol regulatory element-binding protein-1c in a rat model of non-alcoholic fatty liver disease]. *Zhong Xi Yi Jie He Xue Bao.* 9(9):998-1004.

Yang SY. Zhao NJ. Li XJ. Zhang HJ. Chen KJ. Li CD. 2012. Ping-tang Recipe improves insulin resistance and attenuates hepatic steatosis in high-fat diet-induced obese rats. *Chin J Integr Med.* 18(4):262-8.