

Analysis of Metabolic Biomarkers in Non-Alcoholic Fatty Liver Disease (NAFLD); A Comprehensive Review

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ABSTRACT

Non-alcohol fatty liver disease (NAFLD) is one of the most common chronic liver problems across the world accounting 25% of the global population. The major groups that are mostly affected are young children and obese population. It is identified to be correlated with metabolic syndrome such as mellitus diabetes, hypertension, insulin resistance. Non-alcoholic steatohepatitis (NASH) is the robust form of NAFLD which has led to necro-inflammation and liver fibrosis. The standard and well-known diagnostic method till now is 'liver biopsy' but it impedes the examining of the tissue because of its invasive nature. Other diagnostic study usually involved imaging tools MRI or ultrasonography for discriminating simple steatosis with prognostic NASH also have certain limitations. Due to the ever-rising rate of NAFLD, there is an imperative need of developing non-invasive biomarkers for better monitoring and prophecy of the disease. There is also a need for the better treatment for curing NAFLD. In the knowledge of people, it has been observed that medicinal plants have known to possess professional therapeutic properties *Swertia chiraiyta*, a customary indigenous folk plant primordial to the upper regions of temperate Himalayas, Nepal and Bhutan is used in various ailments of liver disorders, ulcers, fever, diabetes, skin, and various other diseases. The current review focuses on epidemiologic, pathogenetic aspects and both the current and prospective biomarkers involved in NAFLD assessment that has the potential to leverage better understanding of solving the problem. Moreover, it characterizes the current treatment of NAFLD while discussing the other newer dimension of formulation for future prospects.

Keywords: Non-alcoholic fatty liver disease, metabolic syndrome, NASH, biomarkers, *Swertia chirata*, Indigenous medicine.

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1 Introduction

With an extreme growing population, concomitant diseases are increasing at its best in today's date. Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases that are concern

for a massive amount of people and pandemic across the globe [1]-[3]. It is a multifarious metabolic disorder which is generally caused by the infiltration of triglyceride in the liver in omission of alcohol consumption [4]. It is stratified with an array of liver diseases starting from simple steatosis to non-alcoholic hepatosteatosis (NASH) that is characterised by inflammation, damage, or ballooning or mallory bodies [5]. The progression of NAFLD develops into liver fibrosis, cirrhosis with certain complications and finally progressing into a dire hepatocellular carcinoma (HCC) which can lead to death of a patient [6]. NAFLD is becoming prevalent in almost across the globe, it has currently estimated to be 25%. It has been evaluated that NAFLD is highly prevalent in South American and Middle East countries with percentage of 31% and 32% respectively [7]. The rates of prevalence in children are unclear due to the non-availability of non-invasive diagnostic techniques. Consequently, the prevalence of the general population is calculated by measuring plasma serum biomarkers of non-alcoholic fatty liver disease. The two most quintessential biomarkers are alanine aminotransferase (ALT) and aspartate aminotransferase (AST). It has scrutinized that there is no reporting of exact threshold of ALT AND AST that could possibility use to indicate NAFLD in patients. The diagnosis of NAFLD are usually done by ultrasonography that will help in detection of steatosis only when there is certain amount of fat accumulated in the liver; other sensitive techniques are magnetic resonance imaging (MRI) or proton MR spectroscopy but it will impede the prognosis as it is highly-expensive. The only standard and well-known diagnostic method till now are 'liver biopsy'; however, it obstructs the examining of the tissue because of its non-feasible nature, some ethical issues or errors in the sampling and so, hence, the development of non-invasive method is prerequisite [8]. Patients with NAFLD/NASH are associated with other metabolic comorbidities and these are insulin resistance, diabetes mellitus type 2, hypertension, dyslipidaemia and most important etiology is obesity, paralleling with the substantial increase in NAFLD [9]-[10]. Most of the people with NAFLD are obese over-weight. Apart from metabolic disorders, drugs can also induce liver toxicity for instance, tamoxifen, methotrexate, amiodarone. The epidemic of NAFLD/NASH is now considered to be the indicator of liver transplantation in probably next few years from now which will ultimately lend most of the people with exorbitant rates of the treatment [11]. The studies have shown that proper diet and healthy lifestyle can ameliorate the disease to a sufficiently large extent. Still, this requires more efficient methods for its proper evaluation and treatment. Moreover, it is observed that NAFLD is not only the root of liver diseases, but is also a consortium of cardiovascular diseases, kidney diseases, sleep apnea, hepatic cancers and what not [12]. Cardiovascular diseases and chronic kidney disorders have been considered as the main element in causing the high rate mortality in NAFLD/NASH [13]-[14]. In the same context, gender, sex, ethnic background is the chief factors in progressing NASH [15].

2 Epidemiology

2.1 Prevalence

The prevalence of NAFLD is increasing and encompassing large population, corresponding to the amalgamation of obesity, diabetes, hypertension, and stress in next 5 years [16]. It is now seen as the deadliest disease in the United States and possibly the whole world. Consequently, the disease has reached pandemic proportions affecting tremendous amount of people. Furthermore, there has been observed a great variation in the prevalence of NAFLD in population and diagnostic based studies [17]-[19]. The prevalence of NAFLD seems to be elevated in the Middle East and South America with 27% estimation [7]. On the other hand, the prevalence can range from 15%-52% in Asian countries [20]-[21]). Saudi Arabia has 10% prevalence which is known to be evaluated by tomography (CT). Most of these prevalence reports are generally made by diagnosing fatty liver either by measuring liver enzymes or by utilizing MRI, MS techniques and other similar methods [22]. Various studies regarding prevalence have been reported in many papers. In 2007, population-based studies were scheduled to evaluate the prevalence among local people and data was easily collected from the hospital. Liver ultrasonography was universally used to measure fatty liver among the population. In population-based studies, prevalence of NAFLD was

estimated to be 16.6% on ultrasound, 4% prevalence of diabetes and 57% of obesity. It was found that males with 24.6% of prevalence are more prone to NAFLD than in females with 13.6% of prevalence [23]. Current data demonstrate the widespread of obesity to be 39.6% and that of diabetes to be 6.4% in adults which will eventually increase to about 7.7% by 2030. Metabolic syndrome is linked with anomalous amount of liver enzymes and plays the prime role in the development of cardiac heart disorders and diabetes [24]. According to Dionysos studies, the global prevalence was estimated to be 25% and this estimation was corroborated by Younosiss [25]. In last few decades, NAFLD is glowingly recognized as the most fatal chronic liver disorder in the 20%-30% Western countries [26]. The global rate of prevalence of non-alcoholic fatty liver diseases is prominently extending and becoming an important foundation of chronic liver diseases in most of the regions of the world, but the epidemiology facets differ worldwide (Table-1).

Table 1: Outbreak of NAFLD across the world

S. No.	Year	Country	Method of Diagnosis	Prevalence of NAFLD	No. of Patients	Reference
AFRICA						
1.	2014	Sudan	Ultrasound	20	100	[27]
2.	2016	Nigeria	Ultrasound	13	150	[28]
ASIA						
3.	2016	South Korea	NAFLD liver fat score	2761	28,071	[29]
4.	2016	India	Ultrasound	54	176	[30]
5.	2015	India	Ultrasound	85	302	[31]
6.	2014	Japan	-	804	3271	[32]
7.	2015	South Korea	Ultrasound	39,257	139,056	[33]
8.	2015	China	-	220	797	[34]
9.	2014	China	-	71,594	356367	[35]
10.	2014	China	Ultrasound	948	2241	[36]
11.	2014	Taiwan	Ultrasound	1769	6511	[37]
12.	2014	Korea	Biopsy	45	166	[38]
13.	2014	China	Ultrasound	1054	2493	[39]
14.	2013	China	Ultrasound	3906	10605	[40]
15.	2013	Korea	Ultrasound	2553	9159	[41]
16.	2013	Korea	-	38,659	141610	[42]
17.	2013	Korea	Ultrasound	11652	43166	[43]
18.	2012	Korea	Ultrasound	1617	4023	[44]
19.	2012	China	-	625	2523	[45]
20.	2009	Sri Lanka	Ultrasound	975	2985	[46]
EUROPE						
21.	2014	Finland	Fatty liver index	663	1611	[47]
22.	2014	Neth	Ultrasound	779	2292	[48]
23.	2012	UK	Sonographic diagnosis of fatty liver	295	1118	[49]
24.	2012	Hungary	Abdominal sonography	47	208	[50]
25.	2010	Spain	Abdominal echography	198	766	[51]
SOUTH AMERICA						
26.	2016	Brazil	Biopsies	1280	1280	[52]
27.	2011	Colombia	ultrasonography	70	263	[53]

MIDDLE EAST						
28.	2017	Iran	Ultrasound	1412	2804	[54]
29.	2013	Turkey	Ultrasound	338	613	[55]
30.	2013	Israel	Ultrasound	35	141	[56]
31.	2014	Israel	Ultrasound	28	147	[57]
32.	2013	Iran	Ultrasound	127	832	[58]
NORTH AMERICA						
33.	2018	US	Ultrasound	3613	20,050	[59]
34.	2017	US	-	1993	622,393	[60]
35.	2013	US	Ultrasound	1448	6709	[61]
36.	2013	US	Ultrasound	2446	12232	[62]
37.	2013	US	Ultrasound	2366	12454	[63]
38.	2013	US	Ultrasound	521	3056	[64]
39.	2013	US	-	3792	11154	[65]
40.	2013	US	-	2510	10565	[66]
41.	2012	US	-	2492	11613	[67]
42.	2011	US	Ultrasound	151	328	[68]
43.	2011	US	-	2515	11371	[69]
44.	2009	US	Liver biopsies	238	683	[70]

3 Pathogenesis

The Liver is the most cardinal gland in human's body, weighing around 1.5kg. For last past years, it has been subjected with a cluster of diseases including NAFLD, altering its metabolic activities and causing liver death [71]. Triglyceride deposition in the liver is the key hallmark of steatosis and further progression into advanced form of NASH and HCC [72]. The progression of the disease is quite intricate and multifactorial, sometimes the development can be unclear. For better understanding, quite a few theories have been framed that initially includes 'two-hits hypothesis'. The dictum is that in 'first-hit', triglyceride accumulate in the hepatocytes of the liver leading to its damage which is further followed by the 'second-hit', involving mitochondrial dysfunction, inflammation, cytokines, oxidative stress. There is also the formulation of third hit, stating that cell death in a normal liver produces signal for the replication of adult cell which works as a replacement for the damaged hepatocytes. Consequently, NAFLD generated ROS impede the replication process and foster the fibrosis stage [73]-[74]. The 'two-hit hypothesis' theory is not recognised much as NAFLD progression is associated with various other factors such as environment, genetics, dietary habits, obesity [75]. Accumulated triglyceride is mainly formed from the esterification of glycerol and free fatty acids (FFAs). These FFAs procure from adipose tissue via lipolysis or junky-fat diet and hepatic DNL. At the time of their production, they can either undergo esterification or beta-oxidation pathways.

4 BIOMARKERS in play

The gold standard method for NAFLD evaluation is liver biopsy. This method is linked with various limitations i.e. 1. The cost for this method is extortionate 2. Invasive nature 3. Its association with high rate of morbidity and mortality. These three factors make it a [76]-[77]. In addition to this, the chances of errors in sampling and inter-observer variability also interrupt the investigative tool to function properly. The recognition and authentication of NAFLD biomarkers have probable benefits such as reduced cost, ease of analysis, cognizance of pathogenesis and disease mechanism. Since, normal liver biopsy is not a reliable method, there is a growing need to develop non-invasive biomarkers.

4.1 Interleukin-6 (IL-6)

IL-6 is shown to be involve in Insulin resistance through the introduction of inhibitor of cytokine signally-3 in liver. Several studies have indicated strong connotation between IL-6 and NASH. Plasma IL-6 amount

is notably higher with NASH subjects and found to be decreased with the treatments. Additionally, soluble receptor of IL-6 was also heightened up in NASH patients as compared to simple steatosis [78]. In another cohort study, obese subjects were categorized into three groups viz. Non-NASH, credible NASH and NASH. IL-6 was corresponded to the stage of steatosis before the patients encounter the benchmark of NASH. Furthermore, degree of IL-6 as identified by the multivariate logistic regression comes out to be less than 4.81 pg/ml (odds ratio: 33.7%, confidence level: 1.7-680.7, $p \leq 0.002$) as an individualistic factor of the stage of steatosis [79]. The authors finally culminated that IL-6 was particular in absence of NASH at standard level [80].

4.2 Tumour Necrosis Factor -alpha (TNF- α)

TNF- α is recognised as to hinder the activity of tyrosine kinase of receptor insulin and hence, place an utmost importance in insulin resistance. A study reported that TNF- α serum level and their soluble receptors were remarkably elevated in NASH subjects for which cut-off values has not been discovered for clinical purposes [78]. Furthermore, other study has found increased level of TNF- α mRNA in comparison of normal subjects. The authors of the study propounded the cut-off value of TNF- α to be 100ng/ml which projected the condition of NASH [81].

4.3 C- Reactive Protein (CRP)

Degree of CRP was highly accumulated in NASH subjects than normal subjects based on age and BMI index and is suggested to be as a self-sufficient factor for NAFLD. However, reports on this matter are restricted because of less histological evidences of NAFLD diagnosis [82]. Authors are still perplexed with the fact that whether CRP serum levels can help in distinguishing simple steatosis with NASH. For instance, a Japanese study evaluated that high-sensitivity CRP levels were particularly elevated in NASH patients in contrast with patients of steatosis [83]. Furthermore, NASH and advanced fibrosis has high hs-CRP level than NASH with lenient fibrosis.

4.4 Ferritin

Ferritin level were significantly higher in subjects of hepatic steatosis. Insulin resistance in an association with iron, glucose/lipid metabolism disorder has been recognized to be linked with hyperferritinemia and discovers patients that are at a risk of NAFLD. According to a study done by Japanese, NASH patients had significant high amount of ferritin level than patients of steatosis [84]. Additionally, the probable cut-off value for ferritin was 196ng/ml and AUROC was 0.732. In another cohort study, greater ferritin level was linked with iron hepatic deposition and a predictor of adverse fibrosis condition in NAFLD/NASH patients [85]. Japan has recently established a report stating that elevated ferritin level cannot be used as an indicative of NAFLD stage. Since only 19% of the NAFLD patients had known to be histologically diagnosed [86].

4.5 SteatoTest

It is a combination of ten blood tests based on sex, age BMI and has better results than biopsy or magnetic resonance imaging. It provides quantitative evaluation of NAFLD. SteatoTest is known to have good value for the assessment of simple steatosis in comparison of other markers with AUROC 0.80. The test is considered as the better of all because of lesser sensitivity, observer variability, low precision of ultrasonography [87].

4.6 FibroTest

FibroTest is regarded as a universal biomarker that give a qualitative evaluation of fibrosis that have been seen in liver injuries such as NAFLD/NASH, HCV [88]. AUROC characterised for advanced stage fibrosis was estimated to be 0.84 without any intervention of the causes of liver injury, according to last meta-analysis. Additionally, there was no evidence of the difference between the intermediate stages F2 vs F1 in

contrast with adverse stages F3 vs F4 or F1 vs F0. Analysis of advanced-stage fibrosis and cirrhosis was greatly demonstrated by FibroTest based on two different analyses, 1) AUROC value for diagnostic cohort for FibroTest was 0.89 vs 0.79 for NFS, 2) AUROC value for therapeutic trial for FibroTest 0.80 vs 0.70 for NFS.

4.7 MicroRNA

MicroRNAs has been gaining tremendous recognition because of their intrigue feature of dysregulation in human diseases and their as prospective diagnostic and therapeutic targets. They are available in almost every fluid and are more likely to form a novel class of non-invasive biomarkers. MiRNA dysregulation is linked with the evolution and progression of various cancer in humans, consequently, numerous studies on miRNA circulation in plasma have been associated with cancers. The highly abundant liver-specific miRNAs have recognized as a possible biomarker for NAFLD severity. Among several miRNAs, miRNA-122 is of great attention as it is associated with metabolic pathway regulation of liver cholesterol synthesis. Dysregulation of miRNA-122 profile has been seen in hepatocellular carcinoma of poor prognosis, in contrast, increased profile of miRNA-122 was also disclosed [89]. Furthermore, miR-21 was found to be upregulated in various cancer involving HCC [90]. miR-34a was identified as another modulator of miRNA in association with many liver ailments. It was evaluated to upregulated in HCC [90]. A study was done to evaluate the level of miRNAs in 34 NAFLD subjects. It was found that miRNA-122 levels were decently upregulated by 7.2-fold in comparison of healthy control ($p < 0.0001$), miR-16 were upregulated by 5.5-fold ($p < 0.0001$), miR-21 was not changed at all [91]. miR-34a and miR-122 both are identified to correlated with the extremity of disease from simple steatosis to steatohepatitis.

5 Potential treatment for NAFLD

5.1 Chinese herbal formulation

Chinese herbal formulation has been consistently used for the treatment of wide variety of ailments such as stroke, Alzheimer disease, liver disorder, hypertension (Table 2). Currently, it has been evaluated that Chinese herbal formula is in rational trial to ingress its efficacy as an NAFLD treatment. A traditional Chinese herbal formula comprises a combination of two or more medicinal plants which are selected according to the medicinal properties and compatibility [92]. Furthermore, the formula contains the high-level pharmacological activities and complex constituents that help in eradicating the disease [93]. Although the mechanism behind the CHM is quite unknown to the researchers but indeed, they provide a way to suppress the budding ailment.

Table 2: Chinese herbal formulas for the treatment of Non-Alcoholic Fatty Liver Disease

FORMULA NAME	COMPOSITION	MONOMER	MECHANISMS	REF.
Qushi Huayu Decoction	<i>Artemisia capillaries</i> Thunb. <i>Rhizoma polygoni</i> Cuspidati <i>Hypericum japonicum</i> Thunb.	Resveratrol	↓ACAT, ↑CPT expression, ↓TNF α , ↓FAS	[94]
Danning Tablet	<i>Rheum palmatum</i> <i>Polygonum cuspidatum</i> <i>Citrus reticulata</i> Blanco <i>Curcuma rcenyujin</i> Y.	Emodin	↓Fat mass	[95]
Yinchenhao Decoction	<i>Artemisia capillaries</i> Thunb. <i>Gardenia jasminoides</i> Ellis <i>Rheum palmatum</i> L.	Berberine	↓PPAR γ expression	[96]

Ganzhixiao Decoction	<i>Artemisia capillaries</i> Thunb. <i>Rhizoma polygoni</i> Cuspidati <i>Radix bapleuri</i> Chinensis	Schisandrin B	↓ALT, ↓TG, ↓IHCL level	[97]
Tanzhiqing Decoction	<i>Paeonia veitchii</i> Lynch <i>Morus alba</i> L. Lotus leaf Tea	Puerarin	↓TC, ↓TG level, ↓Fat mass	[98]
Cigu Xiaozhi pill	<i>Sagittaria sagittifolia</i> <i>Alisma plantago</i> Aquatica <i>Salvia mltriorrhiza</i> Bge	Bifendate	↓ALT, ↓AST level	[99]
Sini San	<i>Bupleurum scorzonerifolium</i> <i>Paeonia tactiflora</i> Pall <i>Fructus aurantia</i> Immaturus <i>Glycyrrhiza uralensis</i> Fisch	Theaflavin	↓Steatosis, ↓ALT	[100]

5.2 EUROSIL-85

Eurosil-85 is a formulation of silymarin which was developed to heighten up the bioavailability and has potent antioxidant properties. Silymarin is the crucial component of this formulation and has reported the hepatoprotective actions in clinical trials. It acts as a scavenger radical that alternates the enzymes associated with the development of fibrosis, cirrhosis, and liver cell damage. The silymarin extract is a plant-derived compound which is recognised mostly as flavonoids, polyphenolic compounds and flavonolignans [101]. Furthermore, these identified compounds have known to show the antioxidant properties and other biological activities [102]. Among the four flavonolignans, silibinin is most prevalent of all comprising of 50-60% of silymarin [103]. It has been observed that only 20-50% is absorbed during ingestion due to poor solubility and lipophilicity for which it is the need of the hour to improve the oral bioavailability of silymarin [104]. The absorption period of silymarin is 2-4 hours and it remained unchanged during excretion. Further, it instantly metabolized by phase I and II biotransformation reactions in hepatocytes [105]. Eurosil-85 are being commercialize as capsules in the market and formulation is derived from 60% silibinin and has bio-dissolution up to 85% [106]. Human body produces free radicles during biochemical reaction such as ROS which tends to create oxidative stress. Intensive oxidation of FFA or exposure to many different toxins is a potent reason for the production of ROS which may also disturb the natural antioxidants within the body and provide a way for the pathogenesis of liver diseases including cirrhosis. [107]. Silibinin has been seen as an effective ROS scavenger such as hypochlorous acid, hydroxyl, peroxy anions in various models including human platelets, leukocytes, fibroblasts [108].

5.3 Oral probiotics formulation

Probiotics constituents the good living bacteria that confers healthy environment in the gut microbiota [109]. Microencapsulation entrapped in thin semi-permeable membrane has reported to protect the bacterial cells [110]. Ferulic acid (FA) has a potential capacity to lessen the cholesterol and upregulate antioxidant activities. Moreover, the release of FA is associated with feruloyl esterase (FAE) from the food items such as fruits, vegetables, grains, beer. Microbiota residing in human gut have known to show feruloyl esterase activity [111]. FAE activity is responsible for the release of antioxidant compounds and hence it is considered a better criterion for the selection of probiotics for the treatment of liver disarrays [112]. Microencapsulated *L. fermentum* ATCC 11976 administration has shown to decrease the degree of fatty content and significantly lower the ALT serums [113].

5.4 Kampo formula

Kampo formula consists of three crucial components such as keishibukuryogan (KBG), orengedokoto (OGT), and shosaikoto (SST). The powdered extract of kampo were basically derived from 16 therapeutic plants that have been recognised in Japanese pharmacopoeia. The formula has shown antioxidant and anti-

inflammatory activities in non-alcoholic fatty liver disease models. The study was performed on 56 rabbits which were divided into 7 groups and fed by standard rabbit chow (SRC). The results showed low levels of serum, KBG treatment was seen to be lowering the lipid content amongst the other two kampo formula [114]. Moreover, due to lack of reproducible scientific evidence, it is imperative to do more clinical research on kampo formula in treating NAFLD. Although, it is observed that Japanese and Chinese herbal medicines are doing miracles in correcting wide category of diseases.

5.5 Insulin sensitizers

NAFLD is highly associated with the upregulation of insulin resistance which leads to the confrontation of antilipolytic effect of insulin in adipose tissues [115]. Hence, insulin sensitizers include of those drugs that can possibly reduce insulin resistance by affecting hepatic liver partitioning, hinder the vascular endothelial growth factor (VEGF)-provoked angiogenesis and lowering certain level of Interleukins [116]. For instance, pioglitazone, metformin, rosiglitazone medicines are very constructive in both respects, alone and in combination with other medication [117]. Pioglitazone was considered to be better in NAFLD treatment, but it has also been observed that these drugs has the potential to cause cardiovascular diseases, bladder cancer and fracture problems [118].

6 Conclusion

Non-alcoholic fatty liver disease is emerging at an extremely fast pace and affecting the globe with its characteristic forms. It seems to be more prevalent in obese and young generation. The chronic liver disease is 25% globally prevent and accounts for high rate morbidity and mortality. Nonpharmacological treatments that include exercises, weight loss and healthy diet are necessary for controlling steatosis or liver damage. Additionally, non-invasive biomarkers are of great interest to the researchers in diagnosis and differentiating the stages of NAFLD with NASH and other adverse forms. Various biomarkers of ECM or apoptosis has been used clinically and found to give better results. Nowadays, many herbal plants are also being utilised in correcting various body ailments. Various formulations have been prepared and its efficacies have been evaluated on animals. But there is a need of more clinical studies to commercially approve the medication for NAFLD treatment. Future prospects for treating NAFLD can rely on medicinal herbs that possess the anti-hepatotoxic activity. Researchers can diversify their work and investigate more on medical herbs because future holds better opportunity to eradicate any ailment with nature's decoction.

7 Competing Interests

The authors declared that no conflict of interest exist in this publication.

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