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REVIEW ARTICLE

Decoding the Complexity of NAFLD/NASH: Exploring miRNA Biomarkers and Natural Product Interventions for Diagnosis and Treatment

Himanshu[1],Sarita Sharma[1*],Shitiz Jasrotia[1], Aruna Pai[2], Aziz Ahmed[3], Manisha Bhatia[1], Amit Lather[1], Tanuj Hooda[1]
[1]MM College of Pharmacy, Maharishi Markandeshwar [Deemed to be University], Mullana, Ambala, Haryana, India.
[2]Shri DD Vispute College of Pharmacy & Research center, New Panvel, Mumbai, Maharastra, India.
[3]Jaipur College of Pharmacy, Jaipur, Rajasthan, India.
Correspondence Author: Sarita Sharma
Email: sharmasarita.4416@gmail.com

ABSTRACT
The progression of Non- alcoholic fatty liver disease is one of the major incidence of illness and death. The NAFLD is the chronic inflammatory disease that is distinguished by the development of the liver cancer and the presence of hepatic triglycerides in the liver. In this review, we will discuss about the roles of the microRNA[miRNAs] plays a role in the development of the fatty liver disease and also play a role in the prevention of the development of the Non-alcoholic liver disease. And it also play the role of miRNAs in the processes like gluconeogensis, glycolysis and glycogen metabolism are also the important metabolic responses that lead to the development of Non-alcoholic liver disease [NAFLD].In this review we will also discuss the role on how natural products which is made by the natural things help to treat or control NAFLD by controlling the expression of miRNAs.
Keywords: *miRNAs, NAFLD, gluconeogensis, glycolysis, glycogen metabolism.*

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INTRODUCTION

In this day and ages one of the major chronic liver illnesses that affects the people is Non Alcoholic fatty liver disease [NAFLD]. NAFLD is defined as when the patient liver accumulate abnormal amount of fats mainly triglycerides, without the addiction of alcohol and then its result in increasing the weight of the liver more than the 5% of the normal liver[1,2].Because of the connection with the poor lifestyle and the presence of diseases ,developed countries have higher rates of this condition. If the early diagnosis and the treatment is not received the conditions may get worsens and it may result in developing the NASH[3].Environment and Hereditary factors also raises the risk of carcinoma and Hepatocellular carcinoma[HCC] [4].Apart from the nutrient factor many more factors contribute to developing the Non alcoholic fatty liver disease like gene expression, Insulin resistance, obesity and the diabetes mellitus[1,5].Many air particles which is smaller than the 2.5 micrometers also contribute to developing the NAFLD by activating the toll-like receptor 4[TLR4] and c-Jun N-terminal kinase activator protein 1[5,6].According to the latest research NAFLD is also connected with wide range of the structural variation, genes expression,
Non -coding RNA[INcRNAs] and the micro RNA expression.

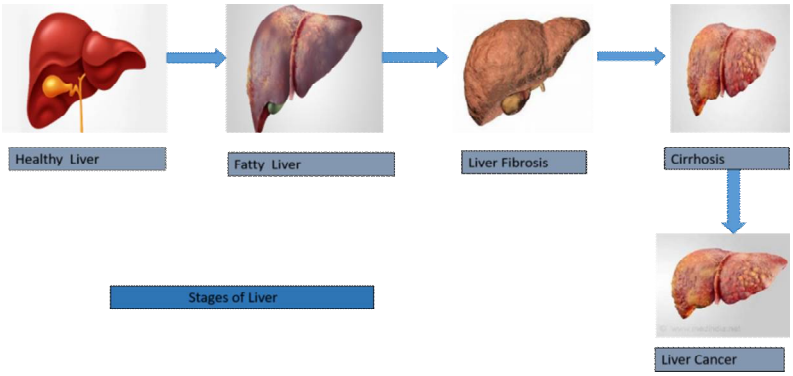

Fig:1 Stages of the liver from a healthy liver to liver cancer.

1. Epidemology: Approximately 40-50% of patients with Non-alcoholic Steatohepatits [NASH] later developed with the hepatic fibrosis and approximately 30-40% of patients with NAFLD also acquire NASH[7].In the meta analysis of 40 studies, NASH raises the risk of liver related death by an approximately 5-10 fold, especially based on extremity of hepatic fibrosis[8].NASH is the third most reason for the liver transplantation in US, NAFLD is slated to chase NASH in US by 2009,where 10% of the patients go through liver transplantation were diagnosed with NASH[9].

2. Mirnas AS BIOMARKERS: For Liver disorders which are need to be early diagnosed for setting the treatment guidelines but yet don't have established diagnostic methods or biomarkers miRNA are proven to be solving the problem. Because miRNAs are stably present in our blood,urine,saliva which is easily to collect from the living things, it can be used as biomarkers. Some studies also been shown that some miRNA are better than the APRI and Fib-4 index which telling the difference between the late and early fibrosis[10,11].For an example the people who suffered from liver cirrhosis had much smaller amount of miR-29a than the healthy people who are suffered from early fibrosis[12].

4. miRNA: A group of RNAs which doesn't made the proteins are called non coding RNAs [ncRNAs]. Basically ncRNAs are divided into two types based on how long they are. Small ncRNA consists of less than 200 nucleotides whereas large ncRNAs consists of more than 200 nucleotide. Small non coding RNAs made up of miRNAs, piRNAs, small nuclear RNAs and transfer RNAs. MicroRNAs [miRNA] are ncRNAs that have been studied a far[13].Victor Ambros was founded the first miRNA,Lin-4 in 1993.From now more than 48860 mature miRNAs,38589 hairpin precursors from 271 different organism are founded in miRBASE Collection[14,15].On the basis of studies it is clear that most of the miRNAs can target three prime untranslated regions[3' UTR] of a single gene. On the basis of action miRNAs are classified into two groups.The first is oncomiR which is over expressed in diseases or cancers and stops the genes from working which is important for the human health. The second group is made up of tumor suppressor miRNA which are silent down in the diseases or cancer. So their ability to stop the growth of cancer[16].

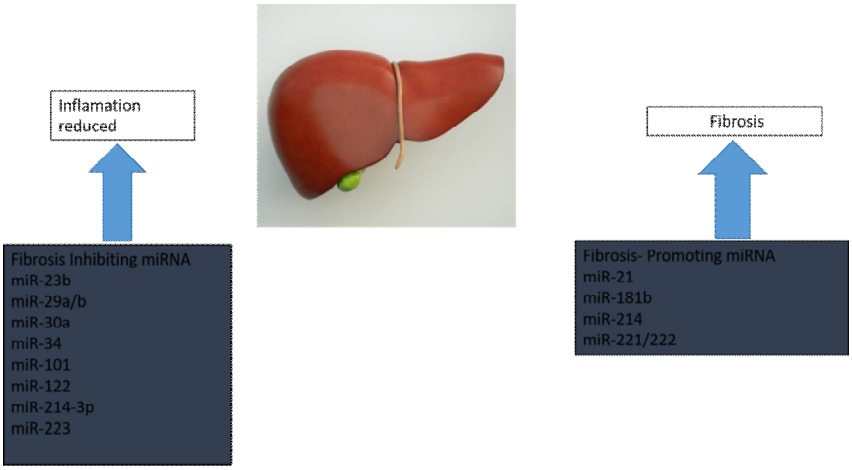

Fig2: Various types of miRNAs which reduced the inflammation or induced the inflammation of liver

5.Up regulation\Down regulation of miRNAs in liver tissues and in blood circulation of patient with NAFLD/NASH[17]:

Table 1. Shows the deregulated miRNAs in the hepatic tissues:

miRNA	Levels
microRNA-122	Down
microRNA-21	Up
microRNA-33	Up
microRNA-34a	Up
microRNA-192	Up
microRNA-375	Down
microRNA-146b	Up
microRNA-221/222	Up
microRNA-132	Up
microRNA-181b	Up
microRNA-422	Down

Table 2. Shows the deregulated miRNA in Blood circulation:

miRNA	Levels
microRNA-122	Up
microRNA-21	Up
microRNA-33	Up
microRNA-34a	Up
microRNA-192	Up
microRNA-375	Up
microRNA-146b	Down
microRNA-221/222	Up
microRNA-132	Down
microRNA-181b	Down

Pathophysiological Control Of Liver Lipid Metabolism By MiRNAs:

Various miRNAs were track down to tightly regulate various parts of the liver fat metabolism [18].Now we are concentrate on three especial miRNAs that is miR-33, miR-34a,miR-122.These miRNAs are well known for playing significant roles in controlling the liver metabolism and also have playing a significant roles in the treatment of fatty liver disease. Approximate 70% of miRNA copies track down in liver is miR-122[19].When miR-122 is blocked in the liver of mice, its indirectly falls lipogenic enzymes like ACC and FASN, which shows more fatty acid β-oxidation and less intracellular triglyceride accumulation[19].It also track down the cholesterol synthesis[20].A new meta-analysis also suggest the better way to understand between the NAFLD and NASH. This study suggest that miR-122 is definitely an important regulator of lipid metabolism.

miR-34a seems to tightly control how fats are broken down. The amount of miR-34a is present to be more in the blood plasma and the liver of people who have NASH, which makes the miRNAs good biomarker for the diagnosing of stage 4 liver disease[21]. Scientist were able to found that blocking miR-34a targets Sirtuin 1 (SIRT1) and PPARα in humans liver cells. This blocks the breakdown of the fatty acids and helps in inducing the fatty liver[22].By blocking miR-34a increased the AMP-activated protein kinase α activity, which is shows a significant metabolic switch that stops lipogenesis. miR-33 levels are also found higher in the bloodstream and in the liver cells of people who is suffering from NAFLD, especially NASH [23].The two types of this miRNAs, a and b are found in the introns of two important lipogenic TFs, SREBP1 and SREBP2, respectively. In the human liver cells miR-33 regulate the metabolism of both cholesterol and the fatty acid by going after cholesterol efflux regulatory proteins (ABCA1 and ABCG1) and fatty acid β-oxidation regulators (CPT1A and AMPKα) [24].According to these researches miR-33 inhibitors are seen to be possible treatment heart diseases and cholesterol[24].

Understanding the part that miRNA plays in how natural products can help prevent and treat NAFLD:

Various researchers do more and more studies and the data showed that the natural products which are made by the natural things can also help protect against or treatment of NAFLD by controlling the expression of miRNAs.

Table 3:Summary of reviewed studies

Researcher	Natural products	Results	Reference
Adi et al.	excess-protein fish oil diet	Prevent the occurence of NAFLD by lowering down miR-155 miR-335 miR-143 miR-21 miR-411	[25]
Wang et al.	Fish oil	Controlling the cholesterol metabolic disorder and hepatic triglycerides levels by controlling the production of certain miRNAS rno-miR-33-5p and rno-miR-34a-5p	[26]
Yang et al.	Berberine	Treat NAFLD by reducing the production of liver uncoupling protein-2 mRNA and controlling lipid metabolism.	[27]
Gracia et al.	Resveratrol	Resveratrol protects opposed the growth of liver fat by decreasing miR-107,miR-103 by lowering the expression of carnitine palmitoyltransferase 1A protein, and miR-122 by lowering the expression of FAS protein	[28]

Epigenetic change in NAFLD that is dependent on miRNA:

In NAFLD many metabolic processes are out of control, that result in build up of the abnormal amount of lipid in hepatocytes. There is

1. more de novo lipogenesis
2. More consume the lipids that's are too high in the blood
3. Less oxidation of lipids
4. Less release of lipids in liver [29,30].

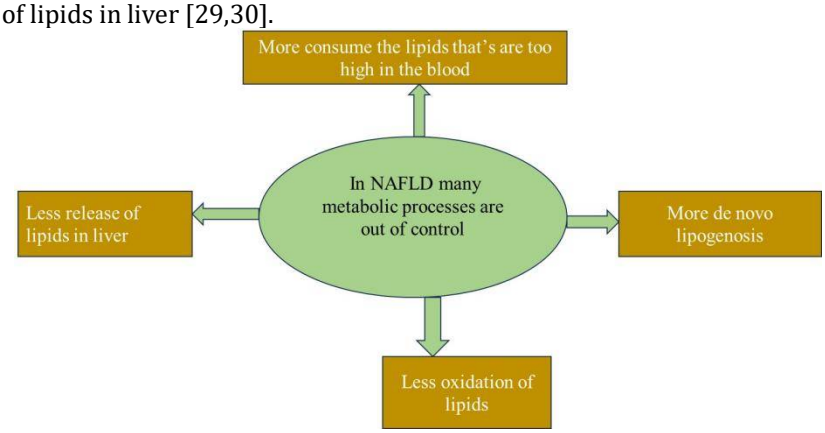

Fig:3 Shows the many metabolic processes are out of control.

Some miRNAs are tightly controls all of these biochemical processes. Because high glucose level causes DNL, change in the process of liver like gluconeogensis, glycolysis and glycogen metabolism that are controlled by some miRNAs are also the significant metabolic responses that lead to the development of the NAFLD. Lastly it was found that miRNA affect the cellular processes that are out of control such as endoplasmic reticulum stress and autophagy and the unfolded protein response[31-33].These processes also linked to development of fatty liver.

CONCLUSION

This content emphasized that NAFLD is a serious and chronic hepatic illness which is affected by unhealthy life styles, both genetic and environmental factor. If NAFLD is left untreated then NAFLD can progress to the NASH[Non-alcoholic steaotohepatitis] and increase the risk of liver transplantation and the liver cell death.miRNAs specially miR-122, miR-34a , miR-33 have been play a important role in controlling the liver metabolism and can be used as biomarkers and treating fatty liver disease.

Additionally epigenitic changes in NAFLD as well as the use of natural products can also affect miRNA impression and also contribute the treatment and prevention of fatty liver diseases.

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