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Non-Alcoholic Fatty Liver Disease, Gut Microbiota and Synbiotics: A Review of the Experimental and Clinical Evidence

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is a multi-cause disease. Several factors are involved in the pathogenesis of NAFLD. Recently, the role of gut microbiota in the pathogenesis of NAFLD has attracted the attention of researchers. This study was performed to review the role of gut microbiota in the pathogenesis of NAFLD. In addition, the mechanisms and clinical effects of synbiotics on NAFLD were reviewed. **Methods**: A narrative review of the most recent advances was conducted regarding the role of dysbiosis in the pathogenesis of NAFLD. In addition, the mechanisms and clinical results obtained from experimental and clinical studies investigating the effects of synbiotics on features of NAFLD were reviewed. Relevant studies published after 2010 were selected. **Results**: Dysbiosis induces hepatic steatosis through stimulating obesity via harvesting energy, inflammation, altering dietary choline and bile acid metabolism, endogenous ethanol production, insulin resistance and increasing gut permeability. Synbiotics can improve levels of liver enzymes and hepatic steatosis. However, the effect of synbiotic on hepatic fibrosis is unclear, and the results are inconsistent. Studies with higher intervention duration showed beneficial effect of synbiotics on hepatic fibrosis. **Conclusions**: Dysbiosis through various mechanisms is linked to the pathogenesis of NAFLD. Synbiotics can improve liver enzymes levels and hepatic steatosis. Investigating the effect of synbiotics on fibrosis can be the main objective of the future investigations in this field.

Introduction

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is the excessive fat accumulation in the liver (Chalasani *et al.*, 2012). NAFLD comprises a range of pathological conditions from simple steatosis to non-alcoholic steatohepatitis (NASH) (Elizabeth *et al.*, 2010). Simple steatosis refers to the liver fat accumulation without inflammation or

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hepatocellular injury, but NASH is the liver fat accumulation along with inflammation and the evidence of hepatocellular injury (Chalasani *et al.*, 2012, Elizabeth *et al.*, 2010). Moreover, NAFLD is an important cause of hepatocellular carcinoma and liver transplantation (Wong *et al.*, 2015). The global prevalence of NAFLD is 24%, and its prevalence is 32% in Middle East, 31% in South America, 27% in Asia, 24% in United States, 23% in Europe, and 14% in Africa (Younossi *et al.*, 2018). Therefore, it is an independent risk factor for type 2 diabetes mellitus (T2DM) and cardiovascular disease (Gaggini *et al.*, 2013, Sangouni *et al.*, 2019).

Inflammation, insulin resistance, oxidative stress, obesity and dyslipidemia are the most important factors involved in the pathogenesis of NAFLD (**Figure 1**). Inflammation, can contribute to the development of NAFLD through increasing the activity of kupffer cells and hepatic stellate cells (HSCs), stimulating nuclear factor κ-B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, increasing the levels of chemokines as well as toll-like receptors (TLRs), and inducing mitochondrial dysfunction (Buzzetti *et al.*, 2016, Sangouni *et al.*, 2019). The evidence revealed a significant reduction of insulin sensitivity in the muscle, liver and adipose tissue of patients with NAFLD (Lomonaco *et al.*, 2012). Also, insulin resistance can increase the activity of Jun N-terminal kinase (JNK), IκB kinase (IKK), sterol regulatory element-binding proteins (SREBPs), and carbohydrate-responsive element-binding protein (ChREBP), reduce the levels of glucagon-like peptide 1 (GLP-1), and stimulate hepatic *de novo* lipogenesis (Gaggini *et al.*, 2013, Sangouni and Ghavamzadeh, 2019, Sangouni *et al.*, 2019). By increasing the activity of kupffer cells, HSCs and myeloperoxidase, inducing mitochondrial dysfunction, stimulating TLRs gene expression, and increasing the levels of reactive oxygen species (ROS), oxidative stress can contribute to the pathogenesis of NAFLD (Ashraf and Sheikh, 2015, Sangouni *et al.*, 2019). Moreover, obesity can increase the levels of chemokines, adipocytokines and free fatty acids (FFAs), stimulate the inflammatory pathways, and induce the main pathways of oxidative stress as well as insulin resistance (Polyzos *et al.*, 2019). The hepatic fat accumulation (due to abnormal lipid metabolism or dyslipidemia) is another factor involved in the development and progression of steatosis. Dyslipidemia can reduce the levels of adiponectin, increase the activity of fatty acid synthase (FAS), acetyl-coA carboxylase (ACC), NF-κB and SREBP, increase FFAs and adipokines production, decrease fat oxidation, stimulate hepatic *de novo* lipogenesis, and induce the pathways of both inflammation and oxidative stress (Ress and Kaser, 2016, Sangouni and Ghavamzadeh, 2019).

Gut microbiota

Gut microbiota as a metabolic organ refers to a community of microbes in the gut (Gomaa, 2020). Bacteria, archaea, fungi, phages and viruses are the microorganisms that live in the human gut (Gomaa, 2020). The main bacteria phyla in the human gut are *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Verrucomicrobia* and *Actinobacteria* (Bull and Plummer, 2014). *Firmicutes* and *Proteobacteria* exist mainly in the proximal of GI tract, while *Bacteriodetes*, *Verrucomicrobia* are the main phyla in the distal of GI tract (Gu *et al.*, 2013). In addition, *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Clostridium*, *Peptococcus*, *Ruminococcus*, *Peptostreptococcus and Faecalibacterium* are the most abundant bacteria genera (Shapira, 2016). Imbalance in the microbial community in terms of qualitative and quantitative changes, distribution, and metabolic activity refers to altered gut microbiota (dysbiosis) (Bull and Plummer, 2014). Factors like age, mode of delivery at birth, exposure to medical treatments, pH of intestinal lumen, diet, physical activity, circadian activity, geographical localization, prebiotics, probiotics and synbiotics can change the gut microbiota composition and distributions (Bull and Plummer, 2014, Clemente *et al.*, 2012). Furthermore, dysbiosis has a critical role in the pathogenesis of atherosclerosis, gastrointestinal diseases, cancers, autoimmune

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diseases, allergic diseases and T2DM (Bull and Plummer, 2014, Clemente *et al.*, 2012). The recent evidence suggested that gut microbiota plays an important role in the pathogenesis of NAFLD (Leung *et al.*, 2016). In this narrative review, the authors focused on the most recent advances regarding the role of gut microbiota in the pathogenesis of NAFLD. In addition, the mechanisms and clinical results obtained from experimental and clinical studies investigating the synbiotic efficacy in NAFLD were reviewed.

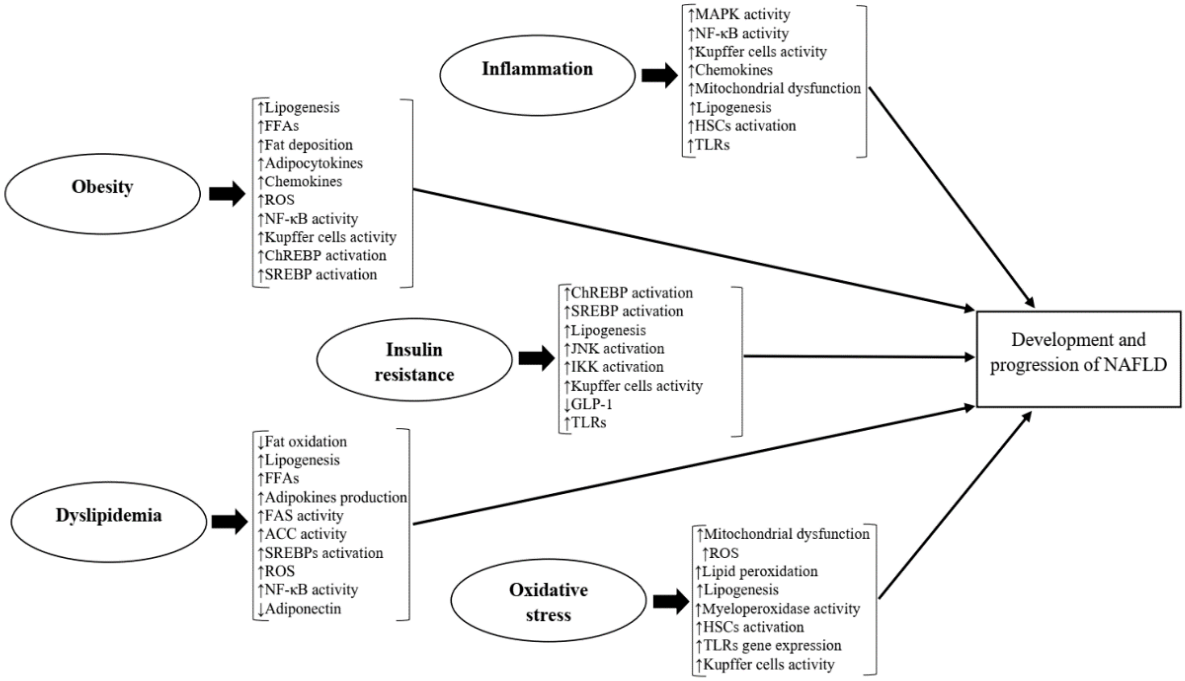


Figure 1. Main mechanisms contributing to the development and progression of NAFLD. ACC: acetyl-coA carboxylase; ChREBP: carbohydrate-responsive element-binding protein; FAS: fatty acid synthase; FFAs: free fatty acids; GLP-1: glucagon-like peptide-1; HSCs: hepatic stellate cells; IKK: IκB kinase; JNK: c-Jun-N-terminal kinases; MAPK: mitogen-activated protein kinase; NAFLD: non-alcoholic fatty liver disease; NF-κb: nuclear factor-κb; ROS: reactive oxygen species; SREBP: sterol regulatory element-binding protein; TLRs: toll-like receptors; VLDL: very low-density lipoprotein.

Materials and Methods

PubMed, Scopus, and Web of Science databases were searched in this narrative review to identify the randomized controlled trials (RCTs) which evaluate the effects of synbiotics on hepatic steatosis, fibrosis and liver enzymes in patients with NAFLD. It was sued the following keywords keywords: "Non-alcoholic fatty liver disease", "Non-alcoholic steatohepatitis", "Synbiotic", "Steatosis", "Fibrosis", "Liver enzyme", "Aspartate aminotransferase", "Alanine aminotransferase", "Gamma-glutamyltransferase", and "Alkaline phosphatase" were reviewed. Eight studies investigating the effects of synbiotics on steatosis, fibrosis or liver enzymes in subjects with NAFLD were also included.

In addition, PubMed, Scopus, and Web of Science databases were searched to identify experimental studies, investigating the main mechanisms and pathways that link the gut microbiota to the NAFLD, and the important mechanisms and pathways were completely extracted by careful reading of various related studies. It should be noted that studies published after 2010 were selected.

Results

Gut microbiota and NAFLD

The role of dysbiosis in the pathogenesis of NAFLD has been revealed (Leung *et al.*, 2016). About 90% of all gut microbial cells belongs to the phyla *Firmicutes* and *Bacteroidetes* (Bull and Plummer, 2014). Patients with NAFLD compared to the healthy controls have higher concentrations of the bacteria belonging to the phylum *Firmicutes*

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(Raman *et al.*, 2013). The abundance of *Porphyromonas*, *Campylobacter*, *Staphylococcus*, *Parabacteroides*, *Dialister* and *Ruminococcus* is higher in subjects with obesity compared to the healthy people (Le Chatelier *et al.*, 2013). In addition, lower concentrations of *Lactobacillus*, *Bifidobacterium*, *Faecalibacterium*, *Akkermansia*, *Methanobrevibacter* and *Coprococcus* in subjects with obesity were found (Gomaa, 2020, Le Chatelier *et al.*, 2013). Patients with NAFLD have increased concentrations of *Dorea* and *Ruminococcus* (Del Chierico *et al.*, 2017). An inverse relationship between concentration of *Bifidobacterium* and levels of alanine aminotransferase levels was found in subjects with higher risk of NAFLD (Karlsson *et al.*, 2012). Moreover, a recent investigation showed that the concentration of *Firmicutes* was more in mild or moderate NAFLD; but, the patients with advanced fibrosis have higher concentration of *Proteobacteria* (Loomba *et al.*, 2017). The abundance of bacteria in the gut in patients with NAFLD and healthy people are summarized in **Table 1**. Dysbiosis can induce hepatic steatosis and NASH through following pathways and mechanisms (**Table 2**).

Table 1. The bacteria abundance in the gut; Patients with NAFLD compared to the healthy people.

Bacteria with increased abundance	Bacteria with decreased abundance
Robinsoniella	*Lactobacillus*
Porphyromonas	*Bifidobacterium*
Campylobacter	*Faecalibacterium*
Staphylococcus	*Akkermansia*
Parabacteroides	*Methanobrevibacter*
Dialister	*Coprococcus*
Ruminococcus	*Eubacterium*
Dorea	
Clostridium	
Klebsiella pneumoniae	

***NAFLD**: non-alcoholic fatty liver disease*

Table 2. Main pathways and mechanisms that link dysbiosis to the NAFLD.

Pathway	Mechanisms
Gut permeability	↑LPS, ↑SIBO, disrupting epithelial tight junctions, ↑degradation of the mucus layer, ↓production of mucus, changing the intestinal barrier, ↑leptin, ↓adiponectin, ↑SREBPs activation, ↑endotoxemia, ↑plasminogen activator inhibitor 1, ↑hepatic TLR4 expression, ↓GLP2, ↑insulin resistance, ↑inflammatory pathways.
Stimulation of obesity	↑GPR43 activation, ↑small intestinal villi density, ↑ChREBPs activation, ↑hepatic lipogenesis, ↓lipolysis, ↓FIAF expression, ↓GLP1, ↑LPL activity.
Stimulation of inflammation	↑LPS, ↑TLR4, ↑NF-κβ pathways activation, ↑TNF-α, ↑HSCs activation, ↑IL-6, ↑MAPK pathways activation, ↑kupffer cells activity, ↑inflammasomes, ↓GLP1, ↑JNK pathways activation, ↓claudin expression, ↓occludin expression, ↓ZO-1 expression
Insulin resistance	↑TLR4, ↑LPS, changing immunity response, ↑endotoxemia, ↑IRS 1 serine phosphorylation, ↓GLP1, ↑IKK, ↑JNK pathways activation, ↓occludin expression, ↓ZO-1 expression.
Dietary choline metabolism	↑dimethylamine, ↑trimethylamine, ↑TMAO, ↑NF-κβ pathways activation, ↑TNF-α, ↑IL-6, ↑MAPK pathways activation, ↑kupffer cells activity, ↑HSCs activation.
Bile acid metabolism	↓FXR activation, GPBAR1 dysregulation, ↓GLP1, ↑hepatic de novo lipogenesis, ↑VLDL, ↑NF-κβ pathways activation, ↑ROS production, ↑lipid peroxidation, ↑kupffer cells activity.
Ethanol production	↑kupffer cells activity, ↑TNF-α, ↑IL-6, ↑IL-1β, ↑ROS production in the liver, ↑hepatic TLR4, ↑liver enzymes levels, ↑passage of gut-derived endotoxins into portal system, ↑gut permeability.

***ChREBP**: Carbohydrate-responsive element-binding protein; **FIAF**: Fasting-induced adipocyte factor; **FXR**: Farnesoid X receptor; **GLP**: glucagon-like peptide; **GPBAR1**: G-protein coupled bile acid receptor 1; **GPR43**: G protein-coupled receptor 43; **HSCs**: Hepatic stellate cells; **IKK**: IκB kinase; **IL-6**: Interleukin-6; **IL-1β**: Interleukin-1β; **IRS1**: Insulin receptor substrate 1; **JNK**: Jun N-terminal kinase; **LPL**: lipoprotein lipase; **LPS**: lipopolysaccharide; **MAPK**: mitogen-activated protein kinase; **NAFLD**: non-nlcoholic fatty liver disease; **NF-κB**: Nuclear factor κ-B; **ROS**: Reactive oxygen species; **SIBO**: Small intestinal bacterial overgrowth; **SREBPs**: Sterol regulatory element-bindings; **TG**: Triglyceride; **TLR4**: Toll-like receptor 4; **TMAO**: Trimethylamine N-Oxide; **TNF-α**: Tumor necrosis factor-α; **VLDL**: Very low-density lipoprotein; **ZO-1**: Zonula occludens-1.*

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Gut permeability

Gut permeability is an important mechanism involved in the pathogenesis of NAFLD. It refers to the decreased integrity of junctions in the gut epithelial wall that leads to an increase in material translocation from the lumen into the bloodstream, other organs, and adipose tissue (Kolodziejczyk *et al.*, 2019). A direct correlation between NAFLD with gut permeability related to the small intestinal bacterial overgrowth (SIBO) and disrupted tight junctions was also observed (Fukunishi *et al.*, 2014, Miele *et al.*, 2009). Lipopolysaccharides (LPS), which are found in the outer membrane of gram-negative bacteria, can enhance SIBO and disrupt tight junctions (Fukunishi *et al.*, 2014, Miele *et al.*, 2009). Moreover, LPS decreases plasma adiponectin, enhances plasma leptin, and triggers expression of liver SREBP-1c (Fukunishi *et al.*, 2014). Dysbiosis decreases the GLP-2 secretion, disrupts tight junctions, and subsequently, increases the gut permeability(Tseng and Wu, 2019). Disrupted tight junctions can enhance the endotoxemia (Miele *et al.*, 2009, Volynets *et al.*, 2012). Moreover, endotoxemia enhances the expression of the plasma plasminogen activator inhibitor 1 and hepatic TLR4, which can stimulate the development of inflammation and insulin resistance (Alisi *et al.*, 2010, Volynets *et al.*, 2012).

Stimulation of obesity

It has been revealed that the abundance of *Bifidobacterium*, *Oscillospira*, *Erwinia*, *Succinivibrio* and *Alistipes* is higher in subjects with normal weight compared to obese individuals (Ignacio *et al.*, 2016, Tseng and Wu, 2019). In addition, a significant relationship between bacteria species such as *Blautia hydrogenotorophica*, *Coprococcus catus*, *Ruminococcus bromii* and *Ruminococcus obeum* and obesity was found (Kasai *et al.*, 2015). The close link between gut microbiota and obesity has also been confirmed. The gut microbiota as an important regulator of the energy harvest can enhance the density of small intestinal villi, produce short-chain fatty acids (SCFAs), induce gut motility, and increase fat deposition (Delzenne and Cani, 2011, Gomaa, 2020). SCFAs reduce the glucagon-like peptide 1 (GLP1) secretion and activate the G-protein coupled receptors 43 (GPR43), inhibit lipolysis and increase fat storage (Morrison and Preston, 2016). SCFAs can activate the ChREBP and increase the expression of proteins which enhance hepatic lipogenesis (Morrison and Preston, 2016). On the other hand, fasting-induced adipocyte factor (FIAF) stimulates changes in the expression of genes controlling energy homeostasis, reduces the lipoprotein lipase (LPL) activity in the adipose tissue, enhances fatty acid oxidation, upregulates uncoupling proteins, and can potentially reduce the amount of fat storage (Arslan, 2014, Shen *et al.*, 2013). Moreover, dysbiosis decreases the synthesis and secretion of FIAF, triggers activity of LPL and increases fat storage in the liver (Arslan, 2014, Delzenne and Cani, 2011, Shen *et al.*, 2013).

Stimulation of inflammation

Dysbiosis induces low-grade inflammation, an important factor in the development of obesity and NAFLD. The evidence suggested that TLR4 contributes to the development of NAFLD (Aron-Wisnewsky *et al.*, 2013, Canfora *et al.*, 2019). The kupffer cells, which can trigger liver expression of TLR4, play a critical role in the liver inflammation by producing inflammatory cytokines, chemokines, and ROS (Aron-Wisnewsky *et al.*, 2013, Paik *et al.*, 2003). LPS increases kupffer cells activity and tumor necrosis factor-α (TNF-α). Also, HSCs trigger endotoxemia and inflammatory pathways in the liver (Aron-Wisnewsky *et al.*, 2013, Paik *et al.*, 2003). The endotoxemia resulted from dysbiosis induces insulin resistance and inflammation via pathways related to the LPS-TLR4, and stimulates JNK and NF-κB pathways (Henao-Mejia *et al.*, 2012, Verdam *et al.*, 2011). Eventually, these actions increase inflammasomes and pro-inflammatory cytokines (Henao-Mejia *et al.*, 2012).

Stimulation of insulin resistance

Dysbiosis increases the ghrelin secretion, and subsequently increases the energy storage and

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insulin resistance (Caricilli and Saad, 2013, Perry *et al.*, 2016). TLR4 is involved in the development of insulin resistance by activating LPS, increasing gene expression of liver SREBP-1c and decreasing level of adiponectin (Caricilli and Saad, 2013, Perry *et al.*, 2016).

Dysbiosis inhibits the expression of tight junction proteins occludin and zonula occludens-1 (ZO-1), increases intestinal permeability, and enhances endotoxemia (Lee *et al.*, 2020). Endotoxemia derived from the gut can trigger mechanisms and pathways related to the LPS-TLR4, and activate the JNK and NF-kB pathways (Lee *et al.*, 2020, Verdam *et al.*, 2011). Additionally, TLR4 activates IKK as well as JNK and reduces insulin receptor substrate 1 (IRS-1) serine phosphorylation and insulin sensitivity (Kolodziejczyk *et al.*, 2019, Lee *et al.*, 2020).

Dietary choline metabolism

Choline has an important role in the hepatic biogenesis of phosphatidylcholine and regulation of S-adenosyl methionine cycle(Kolodziejczyk *et al.*, 2019); through increasing hepatic biogenesis of phosphatidylcholine, Choline is involved in very low-density lipoprotein (VLDL) production, and hepatic lipid export (Aron-Wisnewsky *et al.*, 2013). Meat products, dairy products, soybeans, fishes, nuts and whole grains are dietary sources of choline, while gut microbiome is an important endogenous source of choline (Russell *et al.*, 2013). Choline deficiency is associated with NAFLD, and dysbiosis reduces choline bioavailability by producing toxic metabolites such as dimethylamine and trimethylamine from dietary choline (Russell *et al.*, 2013, Wang *et al.*, 2011). Species such as *Anaerococcus hydrogenalis*, *Clostridium asparagiforme*, *Clostridium hathewayi*, *Clostridium sporogenes*, *Escherichia fergusonii*, *Proteus penneri*, *Providencia rettgeri* and *Edwardsiella tarda* are involved in the conversion of choline to trimethylamine N-oxide (TMAO) (Romano *et al.*, 2015). TMAO derived from dimethylamine and trimethylamine in the liver triggers inflammatory pathways (Wang *et al.*, 2011). Furthermore, choline deficiency stimulates NF-κβ pathways and increases the hepatic levels of inflammatory markers such as TNF-α and IL-6, activating MAPK pathways as well as the activity of kupffer cells and HSCs (Wang *et al.*, 2011). High levels of TMAO increase the abundance of *Clostridium* (Spencer *et al.*, 2011). Moreover, mutation in phosphatidylethanolamine N-methyltransferase (PEMT) gene, which is involved in the formation of endogenous choline, can lead to the progression of NAFLD (Kolodziejczyk *et al.*, 2019, Leung *et al.*, 2016).

Bile acid metabolism

The secondary bile acids are made by the gut microbiota from cholesterol-derived primary bile acids produced in the liver (Ferslew *et al.*, 2015). Farnesoid X receptor (FXR) is the receptor of bile acids (Brighton *et al.*, 2015, Trauner *et al.*, 2010). Accordingly, bile acids activate FXR and G-protein coupled bile acid receptor 1 (GPBAR1), and subsequently activate FXR and GPBAR1 pathways, which are the important regulators of the hepatic *de novo* lipogenesis (Brighton *et al.*, 2015, Hylemon *et al.*, 2009). The level of hydrophobic and cytotoxic BAs species is higher in patients with NAFLD (Ferslew *et al.*, 2015). The enzymes involved in the conversion of deconjugated BAs to secondary BAs are also expressed throughout the gut microbiota (Ridlon *et al.*, 2013). Dysbiosis disrupts enterohepatic circulation and alters structure of bile acids (Swann *et al.*, 2011); it changes expression and function of FXR, secretion of bile acids and contributes to the hepatic steatosis, inflammation and oxidative stress (Kolodziejczyk *et al.*, 2019, Swann *et al.*, 2011).

Ethanol production

Gut microbiota produces ethanol, and the ethanol is transported to the liver by portal system (Leung *et al.*, 2016). Ethanol and its main hepatotoxic metabolites including acetaldehyde and acetate trigger kupffer cells to produce inflammatory markers like TNF-α (Arslan, 2014, Gustot *et al.*, 2006). Ethanol induces the production of ROS by hepatocytes, increases the levels of liver enzymes, and induces the expression of TLRs (Arslan, 2014, Gustot *et al.*, 2006). The

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abundance of ethanol-producer bacteria such as *Proteobacteria*, *Enterobacteriaceae*, and *Escherichia* is higher in subjects with NASH (Zhu *et al.*, 2013). In addition, high-ethanol-Producing *Klebsiella pneumonia*e is abundant in patients with NAFLD. *Klebsiella pneumoniae* is strongly associated with NAFLD, and transplant of *Klebsiella pneumoniae* causes NAFLD (Forsyth *et al.*, 2011, Zhu *et al.*, 2013). Finally, ethanol enhances the gut permeability and increases transfer of gut-derived endotoxins into the liver (Forsyth *et al.*, 2011).

Synbiotics

Synbiotic is a synergistic combination of prebiotic and probiotic (Vyas and Ranganathan, 2012). Prebiotics as the indigestible carbohydrates have a beneficial effect on host health by modifying gut microbiota composition, distribution and activity (Vyas and Ranganathan, 2012). Probiotics are the nonpathogenic living microorganisms, and in sufficient quantities, they can improve the gut microbiota dysbiosis (Vyas and Ranganathan, 2012). *Lacbobacilli*, *Bifidobacteria spp*, *S. boulardii*, and *B. coagulans* are the most common probiotic strains in the synbiotics formulations (Pandey *et al.*, 2015). Fructooligosaccharide (FOS), yloseoligosaccharide (XOS), inulin, and prebiotics from natural sources like chicory are the main prebiotics that are used in the formulations of synbiotics (Pandey *et al.*, 2015). Synbiotics can stimulate the growth of health-promoting bacteria, activate the metabolism of one health-promoting, improve the survival of probiotics and live microbial implantation in the GI tract (Cencic and Chingwaru, 2010, Pandey *et al.*, 2015). Presumably, synbiotics were developed to attenuate the difficulties related to probiotics survival. The beneficial effect of synbiotics on survival of probiotic bacteria during passage through the upper gastrointestinal tract has been observed as well (Cencic and Chingwaru, 2010, Pandey *et al.*, 2015). Synbiotics by improving the implantation of beneficial bacteria in the gut as well as stimulating the growth of probiotics are involved in maintaining intestinal homeostasis and health (Cencic and Chingwaru, 2010, Pandey *et al.*, 2015, Vyas and Ranganathan, 2012).

Synbiotics and NAFLD

Pathways and mechanisms: A NAFLD model revealed that synbiotics can regulate gut microbiota, and reduce the severity of steatosis as well as fibrosis (Cortez-Pinto *et al.*, 2016). The evidence showed that synbiotics decrease endogenous ethanol, levels of TMAO and myeloperoxidase secretion, attenuate the production of ROS as well as lipid peroxidation products, decrease the activity of kupffer cells, HSCs, IKK and JNK, downregulate production of liver inflammatory markers, reduce the activity of NF-κB and MAPK pathways, decrease the mitochondrial dysfunction, increase levels of choline, decrease the expression of TLRs, and subsequently, improve the main causes of NAFLD such as inflammation and oxidative stress (Raso *et al.*, 2014, Sangouni and Ghavamzadeh, 2019). In addition, synbiotics can regulate bile acids; attenuate lipogenesis and fat deposition; decrease levels of LPS and endotoxin, ChREBP and SREBP activity, and TG and VLDL synthesis; , , increase fat oxidation, peptide YY (PYY), GLP-1 and adenosine monophosphate activated protein kinase (AMPK), FIAF expression, and claudin, and occludin and ZO-1 expression; reduce FAS, ACC, IKK, JNK and FXR activity, LPL, calorie intake and energy harvest, and IRS serine phosphorylation, and ultimately, improve gut permeability. They all lead to an improvement in obesity, insulin resistance, and dyslipidemia improvement (Sangouni and Ghavamzadeh, 2019). A narrative review confirmed the beneficial effects of synbiotics on main risk factors of NAFLD such as insulin resistance, obesity, inflammation and oxidative stress (Sangouni and Ghavamzadeh, 2019). The pathways and mechanisms related to the synbiotics efficacy in NAFLD are represented in **Figure 2**.

Synbiotic and hepatic steatosis and fibrosis

Several RCTs have examined the effect of synbiotics supplementation on hepatic steatosis and fibrosis in patients with NAFLD (**Table 3**).

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Mofidi *et al*. (Mofidi *et al.*, 2017) reported a significant reduction in steatosis and fibrosis after 28 weeks of synbiotics supplementation. Moreover, the study of Malaguarnera *et al*. (Malaguarnera *et al.*, 2012) showed an improvement in steatosis and NASH activity score after synbiotics administration; however, synbiotics supplementation could not change fibrosis. In addition, the studies of Asgharian *et al*. (Asgharian *et al.*, 2016), Bakhshimoghaddam *et al.* (Bakhshimoghaddam *et al.*, 2018), and Ferolla *et al.* (Ferolla *et al.*, 2016) demonstrated a significant reduction in the severity of steatosis in synbiotic group. Eslamparast *et al*. (Eslamparast *et al.*, 2014) also showed a significant reduction in fibrosis score after synbiotics supplementation for 28 weeks. However, Malaguarnera *et al*. (Malaguarnera *et al.*, 2012), and Ferolla *et al*. (Ferolla *et al.*, 2016) found that there is no significant difference between synbiotic and control groups in level of fibrosis after synbiotics supplementation. It seems that synbiotics have a therapeutic effect on hepatic steatosis. However, the clinical results of synbiotics on fibrosis are inconsistent. This inconsistency can be due to the difference of studies in intervention duration. Studies with higher intervention duration showed beneficial effect of synbiotics on hepatic fibrosis.

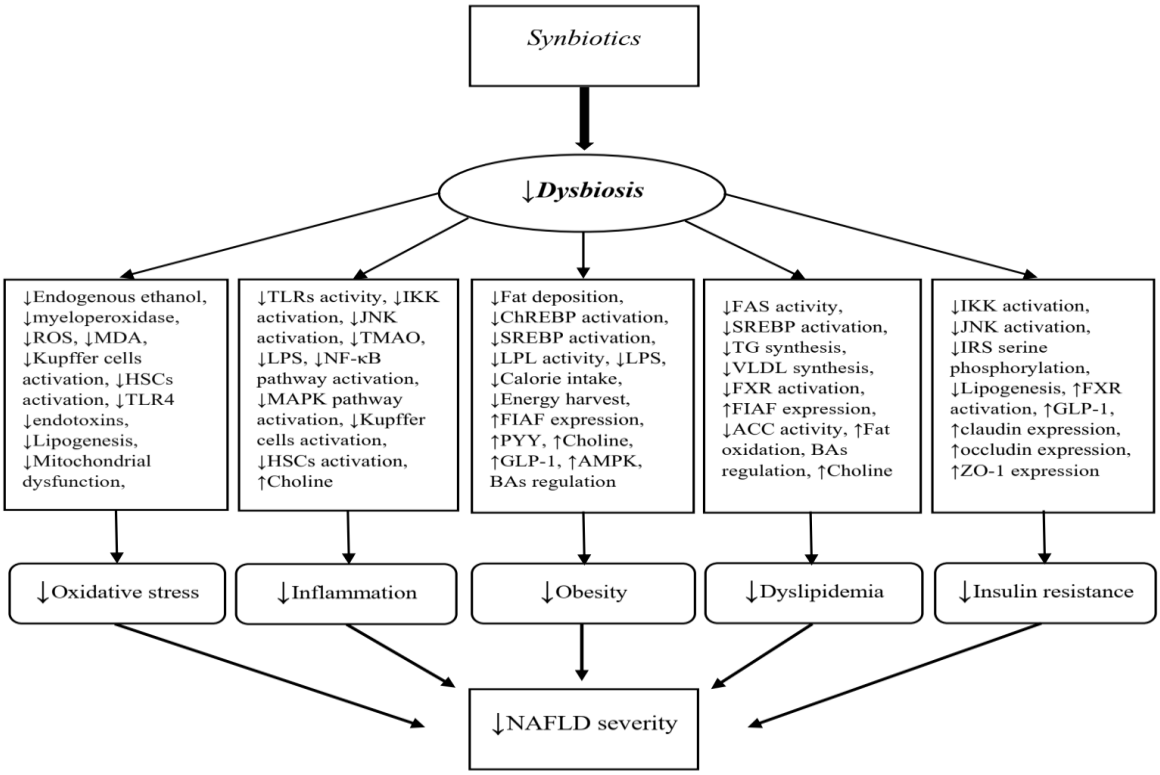


Figure 2. Overview of the mechanistic effects of synbiotics on NAFLD. ACC: acetyl-coA carboxylase; AMPK: adenosine monophosphate activated protein kinase; BAs: bile acids; ChREBP: carbohydrate-responsive element-binding protein; FAS: fatty acid synthase; FIAF: fasting-induced adipocyte factor; FXR: farnesoid X receptor; GLP-1: glucagon-like peptide-1; HSCs: hepatic stellate cells; IKK: IκB kinase; IRS: insulin receptor substrate; JNK: c-Jun-N-terminal kinases; LPL: lipoprotein lipase; MDA: malondialdehyde; NF-κb: Nuclear factor-κb; PYY: peptide YY; ROS: Reactive oxygen species; SREBP: sterol regulatory element-binding protein; TG: triglyceride; TLRs: toll-like receptors; TMAO: trimethylamine N-oxide; VLDL: Very low-density lipoprotein; ZO-1: zonula occludens-1.

Synbiotic and liver enzymes

The effect of synbiotics supplementation on liver enzymes in patients with NAFLD was investigated in several RCTs (**Table 3**). Eslamparast et al. (Eslamparast *et al.*, 2014) found a significant reduction in levels of liver enzymes including aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) after 28 weeks; but, alkaline phosphatase (ALP) remained unchanged. The study of Bakhshimoghaddam et al. showed a greater decrease in AST, ALT, GGT and ALP

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serum levels in synbiotic group compared to the control group after 28 weeks. In addition, in the study by Ekhlasi *et al*. (Ekhlasi *et al.*, 2017), a significant reduction in levels of ALT, AST and ALP was found in the synbiotic group. Moreover, the studies of Malaguarnera *et al*. (Malaguarnera *et al.*, 2012), and Sayari *et al*. (Sayari *et al.*, 2018) found a significant decrease in AST in synbiotic group after intervention period; however, the levels of ALT did not change. Mofidi *et al.'s* study was conducted among lean patients with NAFLD and a significant difference was found between synbiotic and placebo in AST levels; but, there was no significant change in the levels of ALT and GGT after supplementation for 28 weeks. The studies of Asgharian *et al*. (Asgharian *et al.*, 2016) and Ferolla *et al*. (Ferolla *et al.*, 2016) reported that the levels of liver enzymes remained unchanged after synbiotic supplementation. In general, the studies with longer intervention durations showed a greater improvement of liver enzymes.

Conclusions

Modifying gut microbiota composition and distribution can be considered as a therapeutic strategy in NAFLD. The studies investigating the effects of synbiotics on liver enzymes and hepatic steatosis showed promising results. However, the clinical results related to synbiotics and fibrosis are inconsistent. To clarify the clinical effects of synbiotics on fibrosis, more investigations are needed.

Authors' contributions

All the authors have contributed to the various stages of this work.

Conflict of interests

The authors declared no competing interests.

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Table 3. Randomized controlled trials evaluating the effects of synbiotics in patients with NAFLD.

Authors	Study design	Population	Duration	Outcomes	Findings	Limitations/Strengths
Mofidi et al.	Intervention group: Daily 2 synbiotic capsule that each capsule (Protexin; Probiotics International Ltd) contained 200 million bacteria of seven strains (*Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium longum* and *Lactobacillus bulgaricus*) and prebiotic (125 mg fructo-oligosaccharide) and probiotic cultures (magnesium stearate (source: mineral and vegetable) and a vegetable capsule (hydroxypropylmethyl cellulose)) (n = 25) Control group: Placebo (maltodextrin) (n = 25)	50	28 weeks	Steatosis, Fibrosis, AST, ALT, GGT,	Steatosis (↓), Fibrosis (↓), AST (↓), ALT (-), GGT (-)	Limitation: small sample size Strengths: using FibroScan, the first clinical trial on lean patients with NAFLD, long duration of the study.
Eslamparast et al	Intervention group: Daily 2 synbiotic capsule that each capsule (Protexin) contained 200 million CFU of 7 strains (*Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacteriu breve*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Lactobacillus bulgaricus*) and prebiotic (125 mg fructooligosaccharide) and probiotic cultures (magnesium stearate [source: mineral and vegetable] vegetable capsule [hydroxypropyl methyl cellulose]) + advised to follow an energy-balanced diet and physical activity recommendations (n = 26) Control group: placebo (maltodextrin) + advised to follow an energy-balanced diet and physical activity recommendations (n = 26)	52	28 weeks	Fibrosis score, AST, ALT, GGT, ALP	Fibrosis score (↓), AST (↓), ALT (↓), GGT (↓), ALP (-)	Limitation: small sample size Strengths: using FibroScan, long duration of the study.
Bakhshimoghaddam et al.	Intervention group: 300 g/d synbiotic yogurt (starter cultures of *Streptococcus thermophilus* and *Lactobacillus Bulgaricus* +10^8 CFUs *Bifidobacterium lactis* (BB-12)/mL as a probiotic and 1.5 g inulin as a prebiotic) + follow a healthy lifestyle (n = 34) Conventional group: 300 g/d conventional yogurt (starter cultures of *Streptococcus thermophilus* and *Lactobacillus Bulgaricus*) + follow a healthy lifestyle (n = 34) Control group: follow a healthy lifestyle (n = 34)	102	24 weeks	Steatosis, AST, ALT, GGT, ALP	Steatosis (↓), AST (↓), ALT (↓), GGT (↓), ALP (↓)	Limitation: diagnosis of fatty liver grade via ultrasonography Strengths: adequate sample size, long duration of the study.
Ferolla et al.	Intervention group 1: 5 g of the synbiotic, which consisted of 4 g of dietary fiber (partially hydrolyzed guar gum and inulin) and 1 × 10^8 CFU of *Lactobacillus reuteri*, twice daily + nutritional counseling (n = 27)	50	12 weeks	Steatosis, Fibrosis, AST, ALT, GGT, ALP	Steatosis (↓), Fibrosis (-), AST (-), ALT (-), GGT (-),	Limitations: small sample size, short duration of intervention. Strengths: evaluation of intestinal permeability, diagnosis

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	Control group: Nutritional counseling (n = 23)				ALP (-)	of NASH via liver biopsy.
Malaguarnera et al	Intervention group: 1 g/d synbiotic as capsule that contained 1 × 10^8 *Bifidobacterium longum* and 125 mg fructooligosaccharide + advised to lifestyle modification (n = 34) Control group: placebo (maltodextrin) + advised to lifestyle modification (n = 29)	63	24 weeks	Steatosis, NASH activity score, Fibrosis, AST, ALT	Steatosis (↓), NASH activity score (↓), Fibrosis (-), AST (↓), ALT (-)	Limitation: small sample size, Strengths: utilizing liver biopsy, long duration of the study.
Asgharian et al	Intervention group: 500 mg/d synbiotic capsule (Familact containing 7 strains of probiotic bacteria (1 × 10^8 *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Bifidobacterium breve*, *Bifidobacterium longum*, and *Streptococcus thermophilus*) and fructooligosaccharides, (n = 38) Control group: placebo (Starch) (n = 36)	74	8 weeks	Steatosis, AST, ALT	Steatosis (↓), AST (-), ALT (-)	Limitation: small sample size, short duration of the study, diagnosis of fatty liver grade via ultrasonography.
Sayari et al	Intervention group: sitagliptin (50 mg daily) + 500 mg/d synbiotic as capsule that contained 1 × 10^9 colony forming unit (CFU) of 7 strains of friendly bacteria (*Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Streptococcus thermophilus*) and prebiotic (fructooligosaccharide) and probiotic cultures (magnesium stearate [source: mineral and vegetable] vegetable capsule [hydroxypropyl methylcellulose])) (n = 70) Control group: sitagliptin (50 mg daily) + placebo (maltodextrin) (n = 68)	138	16 weeks	AST, ALT	AST (↓), ALT (-)	Limitations: evaluation of steatosis and fibrosis was not performed. Strengths: large sample size.
Ekhlasi et al	Intervention group 1: 2 g/d synbiotic that contained *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, *Lactobacillus bulgaricus* (2 × 10^8 CFU/g) and 250 mg fructooligosaccharide + placebo (corn starch) (n = 15) Intervention group 2: 400 IU/d alpha tocopherol + placebo (corn starch) (n = 15) Intervention group 3: synbiotic + 400 IU/d alpha tocopherol (n = 15) Control group: placebo (corn starch) + placebo (corn starch) (n = 15)	60	8 weeks	AST, ALT, ALP	AST (↓), ALT (↓), ALP (↓)	Limitation: small sample size, short duration of the study. evaluation of steatosis and fibrosis was not performed, Strengths: long duration of the study.

NAFLD: non-alcoholic fatty liver disease; **NASH**: non-alcoholic steatohepatitis; **AST**: aspartate aminotransferase; **ALT**: alanine aminotransferase; **GGT**: gamma-glutamyltransferase; **ALP**: alkaline phosphatase; (↓): significant decrease; (↑): significant increase; (-): no significant change.

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