Title page

Title: Gut-derived systemic inflammation as a driver of depression in chronic liver disease

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Abstract:

Depression and chronic liver disease (CLD) are important causes of disability, morbidity and mortality worldwide and their prevalence continues to rise. The rate of depression in CLD is high compared to that of the general population and is comparable to the increased rates observed in other medical comorbidities and chronic inflammatory conditions. Notably, a comorbid diagnosis of depression has a detrimental effect on outcomes in cirrhosis.

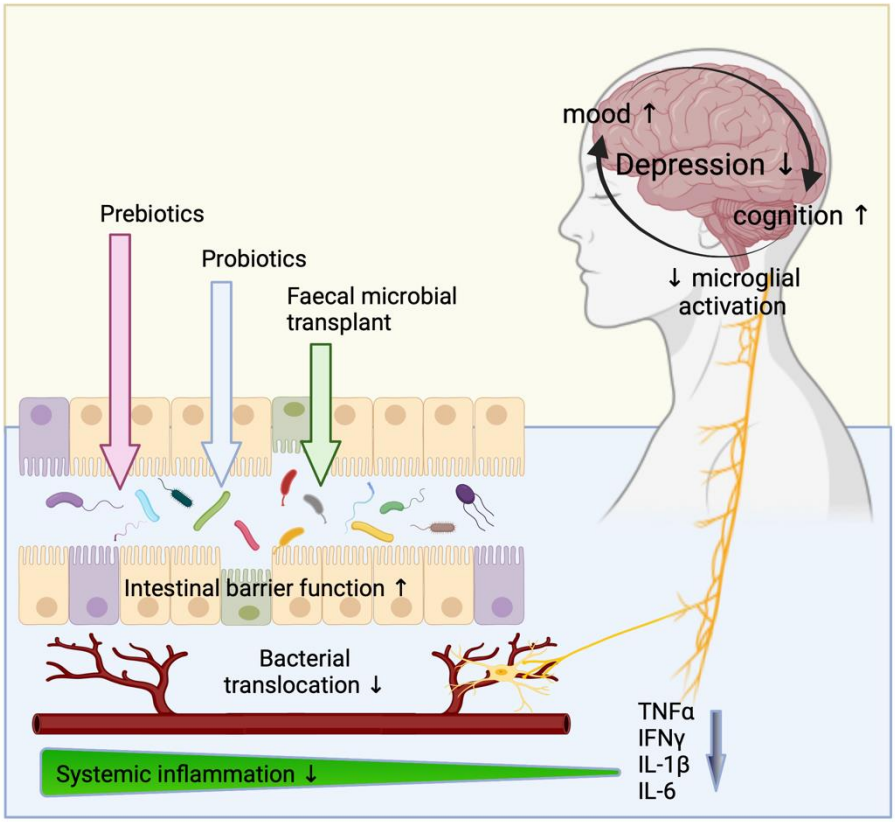
Systemic inflammation is pivotal in cirrhosis-associated immune dysfunction – a phenomenon present in advanced CLD (cirrhosis) and implicated in the development of complications, organ failure, disease progression, increased infection rates and poor outcome. The presence of systemic inflammation is also well documented in a cohort of depressed patients; peripheral cytokine signals can result in neuroinflammation, behavioural change and depressive symptoms via neural mechanisms, cerebral endothelial cell and circumventricular organ signaling, and peripheral immune cell-to-brain signaling. Gut dysbiosis has been observed in both depressed and cirrhotic patients. It leads to intestinal barrier dysfunction resulting in increased bacterial translocation, in turn activating circulating immune cells, leading to cytokine production and systemic inflammation. A perturbed gut-liver-brain axis may therefore explain the high rates of depression in patients with cirrhosis.

The underlying mechanisms explaining the critical relationship between depression and cirrhosis remain to be fully elucidated. Several other psychosocial and biological factors are likely to be involved, and therefore the cause is probably multifactorial. However, the role of the dysfunctional gut-liver-brain axis as a driver of gut-derived systemic inflammation requires further exploration and consideration as a target for therapy for depression in patients with cirrhosis.

KEY POINTS

- The prevalence of depression is high in cirrhosis and depression has an adverse impact on outcome and quality of life.
- Gut dysbiosis causes increased intestinal permeability and bacterial translocation.
- Gut dysbiosis and systemic inflammation are present in cirrhosis and depression.
- Gut-derived TNF-α, IL-1β and IL-6 can influence the brain resulting in depression.
- Favourably modifying the gut microbiome may decrease inflammation and depression in cirrhosis.

Graphical abstract (Figure 2)



1. Introduction

Depression is a principal cause of disability worldwide, affecting 350 million people annually, and frequently co-exists with chronic medical conditions.[1] Common symptoms include anhedonia, low mood, cognitive impairment and anxiety.[2]

Depression is diagnosed using the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) criteria[3], which relies on the identification of a number of key symptoms, assessed via the Structured Clinical Interview for DSM-5 (SCID)[4], an objective psychiatric assessment. Depression screen questionnaires are helpful to detect and assess severity, and are commonly used in research studies, due to the time-consuming nature of structured interviews. Recommended tools include the Hospital Anxiety and Depression scale (HADS)[5] and Beck Depression Inventory second edition (BDI-II).[6] Functional neuroimaging studies have found that, in general, the amygdala and subgenual anterior cingulate have increased activity, but the insula and dorsal lateral prefrontal cortex are hypoactive, in patients with depression.[7,8] However, changes seen on functional neuroimaging are not consistent, and relate to a highly variable clinical presentation and are therefore not routinely used in clinical practice.[9,10]

Whilst the pathophysiology of depression remains to be fully elucidated, inflammation appears to be a key driver in its development.[11] A subgroup of patients with depression exhibit systemic inflammation. Increased levels of plasma pro-inflammatory cytokines and their receptors (including tumour necrosis alpha (TNF-α), interleukin (IL)-1β and IL-6), chemokines and acute phase reactants (such as C-reactive protein (CRP)) have been detected in the plasma of depressed patients.[12,13] Central (brain) inflammation has also been demonstrated; neuroinflammation, including microglial activation, has been found in the brains of depressed patients post-mortem,[14,15] and increased levels of pro-inflammatory cytokines (including TNF-

α and IL-6) have been detected in the cerebrospinal fluid (CSF) of patients with depression.[14]

Chronic liver disease (CLD) continues to rise globally with cirrhosis and the complications of viral hepatitis accounting for 2 million deaths per year, 3.5% of global mortality.[16] Cirrhosis is the pathological end-stage of CLD that leads to portal hypertension and liver failure, and an increased risk of developing hepatocellular carcinoma (HCC).[17]

Depression is more prevalent in patients with cirrhosis than the general population, and has an adverse impact on clinical outcomes.[18] Depression is therefore important to screen for in cirrhotic patients, and the underlying cause for its increased prevalence in cirrhosis needs to be determined to improve quality of life and outcomes in this large patient population.

2. The prevalence of depression in chronic liver disease and its effect on outcome

2.1 Depression and cirrhosis

Studies have emphasised the higher prevalence of depression in cirrhotic patients (18 – 58%)[18–21], compared to the general population (10%).[22] For comparison, studies have revealed 20% prevalence of depression in chronic kidney disease (CKD)[23], 22-57%, 33-50%, 1.5-46% and 11-44% prevalence in patients with oropharyngeal, pancreatic, breast and lung cancer, respectively[24], 17.6% prevalence in patients with Type 2 diabetes mellitus[25] and 21.5% prevalence in patients with heart failure.[26] CLD patients with an earlier fibrotic stage, and not yet cirrhosis, also have a higher rate of depression.[27] Whilst some studies have suggested that depression is associated with severity of liver disease[19,28,29], others have not reported this relationship.[30–32]

Depression in cirrhosis is an independent predictor of mortality, and a principal determinant of reduced health related quality of life (HRQoL), sleep disruption, increased fatigue and hospital readmission.[21,33] Depressed cirrhotic patients have worse health outcomes compared to matched patients without depression; Singh et al (1997) found that patients with depression and decompensated cirrhosis of different aetiologies undergoing liver transplant assessment had an increased mortality at 100 days compared to non-depressed patients, despite comparable incidence of specific features of decompensation and liver disease severity scores (Child Pugh).[32] A diagnosis of depression pre-liver transplant is also associated with decreased survival post-transplant.[33]

2.2 Depression and non-alcoholic fatty liver disease

The association between non-alcoholic fatty liver disease (NAFLD) and depression is well documented; several studies have reported increased prevalence of depression in NAFLD patients.[30,34,35] (**Table 1.**) Whilst the increased prevalence of depression in metabolic disorders, especially diabetes[36], is well recognised, these studies importantly controlled for these confounders.

Some studies have found that a diagnosis of depression correlates with NAFLD severity (based on histology)[28,29] and response to therapy.[28] (**Table 1.**) Conversely, Kim et al (2019) found that, whilst the prevalence of depression was higher in subjects with NAFLD (based on non-invasive indices) than those without, there was no difference in prevalence of depression between those with high probability of advanced fibrosis compared to those with low or intermediate risk. However, the assessment of NAFLD-related advanced fibrosis was assessed using a non-invasive index (Fibrosis-4 score) rather than histologically.[30]

Table 1.

2.3 Depression and other aetiologies of chronic liver disease

Depression is also more common at the pre-cirrhotic level in other aetiologies of CLD. Depression is more common in patients with chronic hepatitis C (HCV) infection, independent of anti-viral treatment use[37], with a prevalence of 30%.[38] Whilst there are numerous psychosocial factors that may contribute, the HCV itself may have a direct biological role on the development of depression[39], through peripherally induced cytokines[40] and direct neuropathic effects of HCV viral particles that can penetrate the blood brain barrier (BBB).[41]

Patients with cholestatic and autoimmune liver disease also exhibit higher rates of depression[42,43], which may be related to their state of immune activation.[44] Fatigue is a common symptom of cholestatic liver disease and has profound effects on quality of life.[45] Fatigue is also a core symptom of depression. A study of 92 patients with primary biliary cholangitis (PBC) found that 42% of patients had depressive symptoms based on Beck Depression Inventory (BDI) criteria, but only 3.7% had depression based on DSM-IV criteria. This discrepancy is likely related to the fact that fatigue and other somatic symptoms are assessed in BDI scores but not DSM-IV, and therefore it is difficult to distinguish if fatigue in PBC is a manifestation of depression, or of the underlying liver disease.[46]

3. Factors involved in the pathophysiology of depression in cirrhosis

3.1 Psychological and psychosocial mechanisms

It has been suggested that patients with depression and cirrhosis have similar health behaviours, including alcohol use, smoking, poor diet and increased treatment non-adherence[47], and have

more difficult social circumstances.[18] Some aetiologies of cirrhosis, such as HCV infection and alcohol misuse, have shared underlying roots with depression.[48,49] Nevertheless, studies have revealed no significant differences in the prevalence of the main lifestyle variables that are a factor in the development of depression (education level, marital status, employment, income and social support level) between depressed and non-depressed cirrhotic patients.[32]

3.2 Hepatic encephalopathy

Hepatic encephalopathy (HE) is a frequent debilitating complication of cirrhosis and is defined as 'brain dysfunction caused by liver insufficiency and/or portosystemic shunting' that presents with a wide array of clinical symptoms ranging from disturbance of sleep/wake cycle, non-specific cognitive impairment and personality changes through to acute confusion and coma.[50] Overt HE affects 20-40% of cirrhotic patients during their disease trajectory[51], and severely impacts on HRQoL and survival.[52] Minimal HE requires the use of neurophysiological or psychometric testing to diagnose, as it is clinically undetectable.[50]

HE and depression share a number of similar clinical signs and symptoms, including cognitive impairment, fatigue and psychomotor retardation, creating a diagnostic challenge. It is often difficult to recognise symptoms as a separate manifestation of the same condition or, conversely, to co-diagnose both conditions. Furthermore, studies involving single photon emission computed tomography (SPECT) have shown an overlap in the neuropathological origin of depression and HE.[18]

The literature on the association between HE and depression is conflicting, with some studies suggesting a positive association[53–60], whilst others refute this.[20,61] (**Table 2.**) Whilst cerebral accumulation of ammonia is central to the pathophysiology of HE, systemic inflammation,

which further exacerbates the toxic effect of ammonia on astrocytes, is also fundamental to its development.[62–64] Thus, whilst they are clearly separate clinical entities, systemic inflammation may be the common link between HE and depression.

Table 2.

3.3 Medications prescribed in cirrhosis

Another postulation is that commonly prescribed medications in cirrhosis may be contributory to the high rates of depression observed.[10] Notably, the anti-viral agent interferon-alpha (IFN-α), previously used to treat HCV, has a well-documented causal role in the development of depression.[65] However, major depression in chronic HCV has been demonstrated to be independent of anti-viral treatment use.[37] Though data regarding the association of beta-blockers, prescribed for primary or secondary prophylaxis for variceal bleeding, are conflicting, a recent systematic review of randomised controlled trials (RCTs) of beta-blockers versus placebo revealed that patients on beta-blockers had lower rates of depression.[66]

Significant pharmacokinetic and pharmacodynamic changes occur in cirrhosis[67], and therefore there is significant concern amongst clinicians when considering antidepressant prescription to cirrhotic patients, due to the potential risk of drug-induced liver injury (DILI) and adverse events.[18] Selective serotonin reuptake inhibitors (SSRIs) and selective noradrenergic reuptake inhibitors (SNRIs), particularly SSRIs, are safe and effective pharmacotherapeutic options to treat depression in cirrhosis, though the maintenance dose of some SSRIs should be halved due to prolonged half-life and reduction in drug clearance.[67]

3.4 Unifying biological theories

The increased prevalence of depression in liver disease, and its detrimental effect on patient outcome, cannot solely be explained by psychological and social factors, severity of liver disease and presence of HE.

Increased rates of depression have been noted in most aetiologies of CLD, including; NAFLD[30,35], alcohol-related cirrhosis[68], viral hepatitis[37,53] and cholestatic and autoimmune liver disease.[42,43] These diseases vary considerably in their pathogenesis, and therefore the increased rates of depression observed over-all suggest a unifying biological mechanism.[18]

Biological theories centre on the dysregulated immune system and pro-inflammatory state observed in both depression[12,14] and cirrhosis.[69] An imbalance in the gut microbiome, and increased bacterial translocation, contribute to the similar inflammatory pathophysiology of both depression and cirrhosis.

4. The role of the immune system and inflammation

4.1 Cirrhosis-associated immune dysfunction

Cirrhosis-associated immune dysfunction (CAID) describes key abnormalities observed in the immune system of patients with cirrhosis; firstly, acquired immunodeficiency with impaired response to pathogens, and secondly, overt systemic inflammation. Whilst innate immune dysfunction has mainly been described, adaptive immune defects have also been established.[70] CAID describes a dynamic pattern; over time the immune response shifts from a pro-inflammatory to anti-inflammatory compensatory response. CAID contributes to disease progression in cirrhosis, increases the propensity to develop infection and is associated with

the progression to acute decompensation (AD) and acute-on-chronic liver failure (ACLF). Furthermore, CAID occurs across the spectrum of all aetiologies of cirrhosis.[69]

Systemic inflammation, in the absence of infection, is the hallmark of CAID and is likely instigated by bacterial translocation from the gut to the systemic circulation.[71] Increased bacteria and resultant pathogen-associated molecular patterns (PAMPs), from enteric microbes, stimulate PRRs on innate immune cells. Increased generation of damage-associated molecular patterns (DAMPs), from necrotic liver cells, also stimulates immune cells. Once stimulated, PRRs activate a transcriptional response inducing gene expression and the synthesis of pro-inflammatory cytokines, chemokines and cell adhesion molecules involved in the adaptive immune response.[72] Further activated PRR responses include; vascular endothelial injury[73], acute phase protein synthesis in the liver[73], leucocyte recruitment to sites of inflammation[69] and augmented phagocytic activity. Such pathways lead to systemic inflammation, without overt sepsis, which carries a poor prognosis. There is a wealth of research data demonstrating evidence of systemic inflammation in cirrhosis including; but not limited to, increased serum level of acute phase reactants (CRP) [72], increased serum levels of markers of endothelial activation (vascular endothelial growth factor (VEGF), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), nitrates/nitrites)[69,73,74] increased pro-inflammatory cytokine production (TNF-α, IL-17, interferon-gamma (IFNγ)) by circulating immune cells[69,75] and increased serum levels of pro-inflammatory cytokines (TNF-α, IFNγ, IL-1β, IL-6, IL-17, IL-18).[69,73–77]

4.2 Non-alcoholic fatty liver disease and inflammation

Whilst the detrimental role of systemic inflammation in cirrhosis of all aetiologies has been discussed, special mention is required in relation to NAFLD.

NAFLD covers a spectrum of disease ranging from excessive fat accumulation/steatosis without necroinflammatory injury to significant hepatocellular injury and inflammation (non-alcoholic steatohepatitis (NASH)) to cirrhosis, and is closely related with obesity, insulin resistance (IR) and the components of the metabolic syndrome; hypertension, type 2 diabetes mellitus and dyslipidaemia.[78]

Whilst the pathophysiology of NAFLD and the metabolic syndrome is outside of the scope of this review, oxidative stress and inflammation appear key to their development. Chronic low-level inflammation along with visceral adipose tissue, adipocyte dysfunction and IR impair lipid and glucose homeostasis in insulin-sensitive tissues[79], and the gene expression of adipose-derived inflammatory cytokines (such as TNF-α and IL-6) is increased in obese patients.[80] Ectopic fat accumulates in NAFLD, and this is linked to increased hepatokine secretion, augmented gluconeogenesis, reduced glycogen synthesis and insulin signaling inhibition.[81] Hepatokines, proteins that are secreted by hepatocytes, can manipulate metabolic processes through autocrine, paracrine and endocrine signaling.[82] Hepatic steatosis provokes changes in hepatokine secretion which result in metabolic dysfunction, promoting IR, and drive systemic inflammation by activating pro-inflammatory pathways.[83] Levels of Fetuin A, a glycoprotein present in the plasma, are increased in NAFLD and increase the risk of IR.[82] Fetuin A also stimulates the production of pro-inflammatory cytokines from adipocytes and macrophages.[84] Excess hepatic lipid also adds to IR, and leads to oxidative stress, chronic inflammation and lipotoxicity, increasing the risk of fibrosis and cirrhosis development.[85] Alongside liver lipid metabolism, adipose tissue dysfunction and inflammation, as in the metabolic syndrome, appear to be central to the development of NAFLD.[78]

Many studies have demonstrated the increased levels of pro-inflammatory cytokines, including TNF-α and IL-6, in the development of NASH.[86,87] Hepatocytes and immune cells produce TNF-α. TNF-α stimulates liver steatosis, and also activates Kupffer cells which promote liver fibrosis.[85] Adipose tissue is the main secretor of IL-6. IL-6 is involved in fatty acid metabolism and, whilst the IL-6 signaling pathway protects against liver steatosis development, it may paradoxically stimulate hepatic inflammation.[88]

Hence, the systemic inflammation observed in NAFLD and NASH may be separate from that seen in CAID, and may therefore explain the increased rates of depression seen NAFLD as well as NASH cirrhosis.

4.3 The role of systemic inflammation in depression in cirrhosis

Whilst the theory that the dysregulated immune system and overt systemic inflammation is key to the increased prevalence of depression in cirrhosis, there are few studies examining this (summarised in **Table 3.**).

Hepatic and systemic inflammation have been shown to trigger neuroinflammation and depressive symptoms in two studies employing mouse models. (**Table 3.**)[89,90]

Human studies are lacking. Ko et al. (2013) demonstrated that depression scores correlate with serum levels of aspartate transaminase (AST) in cirrhotic patients.[31] AST is a cytoplasmic enzyme, its extracellular presence signals cell necrosis and, whilst not specific to the liver, suggests hepatic inflammation and damage. In a separate study Ko et al. (2013) demonstrated that the percentage of CD8 T-cells, but not CD3 or CD4, positively correlated with depression in cirrhotic patients (**Table 3**).[91] The functional state of T-lymphocytes often depends on T-

lymphocyte subset percentage distribution, and they are involved in cell-mediated immunity. An imbalance in T-lymphocyte subsets may therefore facilitate depression in cirrhosis, potentially through increased pro-inflammatory cytokine release (such as TNF-α) or increased permeability of the BBB.[92] Of note, studies have implicated phenotypic and functional changes in CD8 T-cells in cirrhotic patients which may contribute to CAID.[70]

Thus, the innate and adaptive immune system are activated in cirrhosis, resulting in a pro-inflammatory state, similar to that seen in depression.[11] Whilst no published studies have compared the levels of pro-inflammatory cytokines in cirrhotic patients with and without depression, the main pro-inflammatory cytokines implicated in the development of depression (TNF-α, IL-1β and IL-6)[14,93–95] are also notably raised in cirrhotic patients.[77,96]

Table 3.

4.4 The pathway between peripheral and central inflammation

The pathway between peripheral inflammation, neuroinflammation and clinical symptoms of depression remains to be fully elucidated.

Systemic inflammation and oxidative stress increase BBB permeability driving neuroinflammation.[97] Animal models have identified three main cytokines, TNF-α, IL-1β and IL-6 (all of which are increased in cirrhosis)[69] that enable peripheral to central communication in systemic inflammation. There are four well-documented pathways by which peripheral cytokines communicate with the brain; neural routes via peripheral afferent nerve fibre cytokine receptors (such as the vagus nerve)[98], permeable areas of the BBB such as circumventricular organs (CVOs), peripheral immune cell-to-brain signaling and cerebrovascular endothelial cells (CECs).[99] CECs at the BBB become activated by circulating

peripheral inflammatory chemokines, resulting in pro-inflammatory mediator release into the brain. CECs have TNF-α and IL-1β receptors. Their activation generates intracerebral synthesis of nitric oxide (NO) and prostanoids[100] which, in turn, stimulate microglial cells and astrocytes.[101]

In brief, these peripheral cytokine signals can then affect practically all central nervous system (CNS) fields involved in depression, including; neuroendocrine function (by activating the hypothalamic-pituitary-adrenal axis), neurotransmitter metabolism (serotonin, dopamine, noradrenaline, glutamate and kynurenine pathways), and neural plasticity.[11] Furthermore, they can act directly on microglia and astrocytes, the CNS glial cells chiefly implicated in the neuroinflammation of depression.[12]

Microglia are resident cerebral immune cells, essential for mounting a neuroinflammatory response and comprise 5-10% of total brain cells.[102] When activated microglia produce their own pro-inflammatory cytokines which, in health, are vital modulators of various CNS functions.[103] However, excessive pro-inflammatory cytokine activity in the brain disturbs many neuronal functions, including neurotransmitter signaling,[104,105] ultimately affecting the neurocircuits involved in cognition and mood.[106]

5. The role of gut microbiome

There is growing evidence that the gut microbiome plays a central role in the development of the pro-inflammatory state observed cirrhosis[71,107] and the microbiota-gut-brain axis is also proving increasingly important in the pathophysiology of depression.[108]

5.1 The gut-liver-immune axis and inflammation in chronic liver disease and cirrhosis

Patients with cirrhosis have an imbalance between healthy and pathogenic bacteria affecting the microbiome structure and function, termed enteric dysbiosis, which is associated with impaired intestinal barrier function and dysregulated immune homeostasis.[71]

The gut microbiome has been implicated in the development of NAFLD; animal and human studies have revealed an association between intestinal dysbiosis and NAFLD and its severity.[109,110] NAFLD patients have reduced microbial diversity, increased *Firmicutes* and reduced *Bacteriodetes.*[109] Furthermore, differential abundance of *Firmicutes, Bacteriodetes* and *Proteobacteria* phyla has been shown to predict advanced fibrosis in NAFLD patients.[111]

Gut microbiome modifications have been observed in patients with alcohol misuse, alcohol-related liver disease (ARLD) and alcohol-related cirrhosis.[112] Higher proportions of *Enterobacteriaceae* and lower proportions of *Lachnospiraceae, Ruminococcaceae* and *Clostridiales XIV* are observed in patients with alcohol-related cirrhosis.[113] Chronic alcohol abuse can modulate faecal pH which encourages pathogen overgrowth and is also associated with alterations in metabolite secretions affecting gut microbiota function.[112] Alcohol use also impairs the function of the intestinal barrier. Alcohol and acetaldehyde, the toxic metabolite of alcohol, increase intestinal permeability by altering the expression of tight-junction proteins.[114] Patients with chronic alcohol use display higher levels of pro-inflammatory cytokines[115] and are at greater risk of depression. The modified gut microbiome with alcohol use may result in increased bacterial translocation, an activated innate immune system, subsequent systemic inflammation and increase in pro-inflammatory cytokines[115] which signal to the brain and induce depressive symptoms.[99]

Cirrhotic patients exhibit gut dysbiosis, encompassing a significantly reduced bacterial diversity, overexpression of pathogens such as *Fusobacteria, Proteobacteria* and *Streptococaccae* and reduction in species central to healthy microbiome function such as *Bacteriodetes*, *Lachnospiracae* and *Firmicutes.*[116,117] This dysbiosis worsens with more advanced disease.[113] Patients with cirrhosis also exhibit small bowel bacterial overgrowth. Quantitative metagenomics have revealed 75,245 microbial genes differ between cirrhotic patients and healthy subjects.[117] Dysbiosis is greater in cirrhotic patients who develop complications and correlates with plasma endotoxin levels and 30-day mortality.[113]

Cirrhotic dysbiosis encourages intestinal barrier dysfunction in cirrhosis, which allows pathogens to adhere to the mucosa and enables bacteria, their products (such as lipopolysaccharide (LPS), flagellin, peptidoglycan and bacterial DNA) and PAMPs to translocate into the portal circulation. The portal hypertension and endothelial dysfunction that develop in cirrhosis further increase this intestinal permeability.[118] Portal hypertension, in both cirrhotic and non-cirrhotic patients, results in venous congestion and splanchnic neoangiogenesis, which lead to impaired microcirculation and gut barrier dysfunction.[119] Bacterial translocation leads to endotoxemia, and delivers gut-derived pathogens and their products directly to the liver, via the portal vein, activating the innate immune response.[71] Portosystemic shunting in cirrhosis further enables direct delivery of immune-activating bacterial degradation products to the systemic circulation.[120] Endotoxins activate hepatic macrophages via toll-like receptors (TLRs) and stimulate the production of pro-inflammatory cytokines, including TNF-α and IL-8, which recruit monocytes and neutrophils to the liver.[121] Ultimately this drives hepatic injury, systemic inflammation and CAID, promoting the development of infection, decompensation and disease progression.[113]

Research is now focused on restoring gut eubiosis, for example via faecal microbial transplantation (FMT), and repairing intestinal barrier function to prevent complications, infection and decompensation in patients with cirrhosis.[107]

5.2 The gut-microbiota-brain axis and inflammation in depression

The microbiota-gut-brain axis influences behaviour, and is also implicated in the development of depression. Most evidence has come from pre-clinical models[122]; the absence of a gut microbiota induces depression-like behaviour in mice and germ-free (GF) mice transplanted with stool rich from patients with depression resulted in depression-like behaviours not seen with FMT of 'healthy microbiota' from controls.[123]

Human studies have also found significant differences in the gut microbiome in depressed patients compared to healthy individuals.[108,124–126] However, there is disparity in their findings with one study noting *Bifidobacterium* and *Lactobacillus* were reduced in depressed patients[124], another noting that *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* were increased, and *Firmicutes* were decreased in depressed individuals[125] and another noting that the family *Lachnospiraceae* was significantly decreased in depressed patients versus healthy controls.[126] Further studies have reported reduced microbial richness.[108] Interestingly some of these changes, such as decreased *Lachnospiraceae* (involved in short chain fatty acid (SCFA) production) and decreased microbial richness are similar to those observed in cirrhotic patients.[71] A recent observational study determined that depressed patients deemed non-responders to conventional treatment had a lower alpha diversity in the Phylogenetic diversity whole tree index compared to responders during treatment, and also increased microbiome glutamate synthesis.[127]

The exact communication pathways between the gut microbiome and brain need further clarification, but the activated immune system is likely a significant pathway leading to depressive symptoms.[108] Dysbiosis results in gut immune cell activation, cytokine production and increased permeability of intestinal mucosa, leading to increased translocation of bacteria.[71] This triggers cytokine production by circulating immune cells, an exaggerated immune response and resultant neuroinflammation.

Together with the activation of the innate immune system, gut microbiota can produce a variety of metabolites, including neurotransmitters, secondary bile acids, choline, SCFAs, bacteriocins and branched chain amino acids[108] which are immunomodulatory. Mounting evidence suggests that microbiota-host interactions at the gut level result in cytokine, chemokine, neuropeptide, neurotransmitter, endocrine and by-product release that can travel via the systemic circulation and lymphatics, or communicate with the brain via the autonomic nervous system and influence behaviour.[108] The effect of the gut microbiome on microglial homeostasis appears to be key to the gut-microbiota-brain axis and behavioural changes.[128]

The gut is the main source of serotonin in the body.[129] The gut microbiota may also be crucial in the regulation of tryptophan metabolism, affecting serotonin synthesis and downstream kynurenine pathway metabolism in both the periphery and the CNS, affecting behaviour and depressive symptoms.[130]

The vagus nerve, the principal component of the parasympathetic nervous system, is one of the vital modes of communication between the gut and the brain.[131] Vagal afferent fibres are located in the gastrointestinal tract wall but do not cross the epithelium, thus are not in direct contact with gut microbiota.[132] Instead, metabolites can travel across the epithelial cell layer and act directly on vagus nerve afferent fibres to signal to the brain.[133] The luminal wall is also

richly innervated by the enteric nervous system (ENS), which is predominantly responsible for gut motility, and can be targeted by SCFAs and neurotransmitters.[131]

The implication of the gut microbiome in the pathophysiology of depression has led to the notion of psychobiotics –microbiota-targeted interventions, mainly focussing on prebiotics and probiotics, affecting the gut-microbiota-brain axis, used in the treatment of mental health and neurological disorders. Several bacterial strains or combinations, mainly containing *Lactobacillus* and *Bifidobacterium* species, have proved efficacious in multiple studies at treating psychiatric disorders, and have been shown to reduce depression scores and enhance cognition.[108,134,135] Probiotics have been shown to reduce systemic levels of inflammatory biomarkers and pro-inflammatory cytokines.[117]

FMT aims to restore the microbiome of an unhealthy individual to a healthy state, via faecal bacteria transfer from healthy donor to recipient. Whilst the use of FMT is still in its infancy, a recent systematic review, analysing the effect of FMT on psychiatric disorder symptoms from 28 pre-clinical and clinical studies, found a decrease in depressive symptoms post FMT in all studies.[136]

5.3 Targeting the gut microbiome and inflammation in depression and liver disease

Probiotic administration has been shown to improve quality of life, symptom burden and infection rates in cirrhotic patients, but not mortality.[137,138] Furthermore, probiotic administration has been associated with a decrease in pro-inflammatory cytokine levels, such as TNF-α, in patients with CLD.[139] A pre-clinical study found that administering VSL#3 (a proprietary name for a group of eight probiotics) improved 'fatigue-like' behaviours in mice with liver inflammation, independent of changes in liver injury severity. Furthermore the mice treated with VSL#3 had decreased levels of TNFα which was linked to reduced microglial

activation, monocyte:CEC interactions and cerebral monocyte infiltration.[140] Such observations suggest that altering the gut microbiome can modify systemic immunity in liver disease, which can consequently affect the brain and behaviour.

Similarly, in a cirrhotic mouse model, transfer of faecal material from cirrhotic patients resulted in higher levels of neuroinflammation, microglial activation and dysbiosis than faecal material from healthy controls. There was no change in liver histology severity. This neuroinflammation was then reduced significantly when faecal material obtained from the same patients 15 days after undergoing FMT from healthy controls was transplanted into the same mice.[141] This demonstrated that the attenuation of neuroinflammation by FMT is independent of liver inflammation.

Trials of FMT in cirrhosis are ongoing and have mainly focused on its safety. However, FMT has been shown to have a beneficial impact on cirrhotic patients with HE, with improvement in cognition, and on patients with alcohol-related cirrhosis and alcohol use disorder (AUD) with again improved cognition, improved psychosocial quality of life and a reduction in serum IL-6 levels.[142]

As such, our exploration of the literature lends further weight to the hypothesis that the gut dysbiosis observed in cirrhosis, and resultant systemic inflammation, may explain the increased rates of depression seen (**Figure 1.**). The observations and trials described demonstrate the potential role of the gut microbiome and immune dysfunction in driving the behavioural changes and increased rates of depression observed in cirrhosis and highlight the need for further work, involving larger clinical trials investigating potential psychobiotic treatments (**Figure 2.**).

Figure 1.

Figure 2.

6. Future developments in the field

The gut-liver-immune axis in cirrhosis is well documented[107] and research into this area is growing exponentially. The microbiota-gut-brain axis has also been clearly demonstrated.[108]

Whilst our hypothesis that the high rates of depression seen in cirrhosis are a consequence of gut-derived systemic inflammation is logical, and certainly is not contradictory to current literature, there is a paucity of direct evidence to date. As depicted in **Table 3.** published studies examining the relationship between systemic inflammation, depression and liver disease are few, and arise from two research teams. One research group demonstrated the link between hepatic inflammation and sickness behaviour in bile duct ligated (BDL) mice, with evidence of microglial activation.[89,90] Cross-sectional data from a separate team corroborated the relationship between depression and inflammation in cirrhosis, though correlation was not strong.[31,91] Further mechanistic work, including prospective longitudinal studies in cirrhotic patients to assess the gut microbiome, immune system and depression (confirmed by clinical psychiatric evaluations such as the Structure Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders 5 (SCID))[4], is required to lend further support to this hypothesis.

Therapeutic interventions that target dysbiosis are being investigated in cirrhosis, and targeting the microbiome may be key to improving mood and alleviating depression in cirrhosis.

6.1 FMT

FMT has shown beneficial effects in cirrhotic patients, with improved cognition in patients with HE, reduction in episodes of overt HE[143,144] and improved quality of life.[142] The effect of FMT on psychiatric disorder symptoms in other illnesses, such as depression and irritable bowel syndrome (IBS), is promising[136], however has not been evaluated in cirrhosis. The upcoming UK multicentre randomised controlled PROMISE (PROspective double-blind placebo-controlled multicentre trial of faecal MIcrobiota tranSplantation to improve outcomEs in patients with cirrhosis) [https://fundingawards.nihr.ac.uk/award/NIHR130730] trial will assess efficacy of encapsulated FMT to reduce infection and mortality in ARLD and NAFLD cirrhosis. Primary endpoint is time to hospitalisation with infection, however secondary endpoints include change in depression and anxiety (measure by HADS score) and change in quality of life (measured by EQ-5D-3L score). As such, this study should yield crucial data on the effect of FMT on depression in cirrhosis.

6.2 Rifaximin

Rifaximin is an oral non-absorbable gut-selective antibiotic, used effectively to treat HE in cirrhosis.[145] It has been shown to modulate the gut microbiome, reduce endotoxemia and improve cognitive performance in cirrhotic patients[146] raising its potential as a psychobiotic-like treatment. The recently published RIFSYS trial, a placebo-controlled RCT of rifaximin in cirrhotic patients with HE, revealed significantly reduced TNF-α levels at 30-days in the treatment arm, in conjunction with a reduction in markers of gut-derived systemic inflammation, abundance of metagenomic species in both faecal and salivary compartments and resolution of HE.[147]

Non-selective beta-blockers

Non-selective B-blockers (NSBBs) are a well-established treatment for portal hypertension and reduce splanchnic blood flow. NSBBs ameliorate intestinal permeability and reduce bacterial translocation, by modulating gut motility[148], demonstrated by lower levels of IL-6 and LBP in cirrhotic patients receiving NSBBs.[119] The M-BOP mechanistic sub-study to the current UK multicentre randomized controlled BOPPP trial (NCT03776955), investigating the use of NSBBs or placebo for primary prophylaxis of oesophageal varices, will further explore the effect of NSBBs on bacterial translocation and risk of decompensation in BOPPP participants.

Albumin

Whilst human albumin solution is commonly used for various indications in cirrhosis, it has further immune-restorative effects that may prove beneficial in cirrhosis.[149] Trials of albumin infusion in decompensated cirrhosis have shown conflicting results. The open-label randomised ANSWER trial resulted in a 38% reduction in the mortality hazard ratio in cirrhotic patients receiving weekly albumin infusions.[150] The recent UK multicentre randomised open-label ATTIRE study investigated the effect of intravenous 20% albumin infusions in hospitalised patients with cirrhosis (targeting a serum albumin level ≥30 g/L) compared to standard of care. Conversely, there was no benefit, and no difference in composite end point (new infection, renal dysfunction and death at 15-days) was observed.[151] The current MICROB-PREDICT study, which aims to validate microbiome-based markers to predict treatment response to albumin, may shed further light on this area.

7. Conclusion

The prevalence of depression is high in liver disease. Importantly, a comorbid diagnosis of depression appears to have an adverse impact on outcomes in cirrhosis.

Gut dysbiosis results in increased permeability of the intestinal mucosa, resulting in increased bacterial translocation culminating in the activation of circulating immune cells, cytokine production and systemic inflammation. Such pathways are central to CAID, and are implicated in the increased incidence of infection in cirrhosis, disease progression and the development of organ failure and complications. Peripheral inflammation can extend to the CNS and brain via neural mechanisms, CEC and CVO signaling, and peripheral immune cell-to-brain signalling resulting in depressive symptoms. The overt systemic inflammation present in cirrhosis may therefore explain the high rates of depression.

Whilst the mechanism underlying the crucial link between depression and cirrhosis remains to be fully elucidated, and given the various psychosocial and other biological factors involved, is likely to be multifactorial, the role of the gut microbiome and inflammation requires further exploration and consideration as a target for therapy.

Abbreviations:

ACLF: acute-on-chronic liver failure

ARLD: alcohol-related liver disease

AST: aspartate transaminase

AUD: alcohol use disorder

BBB: blood brain barrier

BDL: bile duct ligated

BDIL Beck Depression Inventory

BDI-II: Beck Depression Inventory second edition

CAID: cirrhosis-associated immune dysfunction

CECs: cerebrovascular endothelial cells

CLD: chronic liver disease

CKD: chronic kidney disease

CNS: central nervous system

CRP: C-reactive protein

CVOs: circumventricular organs

DAMPs: damage-associated molecular patterns

DILI drug induced liver injury

DSM-5 Diagnostic and Statistical Manual of Mental Disorders 5

ENS enteric nervous system

FMT: faecal microbial transplantation

GALT: gut-associated lymphoid tissue

GF: germ-free

HCC: hepatocellular carcinoma

HCV: hepatitis C virus

HE: hepatic encephalopathy

HRQoL: health related quality of life

IBS: irritable bowel syndrome

ICAM-1: intercellular adhesion molecule-1

IFN-α: interferon alpha

IFN-γ: interferon-gamma

IL: interleukin

IR: insulin resistance

LPS: lipopolysaccharide

LBP: lipopolysaccharide-binding protein

NAFL: non-alcoholic fatty liver

NAFLD: non-alcoholic fatty liver disease

NASH: non-alcoholic steatohepatitis

NK: natural killer

NO: nitric oxide

NSBB: Non-selective beta-blocker

PAMPs: pathogen-associated molecular patterns

PBC: primary biliary cholangitis

PRRs: pattern recognition receptors

RCT: randomised controlled trial

SCFA: short chain fatty acid

SCID Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders 5

SNRI selective noradrenergic reuptake inhibitors

SPECT: single photon emission computed tomography

SSRI Selective serotonin reuptake inhibitors

TLR: toll-like receptors

TNF-α: tumour necrosis factor alpha

VEGF: vascular endothelial growth factor

VCAM-1: vascular cell adhesion molecule 1

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Figure 2 was “created with BioRender.com.”

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Tables

Table 1.

Author and Year	Study design	Subjects	NAFLD diagnosis	Psychiatric assessment	Findings and significance
Kim et al (2019)[30]	Cross-sectional	10 484 subjects Identified from a national database	FLI, HSI, USFLI	PHQ-9	Prevalence of depression higher in subjects with NAFLD. Patients with depression 1.6-2.2 fold more likely to have NAFLD. Depression was not associated with NAFLD-related advanced fibrosis.
Labenz et al (2020)[35]	Retrospective cohort	19,871 patients with NAFLD, 19,871 matched controls	Database ICD-10 coding (NAFLD/NASH)	Database ICD-10 code (depression)	Within 10 years, 21.2% patients with NAFLD were diagnosed with depression, compared to 18.2% controls (p<0.001). HR for depression was 1.21 (p<0.001) and for first prescription of antidepressant medication (HR 1.21, p<0.001).
Tomeno et al (2015)[28]	Prospective cohort	258 patients with NAFLD	Histological	MDD diagnosis based on DSM-IV-TR. Stable/unstable based on being in full/partial remission as per DSM-IV-TR criteria.	12% comorbid with MDD. MDD NAFLD patients had more severe histological steatosis, higher NAFLD score, high levels of AST, GGT and ferritin. MDD NAFLD patients had poorer response to standard of care for NAFLD, including weight loss.
Weinstein et al (2011)[34]	Cross-sectional	878 CLD patients	Pathology and/or radiologic	Self-reported depression (yes/no) and	23.6% of CLD patients had a diagnosis of

		(184 NAFLD, 190 HBV, 504 HCV)	testing (not specified)	use of antidepressant medication	depression, 27.2% of NAFLD patients had a diagnosis of depression.
Youssef et al (2013)[29]	Cross-sectional	567 patients with NAFLD	Histological	HADS	Subclinical and clinical depression observed in 53% and 14% of patients, respectively. Depression associated with more severe hepatocyte ballooning in dose-dependent manner.

Table 1. Published studies analysing NAFLD and depression.

Abbreviations; AST: aspartate aminotransferase; CLD: chronic liver disease; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision; FLI: Fatty Liver Index; GGT: gamma glutamyl transferase; HADS: Hospital Anxiety and Depression Scale; HBV: hepatitis B virus; HCV: hepatitis C virus; HR: Hazard Ratio; HSI: Hepatic Steatosis Index; ICD-10 International Classification of Diseases; MDD: Major Depressive Disorder; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; PHQ-9: Patient Health Questionnaire-9; USFLI: US Fatty Liver Index.

Table 2.

Author and Year	Study design	Subjects	Psychiatric assessment	Neuro-psychological assessment	Findings and significance
Barboza et al (2016)[53]	Observational	43, HCV cirrhosis	BDI-II	D-KEFS TMT NCT WAIS-III	Positive association between depressive symptoms and HE severity.
Hassan et al (2014)[61]	Case - control	35, HCV cirrhosis	HAM-D	CASI	No association between depression and mHE.
Hilsabeck at al (2003)[54]	Observational	21, chronic HCV	BDI-II	BVMT-R SDMT TMT WAIS-III	Trend towards higher BDI-II scores in patients with more cognitive complaints.
Malaguarnera et al (2011)[55]	Randomised double blind placebo controlled	33 + 34 (placebo), cirrhosis and mHE	BDI	PHES TMT	BDI score pre intervention indicative of moderate depression.
Malaguarnera et al (2018)[56]	Randomised placebo controlled, observational	35 + 35 (placebo), cirrhosis and mHE	BDI	PHES	BDI score pre intervention indicative of moderate depression.
Nardelli et al (2013)[20]	Observational	60, cirrhosis	Zung-STH	PHES	No differences in psychological test score between patients with or without minimal HE.
Stewart et al (2011)[57]	Observational	75, cirrhosis	BDI-II	CVLT TMT WAIS-III	Higher BDI-II scores in patients with decrease in cognitive function in domains of working memory.
Telles-Correia et al (2015)[58]	Observational	60, cirrhosis	HADS	PHES	No correlation between HADS and PHES, but correlation

					between anhedonia, loss of energy and some parts of PHES.
Xiao et al (2018)[60]	Cross-sectional	341, HBV cirrhosis	HADS	NCT-A	HADS-D subscore higher in NCT-A positive patients.

Table 2. Published studies analysing depression and hepatic encephalopathy in cirrhosis.

Abbreviations: BDI, Beck Depression Inventory; BDI-II, Beck Depression Inventory second edition; BVMT-R, Brief Visuospatial Memory Test – Revised; CASI, Cognitive Abilities Screening Instrument; CVLT, California Verbal Learning Test; D-KEFS TMT, Delis-Kaplan Executive Function System Trail Making Test; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Depression Rating Scale; HE, hepatic encephalopathy; HBV, hepatitis B; virus; HCV, hepatitis C virus; mHE, minimal hepatic encephalopathy; NCT-A, Number Connection Test – A; NCT, Number Connection Test; PHES, Psychometric Hepatic Encephalopathy Score; SDMT, Symbol Digital Modalities Test; TMT, Trail Making Test; WAIS-III, Wechsler Adult Intelligence Scale third revision; Zung-STH, Zung Self Rating Depression Scale.

Table 3.

Author and Year	Study design	Subjects	Psychiatric assessment	Findings and significance
D'Mello et al (2009)[90]	Animal study	Mouse model of inflammatory liver injury (BDL ligated)	Sickness behaviour	In the presence of hepatic inflammation, TNF-α signaling stimulated cerebral microglia to produce MCP-1/CCL2 to recruit monocytes into the brain. Inhibition of monocyte recruitment led to improvement in sickness behaviour of the mice.
D'Mello et al (2013)[89]	Animal study	Mouse model of inflammatory liver injury (BDL ligated)	Sickness behaviour	Increased monocyte specific rolling and adhesion along CECs was observed in mice with hepatic inflammation. Peripheral TNF-TNFR1 signaling and P-selectin were found to be central to monocyte-CEC adhesion which led to microglial activation and development of sickness behaviour.
Ko et al (2013)[31]	Cross-sectional	125 patients with cirrhosis (varying aetiologies)	HAM-D	HAM-D was correlated with AST, but not Child Pugh score.
Ko et al (2013)[91]	Cross-sectional	59 patients with cirrhosis (varying aetiologies)	HAM-D	The percentage of CD8 T-cells, but not CD3 nor CD4 cells, positively correlated with depression, after controlling for age and Child Pugh score.

Table 3. Published studies examining the relationship between systemic inflammation, depression and liver disease.

Abbreviations; AST: aspartate aminotransferase; BDL: bile duct ligated; CECs; cerebrovascular endothelial cells; HAM-D: Hamilton Depression Rating Scale; MCP-1/CCL2:

monocyte chemoattractant protein-1; TNF – α: tumour necrosis factor alpha; TNFR1: tumour necrosis factor receptor 1.

Figure Legends

Fig. 1. The role of gut-derived systemic inflammation in the pathophysiology of cirrhosis and depression.

Gut dysbiosis occurs in cirrhosis with decreased microbial diversity, increased pathogenic microbes and small bowel bacterial overgrowth. This reduces intestinal barrier function resulting in increased translocation of bacteria (and their products (LPS, peptidoglycan, flagellin, bacterial DNA)) and PAMPs into the portal circulation leading to endotoxaemia. This results in systemic inflammation and increased levels of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6). These cytokines communicate with the brain via neural pathways, CEC ad CVO signaling and peripheral immune cell-to-brain signaling leading to microglial activation, changes in neural activity and ultimately depressive symptoms.

In cirrhosis reduced synthetic and reticuloendothelial function results in an acquired immunodeficiency and innate immune dysfunction which, coupled with systemic inflammation, is referred to as cirrhosis-associated immune dysfunction (CAID).

Fig. 2. Potential treatment options to restore gut eubiosis and treat depression in cirrhosis.

The administration of prebiotics, probiotics and faecal microbiota transplant results in favourable gut microbiota composition, decreased bacterial translocation and reduced systemic inflammation. The consequent reduction in pro-inflammatory cytokines may lead to decreased

microglial activation, improved cognition and mood and fewer depressive symptoms. Created with BioRender.com.

Abbreviations: TNF-α: tumour necrosis factor alpha; IFN-γ: interferon-gamma; IL-1β: interleukin 1 beta; IL-6: interleukin 6.

Figures

Figure 1.

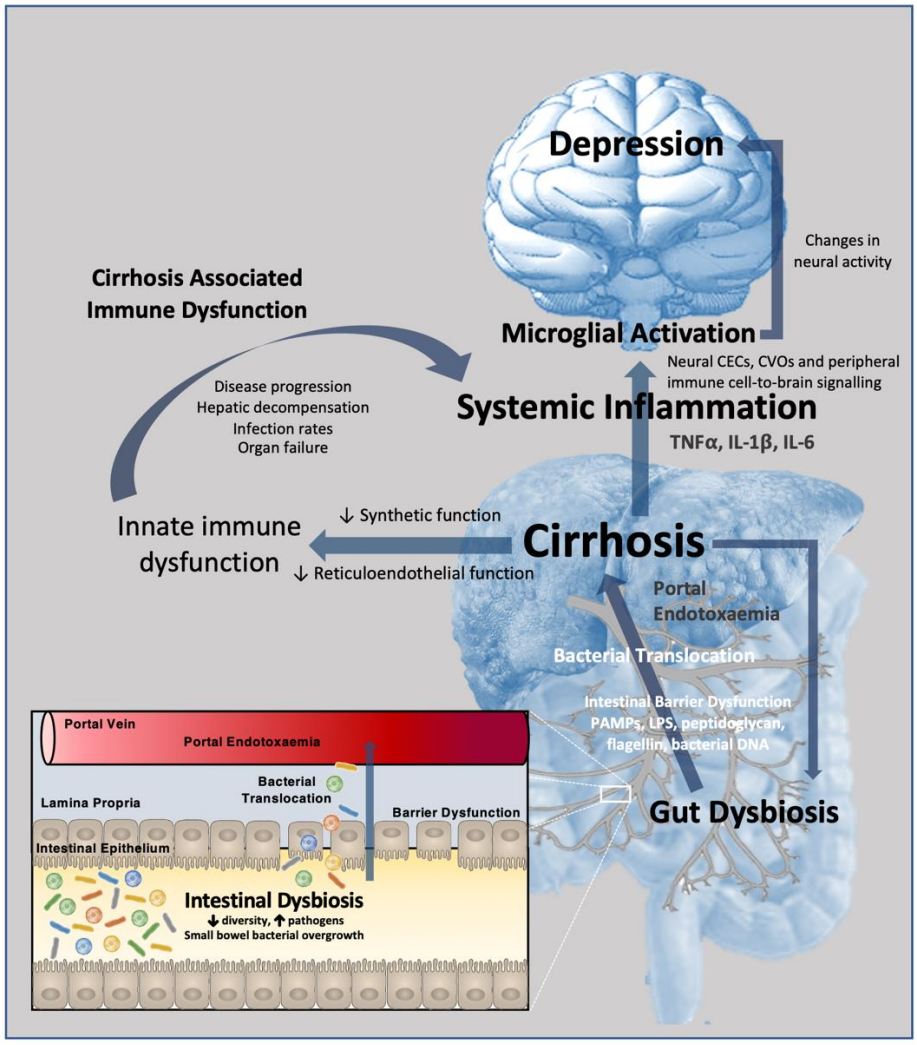
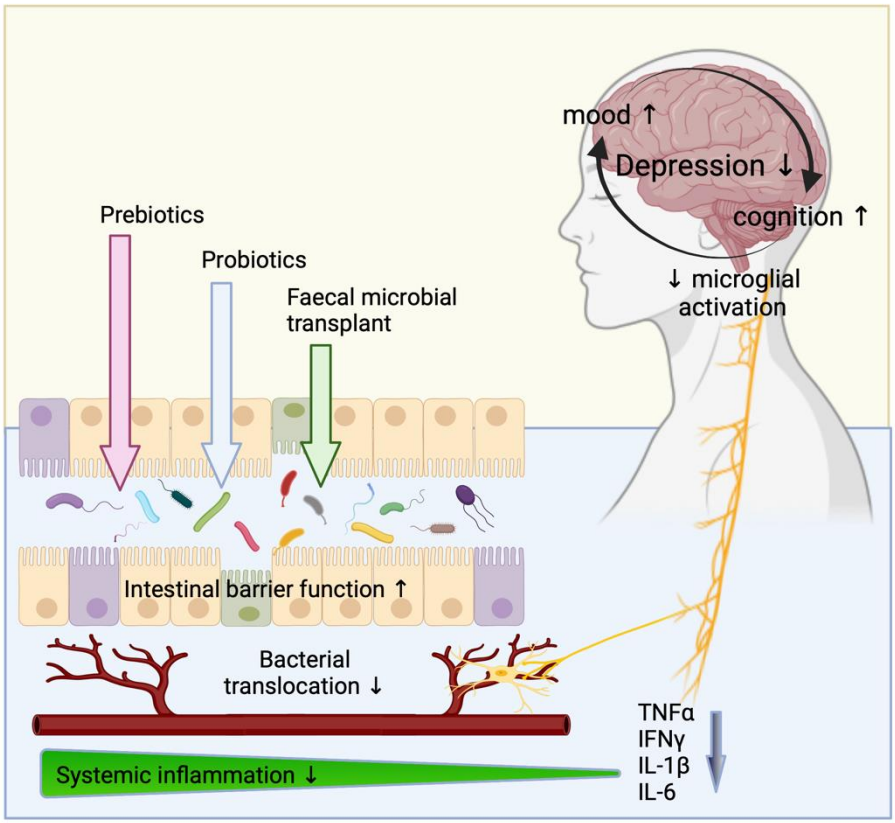


Figure 2.


mood ↑
Depression ↓
cognition ↑
↓ microglial activation
Prebiotics
Probiotics
Faecal microbial transplant
Intestinal barrier function ↑
Bacterial translocation ↓
Systemic inflammation ↓
TNFα
IFNγ
IL-1β
IL-6