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Review

Cannabis and cannabinoid-microbiome interactions in varied clinical contexts: A comprehensive systematic review

May Soe Thu [a,b,c], Barry J. Campbell [c,*], Nattiya Hirankarn [a,c,**], Tanawin Nopsopon [d,g,h], Thunnicha Ondee [d], Szaye Rawicha Hall [e], Ananya Jagota [d], Joanne L. Fothergill [f], Krit Pongpirul [c,d,i,j]

[a] Center of Excellence in Immunology and Immune-Mediated Diseases, Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand
[b] Joint Chulalongkorn University-University of Liverpool Ph.D. Programme in Biomedical Sciences and Biotechnology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand
[c] Department of Infection Biology and Microbiomes, Institute of Infection, Veterinary and Ecological Sciences, Faculty of Health & Life Sciences, University of Liverpool, Liverpool L69 3GE, UK
[d] Center of Excellence in Preventive and Integrative Medicine, Department of Preventive and Social Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand
[e] School of Life Sciences, Faculty of Health & Life Sciences, University of Liverpool, Liverpool L69 7ZB, UK
[f] Department of Clinical Infection, Microbiology and Immunology, Institute of Infection, Veterinary & Ecological Sciences, Faculty of Health & Life Sciences, University of Liverpool, Liverpool L69 3GE, UK
[g] School of Global Health, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand
[h] Division of Allergy and Clinical Immunology, Department of Medicine, Brigham & Women's Hospital, Boston, MA 02115, USA
[i] Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA
[j] Bumrungrad International Hospital, Bangkok 10110, Thailand

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ABSTRACT

With legalisation of cannabis for both medicinal and recreational use expanding to more world nations, grasping its effects on the human body is vital. The microbiome is critical to human health and disease, and accumulating data suggests that it is influenced by a variety of external variables, including marijuana/cannabis and cannabinoids. We therefore conducted a comprehensive assessment of the literature to analyse cannabis and cannabinoid effects on the human microbiota. We searched PubMed, Embase and Cochrane Library CENTRAL databases for studies involving the use of marijuana, medical cannabis, cannabinoids and cannabinoid-like lipid mediators on microbiota, across all clinical conditions. Nine studies were identified: 2 clinical trials and 7 observational studies examining cannabis and cannabinoid impact on oral, gastrointestinal, faecal and vaginal microbial abundance and diversity. Outcomes illustrated positive and negative impacts of cannabis use/cannabinoid actions on microbiota in adults with cognitive deficiency, depression, HIV infection, inflammation/pain, oral disease or obesity. Changes in alpha diversity were identified with cannabis/cannabinoid use, although this varied depending on the clinical context. A positive association exists between serum endocannabinoids and gut microbiota, via elevation in SCFAs and anti-inflammatory actions, beneficial for musculoskeletal pain relief and to counter obesity. Marijuana use in HIV patients showed protective effects by decreasing abundance of pro-inflammatory *Prevotella*, though excessive consumption leads to reduced microbiome richness and diversity, and increased systemic inflammation. Overall, this review underscores the need for further exploration in understanding the complex effects of cannabis, cannabinoids and cannabinoid-like mediators on composition and metabolic activity of the human microbiota.

* Corresponding author.
** Corresponding author at: Center of Excellence in Immunology and Immune-Mediated Diseases, Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.
E-mail addresses: bjcampbl@liverpool.ac.uk (B.J. Campbell), Nattiya.H@chula.ac.th (N. Hirankarn).

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1. Introduction

Cannabis, derived from the plant *Cannabis sativa* L. (Linnaeus), with subspecies *sativa, indica* and *ruderalis* [1], has a long history of use both for recreational and therapeutic purposes [2,3]. It is a complex mixture of over 120 natural phytocannabinoids, with the two major forms being lipophilic cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) [2]. The chemical structure of CBD, which in its pure form has no psychoactive activity, was first determined in 1963, and the structure of the main psychoactive component THC was identified in 1964 [4]. Following alcohol and tobacco, cannabis or marijuana (containing substantial amounts of THC) ranks as the third most commonly used psychoactive substance worldwide, and can be consumed in a variety of ways, such as smoking, inhalation, ingestion and as cannabis extracts, infusions or topicals [5].

In 2020, the global cannabis user population was over 4 % [6]. Intriguingly, data coming from the general population in Washington state (USA) revealed that the prevalence of no cannabis use for the past year in adults aged 50–64 years declined significantly (84.2 % in 2014, to 75.1 % in 2016 for women; 76.8 % in 2014, to 62.4 % in 2016 for men) along with a strong relation to the oral administration and vaping, suggesting this particular state legalisation for use of cannabis in adults has perhaps encouraged former non-users to start using cannabis [7]. According to a 2022 national survey report update in the United States, 24.9 % of people aged > 12 years (70.3 million) used illicit drugs in the previous year, with the highest proportion using marijuana (22 %) [8]. With recent changes in societal attitudes, and an expansion of countries where cannabis and its constituent phytocannabinoids have been legalised for recreational use and/or marketed for medicinal use, more research studies are being undertaken to evaluate the potential therapeutic benefits and any adverse outcomes of such products.

The effects of cannabis are mediated via the endocannabinoid system (ECS), comprising endogenous cannabinoids (endocannabinoids), cannabinoid receptors, and the enzymes responsible for the synthesis and degradation of endocannabinoids [9]. Endocannabinoids are naturally occurring lipid-based neurotransmitters made by the human body, such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG). The most abundant cannabinoid receptors are G protein-coupled receptors CB1 and CB2, however transient receptor potential (TRP) channels (such as TRPV1), and peroxisome proliferator-activated receptors (PPARα and PPARγ) are also engaged by some cannabinoids [9]. Key enzymes involved in the metabolism of endocannabinoids include fatty acid amide hydrolase (FAAH) that breaks down AEA into arachidonic acid and ethanolamine, and monoacylglycerol lipase (MAGL) that breaks down 2-AG into AEA and glycerol [9]. Although the ECS has been linked to immune, metabolic and nervous system homeostasis, and likely plays a regulatory role via the gut-brain axis, the precise physiological processes are still being studied [10–13]. Nonetheless, numerous active studies on phytocannabinoids are providing key evidence to support their potential efficacy in treating cardiovascular disease, cancer and inflammation [14–16].

In addition, cannabis has been used for millennia to treat many ailments [17], including attenuation of gastrointestinal tract inflammation, as well as providing relief of functional problems, such as cramps and stomach pain, nausea, vomiting and diarrhoea [18,19]. The most frequent physical health reasons for use of medical cannabis are to alleviate and manage pain (53 %), treat sleep disorders (46 %), relieve headaches/migraines (35 %), control of appetite (22 %) and to reduce nausea/vomiting (21 %); whilst the most prevalent mental health reasons to use cannabis are to combat anxiety (52 %), depression (40 %) and for post-traumatic stress disorder (PTSD) and other traumatic events (17 %) [20]. Despite the potential for benefit, adverse effects have been reported in medical and recreational cannabis users compared to those not using cannabis [21]. The serious adverse events identified include neural and psychiatric disorders, disorders of the cerebrovascular, gastrointestinal, renal, urinary, respiratory, thoracic and mediastinal systems, as well as increased risk of other conditions, such as neoplasia [21].

It is well established that the gastrointestinal system and the brain are closely linked. The diverse population of microorganisms within the gastrointestinal tract engage in a mutually beneficial relationship with the host, impacting on neurological networks through the gut-brain axis and the bilateral communication between the central and enteric nervous systems, as well as regulating endocrine and immunological processes [22,23]. The genus *Bifidobacterium*, known to improve gut mucosal barrier integrity and function, also has an antidepressant effect that is partially mediated via gut enteroendocrine cell mediators and microbiota modulation [24]. According to a comprehensive analysis of the gut microbiota in anxiety disorders, several taxa and their modes of action may be connected to the pathophysiology of depression and anxiety, by communicating with the brain through peripheral inflammation [25]. *Akkermansia muciniphila*, a resident symbiotic bacterium of the intestinal mucus layer which utilises mucins as an energy source [26], has known beneficial effects, including metabolic modulation, immune regulation, enhancement of gut barrier protection and influencing neuropsychic brain function via the gut-brain axis [27].

The endocannabinoidome (eCBome), which encompasses a more extensive network of lipid signaling molecules and receptors related to endocannabinoid function, plays a significant role not only within the central nervous system, but also in communication with enteric neurons regulating gut motility, and in the modulation of the gut enteroendocrine system [28,29]. This occurs primarily through CB1 receptors and TRPV1 channels localised to enteric nerves of the myenteric plexus and in afferent fibres of the vagus nerve, and via PPARα and GPR119 receptors on enteroendocrine cells of the intestinal epithelium [29,30]. These receptors influence the release of gastrointestinal neuropeptides, the activity of myenteric neurons, and the function of the autonomic nervous system (both vagal and sympathetic components), all of which may modify the ECS [30]. Key commensals of the gut microbiota are now known to synthesise endocannabinoid-like molecules structurally similar to those component molecules of the eCBome, such as *N*-acylated ethanolamines, glycines and amine neurotransmitters. These microbiota-generated lipid moieties interact with GPCRs that regulate gastrointestinal physiology, impact on metabolic hormones and glucose regulation in a manner like that seen by human ligands [31]. Changes in the level and/or composition of the gut microbiota, as observed in germ-free or antibiotic-treated mice, can significantly impact the expression of eCBome receptors and key cannabinoid metabolic enzymes, influencing the levels of eCBome mediators in the gut and brain, through as yet unknown pathways [32,33]. Gut microbiota dysbiosis in mice, driven by broad-spectrum antibiotics, notably lower intestinal levels of *N*-oleoyl- and *N*-arachidonoyl-serotonins that impact on the gut-brain axis, leading to increased intestinal inflammation and depression disorder-like symptoms [34].

In a murine model of Staphylococcal enterotoxin-B-induced acute respiratory distress syndrome (ARDS), administration of the phytocannabinoid THC was seen to attenuate lung inflammation in this fatal condition, altering the gut microbiota, with beneficial bacterium *Ruminococcus gnavus* identified as being more prevalent in both lung and intestinal tissue of THC treated mice, with a concomitant enrichment of short-chain fatty acids (SCFAs), particularly anti-inflammatory propionic acid [35]. Another key study found that combined treatment with THC and CBD markedly reduced the clinical signs and high observed levels of lipopolysaccharide within the brain of mice with experimental autoimmune encephalomyelitis [36]. Combined THC/CBD treatment increases anti-inflammatory cytokines and drives decline in pro-inflammatory cytokines, as well as reduction in abundance of mucin-degrading *A. muciniphila* [36]. Collectively, these findings indicate that phytocannabinoids significantly impact on the gut microbiome.

Overall, the current body of literature lacks a comprehensive and systematic synthesis of research on the intricate relationship between

cannabis/cannabinoids and the microbiome across diverse clinical conditions. Existing studies have explored aspects of this interaction, but there is a notable absence of a unified and rigorous analysis that integrates findings from different clinical scenarios. To promote more in-depth research, this review will be the first to assess the microbiome of multiple observational studies and interventional clinical trials of cannabis/marijuana and cannabinoid use in humans with a variety of disorders.

2. Methods

2.1. Protocol and registration

The systematic review was registered on PROSPERO (www.crd.york.ac.uk/prospero); ID 2022 CRD42022354331.

2.2. Literature search, study selection and data extraction

The systematic review was conducted in compliance with the PRISMA declaration standards [37]; see Supplementary materials - Supplementary Information File S1. Studies published up until 9 December 2023 were identified from the databases of PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (www.embase.com), and CENTRAL (www.cochranelibrary.com/central). The search was limited to studies that addressed cannabis/cannabinoid microbiota associations, as well as marijuana use and how it impacts on the human microbiome. The full search term strategy is detailed in Supplementary materials – Supplementary Information File S2.

Interventions examining the effects of cannabis/marijuana use, actions and associations of phytocannabinoids, endocannabinoids and endocannabinoid-like molecules on microbiota/microbiome, with or without active or placebo controls in humans, are all reflected in the inclusion criteria. Studies not written in English, animal studies, *in vitro* research, procedures/protocols, reviews, opinions, editorial letters, commentaries and study guidelines were all excluded. Sourced publications identified from the databases were imported into the Covidence platform (www.covidence.org/) for systematic screening. Data extraction was performed independently by two reviewers (MT and SR) to determine whether the identified papers met the eligibility requirements for inclusion within the systematic review. This was based on an initial review of the abstract and then by full-text screening. Any discrepancies in selection for inclusion were settled through discussion and consensus agreement.

Data extraction from selected articles was carried out as follows: Initial research attributes were identified, including author details, year of publication, type of study, the nation where the study was undertaken, the sample size and the participant age range. Following this, data extraction progressed with a thorough examination of pertinent text, tables and figures. We then identified baseline study characteristics, detailed participant information and clinical conditions reported for both patients and control subjects. This was followed by identification of subgroup evidence, such as microbial profile and diversity, classified by specific diagnostic health problems, and screening for any reported adverse reactions associated with cannabis/marijuana consumption and cannabinoid intervention.

2.3. Analysis for risk of bias

The independent team (MT and SR) also assessed the risk of bias (ROB) in the retrieved randomised clinical intervention study [38] using the Cochrane Risk of Bias tool 2.0 (ROB2; https://methods.cochrane.org/risk-bias-2). For the retrieved non-randomised clinical trial [39], we utilised the ROB In Non-randomised Studies - of Interventions tool (ROBINS-I; www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-i/), and for all other cohort studies [40–46], we employed the Newcastle-Ottawa Quality Assessment Scale (NOS; www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

2.4. Statistics

Demographic and clinical characteristics of participants from all included studies were reviewed, and the prevalence of the characteristics, distinguishing between patients and controls, were described by total number and percentages. The overall mean age of participants within all studies was calculated, generating combined means and standard deviations (SD) using the R Studio software (version 2023.09.1).

3. Results

3.1. Study selection

In the initial literature search, 5000 articles were identified across all databases, and 1533 duplicates were removed. After reviewing the titles and abstracts of the remaining 3467 papers, 3428 were removed based on preset criteria, leaving 39 for full-text screening. Of these, 29 publications were disregarded; 1 editorial, 1 letter to the journal editor, 6 protocol papers, 15 non-peer-reviewed articles and 7 non-eligible studies (i.e. with no microbiota assessment in terms of cannabis/marijuana use or cannabinoid intervention). Finally, the systematic review included 9 studies that met the eligibility criteria (shown in Fig. 1).

3.2. Study characteristics

The 9 eligible studies identified, published between 2018 and 2023, were conducted across four different countries: Iran, Israel, the United Kingdom (UK) and the United States of America (USA). The studies identified included 7 cohort studies [40–46], and 2 clinical trials, one randomised [38] and the other non-randomised [39]. In total, 2473 participants were involved across all 9 studies included in the systematic review; see Table 1.

3.3. Subject characteristics

The demographic and clinical characteristics of participants across all included studies, distinguishing between patients and controls are outlined in Table 2. Of note, the patient group, constituting 42 % of the total number of participants, exhibited a broader age range and a higher mean age (56.5 years) compared to a skewed control group, with a mean age of only 28.4 years. This skew was primarily due to the large control group in the study of Vallejo et al., with a mean age of 27 years [44]. Furthermore, a gender imbalance was observed, with a higher percentage of females within both the patient and control groups, largely influenced by the studies of Vallejo et al. [44] and Minichino et al. [41], both conducted predominantly with female participants. Most patients were from the UK (79 %), whereas controls predominantly originated from the USA (95.2 %), reflecting the geographical focus of the same two respective studies [41,44]. Clinically, patients presented with diverse conditions, with cognitive deficits/impairment being notably prevalent (74.5 %), primarily due to the substantial sample size of the UK study conducted by Minichino et al. [41]. Despite biases stemming from specific studies, it is important to note that the current review focused solely on qualitative analysis, therefore not impacting the individual study outcomes.

3.4. Risk of Bias assessment

Among the 7 identified observational studies [40–46], the study by Minichino et al. [41] displayed a high risk of bias due to the absence of a description of the non-exposed cohort, the inability to blind the outcome assessors, and a lack of follow-up information (shown in Fig. 2A). Similarly, the cohort studies by Newman et al. [42] and Vallejo et al.

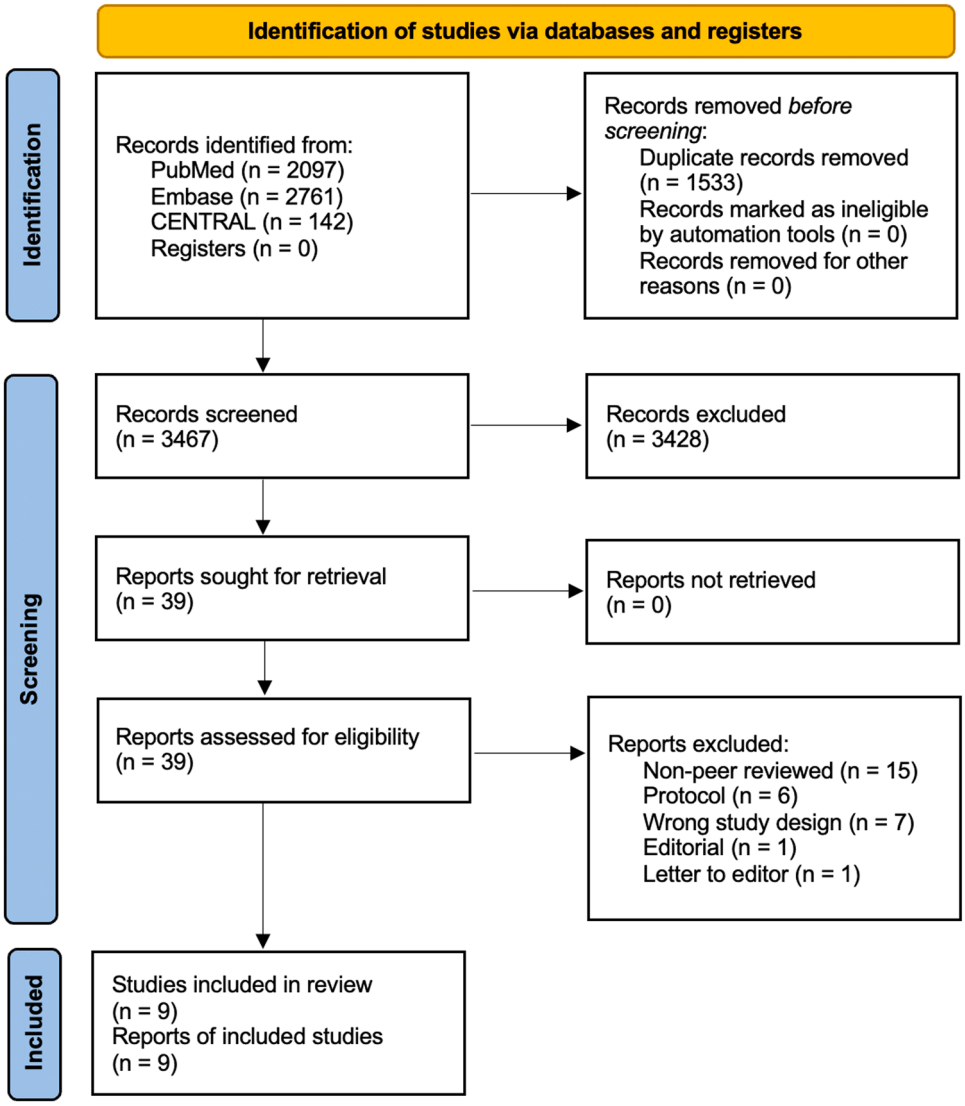

Fig. 1. Flow diagram for identifying studies in the systematic review.

Table 1
Baseline characteristics within the identified studies.

#	Primary author	Publication year	Study period	Study type	Country	Sample size	Age range	Reference
1	Payahoo	2019	2016–2018	Randomised double-blind clinical trial	Iran	56	18–59	[38]
2	Habib	2021	2019–2020	Non-randomised clinical trial	Israel	16	27–78	[39]
3	Panee	2018	-	Cohort study	USA	39	21–36	[43]
4	Fulcher	2018	2014–2016	Cohort study	USA	37	28–39	[40]
5	Newman	2019	-	Cohort study	USA	39	18–58	[42]
6	Vijay	2021	2018–2020	Cohort study	UK	78	> 45	[45]
7	Minichino	2021	-	Cohort study	UK	786	18–101	[41]
8	Vallejo	2021	2019	Cohort study	USA	1380	20–34	[44]
9	Morgan	2023	-	Cohort study	USA	42	16–20	[46]

[44] also exhibited biases due to challenges in outcome assessment blinding and the absence of a follow-up timeline description. Furthermore, within the reported results of the randomised control trial conducted by Payahoo et al. [38], there was evidence of selection bias, as they did not include the specified lipid profile analysis mentioned within their protocol (shown in Fig. 2B). In comparison, the non-randomised control trial by Habib et al. [39] demonstrated a well-performed risk assessment (shown in Fig. 2C).

3.5. Microbiota alteration by marijuana use, cannabis phytocannabinoids, endocannabinoids and endocannabinoid-like molecules

The 9 identified studies were each reviewed and evaluated for any microbiota changes in response to marijuana use or following intervention with medical cannabis or endocannabinoid-like lipid mediator supplements (such as *N*-palmitoylethanolamine (PEA), and *N*-oleoylethanolamine (OEA)), as well as data obtained from a six-week exercise intervention study examining associations of endocannabinoids and

Table 2
Baseline characteristics of the included clinical studies.

Characteristics	Patients	Controls
Participants, n (%)	1043 (42)	1430 (58)
Age range (years)	16–101	16–87
Age, mean (SD)	56.5 (14.6)	28.4 (11.3)
Gender, n (%)		
Male	162 (15.5)	69 (4.8)
Female	881 (84.5)	1361 (95.2)
Region, n (%)		
USA	176 (16.9)	1361 (95.2)
Iran	27 (2.6)	29 (2.0)
Israel	16 (1.5)	0 (0)
UK	824 (79)	40 (2.8)
Clinical consideration, n (%)[a]		
HIV infection	137 (12.7)	-
Pain/ Inflammation	54 (5.0)	-
Obesity	64 (5.9)	-
Cognitive deficits/ Amotivation	805 (74.5)	-
Oral disease	20 (1.9)	-

[a] Prevalence (as a %) of included patients for each clinical condition, across all studies.

related *N*-acylethanolamine mediators with microbiome composition. Data collected spanned patients with a range of clinical conditions, as summarised in Fig. 3. A qualitative synthesis of the microbial diversity and related parameters was conducted and is presented in Table 3.

In the study by Fulcher and colleagues [40], which focused on drug use of HIV-positive men who have sex with men, analysis of the rectal microbiome of study participants showed that those individuals using marijuana had a lower abundance of *Prevotella,* as well as lower abundance of other genera such as *Acidaminococcus, Dialister, Anaerostipes* and *Dorea*. Additionally, there was a positive correlation between marijuana use and elevated levels of *Fusobacterium*, *Ruminococcus*, *Clostridium* cluster IV, *Solobacterium* and *Anaerotruncus*; see Fig. 3. The prevalence of *Trichomonas* infection in rectal samples decreased from 14 % to 5 % over a half-year ($p = 0.08$), while gonorrhea and syphilis infections increased from 8 % to 11 % ($p = 0.66$) and 0–5 % ($p = 0.16$), respectively [40]. Additionally, marijuana users among HIV patients were identified by Vallejo *et al.* to engage in higher-risk sexual behaviour, which can result in bacterial vaginosis characterised by an overgrowth of facultative anaerobic organisms, such as *Gardnerella vaginalis, Prevotella, Bacteroides* and *Peptostreptococcus*, and absence of Lactobacilli [44].

The study conducted by Vijay et al. [45] revealed a positive association between serum levels of endocannabinoid AEA and OEA, and abundance of gut microbiota that significantly produce SCFAs during fermentation of dietary fibre, such as *Bifidobacteria* and key Firmicutes (Bacillota), such as *Faecalibacterium* and *Coprococcus*.

In the clinical prospective study evaluating saliva samples of individuals before and after using medical cannabis to alleviate continuous musculoskeletal pain, changes in oral microbiota were observed following cannabis use [39]. Specifically, there was observed elevation in the abundance of *Streptococcus mutans* and *Lactobacillus* spp., despite *S. mutans* being less abundant after the initial week of cannabis use [39].

Neurological disease and mitochondrial dysfunction are closely linked to gut dysbiosis [47,48] and it has recently been shown that THC acts through activation of CB1 receptors to decrease mitochondrial respiration and energy production [49]. The study by Panee et al. also examined marijuana use and its impact on cognitive functioning, peripheral blood mononuclear cell mitochondrial function, and faecal microbiota changes [43]. The results revealed that chronic marijuana users in the patients with cognitive impairment had a lower faecal *Prevotella:Bacteroides* ratio compared to marijuana non-users [43]. *Prevotella* abundance correlated positively with mitochondrial function and cognitive scores, particularly in the marijuana users [43]. These findings suggest that lifetime marijuana use is associated with alterations in gut microbiota and mitochondrial function, potentially contributing to cognitive deficits.

The randomised clinical trial conducted by Payahoo and colleagues, highlighted that supplementation with the endocannabinoid-like molecule OEA significantly decreased the energy, fat, protein and carbohydrate intake of obese participants [38]. Moreover, *A. muciniphila* abundance increased considerably compared to the placebo group [38], suggesting that OEA could be used as an anti-obesity supplement.

3.6. Adverse events

No studies reported any negative consequences associated with marijuana/cannabis use and intervention with cannabinoids.

4. Discussion

This systematic review encompassed studies of patients with oral disease, obesity, inflammation/pain, cognitive deficits/amotivation and HIV infection, employing either marijuana (through smoking or use of oral capsules), medical cannabis (containing CBD and THC), or endocannabinoids and endocannabinoid-like lipid mediator intervention. Given the diverse methodological approaches utilised across the identified studies, including *16S* rDNA sequencing, qRT-PCR, pathogen DNA probes and microbial culture, there may be inherent heterogeneity in the data, complicating the integration and comparison of results. In addition to changes in microbial composition, health benefits may arise from the production of key bacterial metabolites and their interactions with metabolic pathways and immune system of the host [50]. Therefore, a comprehensive systematic review exploring the interaction between cannabis/cannabinoids and the microbiome, not limited to bacterial metabolites, is essential for a nuanced understanding of potential health implications stemming from this intricate relationship.

4.1. Microbiota alterations in HIV patients using marijuana

Evidence has revealed that intestinal dysbiosis, marked by a decrease in the genus *Bacteroides* and an increase in *Prevotella*, is linked to HIV infection [51,52]. According to recent research, an elevated abundance of *Prevotella* in HIV may be a contributing factor to the ongoing inflammation within the gut, and a cause of mucosal dysfunction and systemic inflammation [53,54]. The identified study by Fulcher et. al. [40] profiled the rectal mucosal microbiome of HIV-positive men who have sex with men using drugs, revealing decreased abundance of *Prevotella* with marijuana use. Thus, there is clinical potential for medical cannabis to be used to modulate inflammation and promote gut health of these patients.

Chronic THC exposure though may result in CB1 receptor downregulation, which lessens the capacity of the ECS to control neurotransmitter release [55]. A study carried out among young sexual and gender minorities highlighted a significant negative relationship with Shannon diversity and microbial community richness with long-term, high-dose cannabis use [46], suggesting that chronic cannabis consumption adversely affects the gut microbiota, resulting in decreased bacterial diversity. In individuals with HIV, decreased bacterial richness and intestinal dysbiosis, and increased systemic inflammation driven by enhanced microbial translocation from the gut to the circulation, have all been reported [56,57]. The additional impact of chronic, high-dose cannabis consumption could exacerbate these alterations, potentially worsening gut-related symptoms and systemic inflammation.

Furthermore, it was found that 28.4 % of marijuana users had a history of asthma, contrasting with 18.3 % of non-users [40]. Despite the bronchodilator effect of cannabis, which suggests potential benefits for asthma patients, there are acknowledged detrimental effects on the lungs [58]. This dual impact prompts careful consideration in the use of cannabis, whether medicinal or recreational, especially given reported improvements in asthma symptoms.

The study by Vallejo et al. demonstrated a significant association

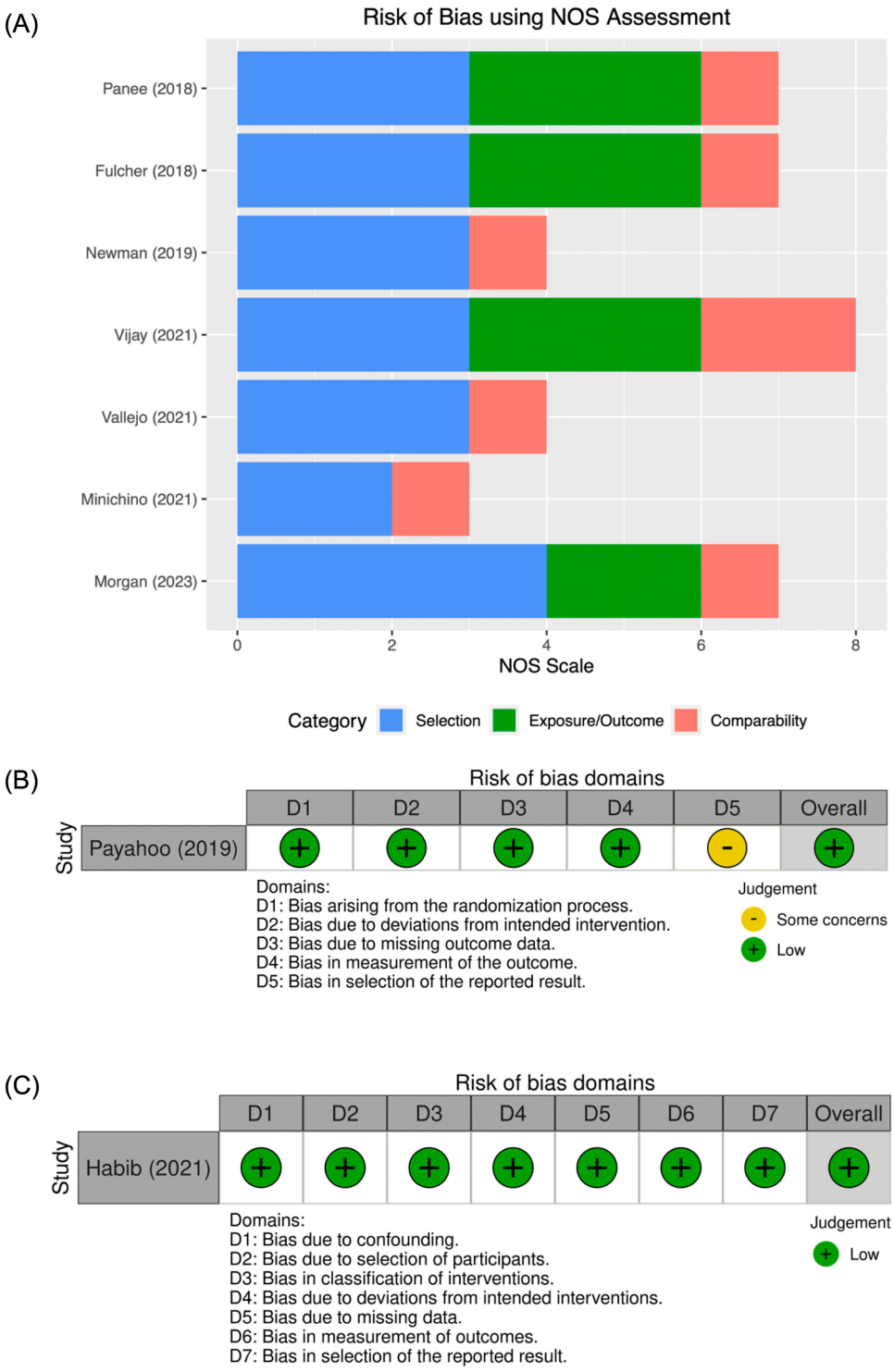

Fig. 2. Assessment of risk of bias (ROB), using (A) NOS for cohort and case-control studies; (B) RoB2 for randomised controlled trials; and (C) ROBINS-I for non-randomised studies of interventions. Abbreviations: NOS, Newcastle-Ottawa Scale; RoB 2, Cochrane Risk-of-Bias tool for randomised trials (version 2); ROBINS-I, Risk Of Bias In Non-randomised Studies of Interventions.

between marijuana use and recurrent bacterial vaginosis, an overgrowth of facultative anaerobic organisms, and absence of Lactobacilli [44]. Typically, HIV patients have lower level of *Lactobacillus* and other beneficial gut microbes, alongside increased occurrence of potentially opportunistic infections [52]. This suggests that marijuana use in those with HIV may disrupt the vaginal microbiota, increasing the risk of bacterial vaginosis. It is worth noting that marijuana has recognised anti-oestrogenic activity [59] and as a consequence may result in lower levels of oestrogen that would normally encourage growth of beneficial *Lactobacillus* spp., thus having a detrimental impact on vaginal microbiome homeostasis [60]. In addition, a study of economically disadvantaged African-American female teenagers who used marijuana and reported high risk sexual behaviour within the previous 6 months, has identified that these individuals were over six times more likely to test positive for *Trichomonas vaginalis*, indicating a potential association of cannabis use with increased risk of sexually transmitted infections in this

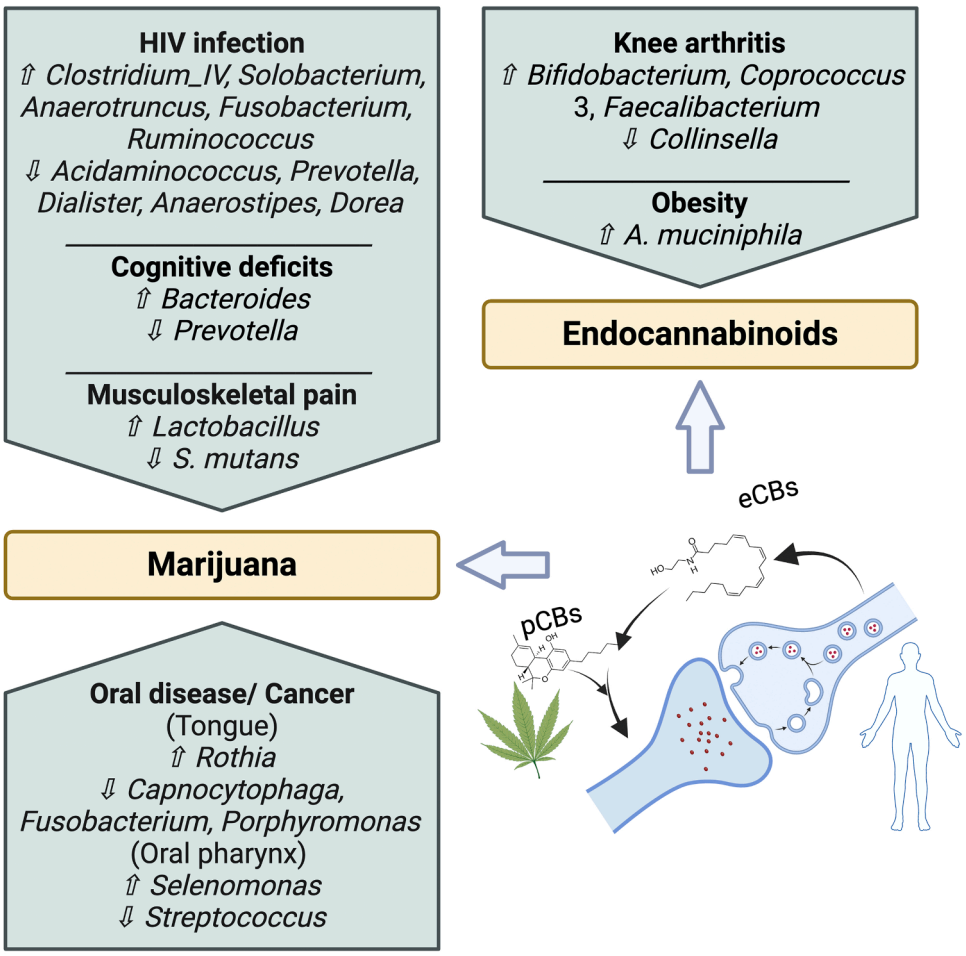

Fig. 3. Positive and negative associations of microbiome profiles in varied clinical conditions, examining the impact of different forms of cannabis use. Abbreviations: ↑, increased abundance; ↓, decreased abundance; THC: tetrahydrocannabinol.

socio-demographic group [61].

4.2. Impact of marijuana and cannabinoids on microbiota in the context of inflammation and pain

The group of Vijay et al. [45] found a positive association between serum endocannabinoids and gut microbiota, along with a significant increase observed in levels of SCFAs, particularly butyrate. Butyrate, propionate and acetate, generated predominantly by bacterial species within the phyla Firmicutes (Bacillota) and Bacteroidetes (Bacteroidota) [62], are the primary mediators influencing gut microbiome and host epithelial and immunological homeostasis [63]. Several other studies have also highlighted the ability of cannabinoids, such as AEA and THC, to raise levels of anti-microbial peptides (AMPs) and elevate SCFAs, that can reduce the release of inflammatory cytokines in mouse models of inflammation [64,65].

GPR109A is a receptor for butyrate in the colon, where signaling promotes anti-inflammatory properties in colonic macrophages and dendritic cells, enabling them to induce differentiation of Treg cells and IL-10-producing T cells [66]. Activation of GPR109A by butyrate, prevents the activation of pro-inflammatory/oncogenic nuclear factor kappa B and induces apoptosis in colon cancer cells, suppressing inflammation and carcinogenesis in the murine colon [66,67]. Through the inhibition of histone deacetylases (HDAC), gut microbiota-derived butyrate also promotes epithelium homeostasis and modulates mucosal immune responses, markedly suppressing production of pro-inflammatory cytokines, such as IL-6 and IL-12, induced by bacterial lipopolysaccharide [68]. This suggests that cannabinoids impact on the gut microbiota and immune responses through the modulation of endocannabinoids and SCFAs. Moreover, abundance of pro-inflammatory genus *Collinsella* [69] was observed to be lower where higher levels of endocannabinoids were detected. Elevated circulating levels of AEA correlated with higher serum levels of butyrate, which in turn significantly correlated with lower circulating levels of pro-inflammatory cytokines TNF-α and IL-6. Additionally, AEA and OEA were associated with a higher α-diversity in the gut microbiome. Endocannabinoids AEA and 2-AG are known to modulate inflammatory cells via activation of cannabinoid CB1 and CB2 receptors [70]. Endocannabinoid-like PEA is also known to have cytoprotective and anti-inflammatory activity, and is an agonist of cannabinoid receptors, whilst OEA, also anti-inflammatory, does not appear to act via cannabinoid receptors [71]. Overall, data confirms the involvement of the ECS in anti-inflammatory actions, including mediation of levels of anti-inflammatory SCFAs, highlighting the potential of additional mediator pathways in the regulation of the immune system by the gut microbiota.

Musculoskeletal pain, a prevalent cause of chronic non-cancer pain, has led patients to perceive cannabis as being beneficial for pain relief, with minor adverse effects and an improvement in psychological well-being [72]. Cannabis use is also known to have a positive impact to prevent inflammatory bowel disease (IBD) flares and abdominal pain [73]. Both visceral and musculoskeletal pain are modulated by the gut microbiota [74,75], but whether cannabinoid signaling elements impact on pain through alteration and modulation of the gut microbiome is less clear. In an experimental rodent model, oral administration of probiotic Lactobacilli has been shown to reduce visceral sensitivity

Table 3
Qualitative analysis of the impact and associations of cannabis, cannabinoids and cannabinoid-like lipid mediators on microbiota.

Author (year)	Clinical background	Study participant gender	Cannabis/ Cannabinoid	Sample analysis	Microbial profile and diversity	Effect of cannabis use and key findings	Ref.
Fulcher *et al.* (2018)	HIV−1 infection	37 males	Marijuana	Rectal swab *16S* rRNA sequencing	Positive association: *Clostridium_IV, Solobacterium, Anaerotruncus, Fusobacterium, Ruminococcus.* Negative association: *Acidaminococcus, Prevotella, Dialister, Anaerostipes, Dorea* Marijuana use was the critical driver of rectal microbiome variation [R^2= 0.01, $p = 0.14$].	Microbiome within individuals was relatively stable over 6 months intervals between visits. During the 6-month period, the CD4 + T-cell count increased significantly, from 427 cells/μL to 532 cells/μL.	[40]
Vallejo *et al.* (2021)	HIV patients with vaginal discharge	1380 females	Marijuana	Affirm Vaginal Pathogens DNA Direct Probe using vaginal discharge	-	Marijuana use in reproductive-aged women (15–45 years old) increases the odds (aOR=2.05, 95 % CI 1.19 – 3.44) of developing recurrent bacterial vaginosis (BV). Marijuana users engage in higher risk sexual practices leading to BV, and history of asthma to recurrent BV. Marijuana and its active metabolite THC exert immediate and modest bronchodilator effects but subsequently can trigger bronchitis-like symptoms as a delayed effect.	[44]
Morgan *et al.* (2023)	HIV−1 infection	42 males	Marijuana	Rectal swab *16S* rRNA sequencing	Problematic marijuana use (CUDIT score ≥ 8, indicating hazardous levels) was inversely associated with rectal microbial community richness (adj. $\beta = -8.13$, 95 % CI: 15.68 to −0.59) and Shannon diversity (adj. $\beta = -0.04$, 95 % CI: −0.07–0.009).	The CUDIT questionnaires revealed no significant association between the score and community evenness, nor was there any substantial moderating by HIV status.	[46]
Vijay *et al.* (2021)	Knee arthritis	18 males 60 females	2-AG, AEA, OEA and PEA	Faecal *16S* rDNA sequencing	The exercise intervention highlighted that eCBs were positively associated with Shannon diversity, increases in *Bifidobaterium*, *Coprococcus* 3 and *Faecalibacterium*).	A positive correlation of eCBs showed an increase in beneficial SCFAs, increase in anti-inflammatory IL−10, and decreased pro-inflammatory cytokines.	[45]
Habib *et al.* (2021)	Musculo-skeletal pain	2 males and 14 females	Medical cannabis (THC/CBD)	Microbiological culture of saliva	Medical cannabis use was associated with increased salivary levels of oral *Streptococcus mutans* and *Lactobacillus* species.	Medical cannabis use has no effect on saliva volume or pH level.	[39]
Minichino *et al.* (2021)	Anhedonia/ amotivation	52 males 734 females	PEA	Faecal *16S* rDNA sequencing	Relative abundance of two taxa (*Blautia* and *Dorea*) was significantly associated with both faecal PEA and anhedonia/ amotivation. Microbial α-diversity was associated with faecal PEA ($\beta = -0.31$; $p < 0.001$) and severity of anhedonia/ amotivation ($\beta = -0.10$; $p = 0.02$).	Faecal PEA associates with anhedonia/ amotivation ($\beta = 0.13$; $p < 0.01$).	[41]
Panee *et al.* (2018)	Cognitive deficit	25 males 14 females	Marijuana (THC positive)	Faecal *16S* rDNA sequencing	The ratio of *Prevotella:Bacteroides* was significantly lower in marijuana users compared to non-users ($p = 0.34$).	Lower *Prevotella* associated with lower mitochondrial function in the marijuana users. Marijuana use and associated dietary change contributes to microbiome alteration. Lower dietary intake of antioxidants alters mitochondrial antioxidant protection and gut SCFA.	[43]
Newman *et al.* (2019)	Oral cancer/ disease	33 males 6 females	Marijuana smoke	Lateral border of the tongue and oro-pharynx swab *16S* rDNA sequencing	Tongue Site: Genera (*Capnocytophaga, Fusobacterium, Porphyromonas*) enriched in HNSCC mucosa were low in marijuana users. *Rothia*, found at reduced levels in HNSCC, was high now. Oral Pharynx Site: Distinct bacterial differences observed. High *Selenomonas* and low	Daily or almost daily inhalation of marijuana in the past month correlates with differentially abundant taxa of oral microbiome in samples taken from the lateral border of the tongue and from the oral pharynx. No evidence found for marijuana product-contaminating bacteria	[42]

(*continued on next page*)

Table 3 (*continued*)

Author (year)	Clinical background	Study participant gender	Cannabis/ Cannabinoid	Sample analysis	Microbial profile and diversity	Effect of cannabis use and key findings	Ref.
					Streptococcus, which contrasts with patterns seen in HNSCC.	contributing to observed differences.	
Payahoo *et al.* (2019)	Obesity	22 males 34 females	OEA	qRT-PCR using faeces	*A. muciniphila* was significantly increased for the intervention ($p < 0.001$).	In the intervention, energy intake (fat, protein, carbohydrate) was decreased significantly ($p = 0.035$).	[38]

Abbreviations: *16S* rDNA, 16S ribosomal subunit deoxyribonucleic acid; 2-AG, 2-arachidonoylglycerol; AEA, anandamide; aOR, adjusted odds ratio; CBD; cannabidiol; CHO, carbohydrate; CUDIT, Cannabis Use Disorder Identification Test; eCBs, endocannabinoids; ECs, endocannabinoids system; HIV, human immunodeficiency virus; HNSCC, head and neck squamous cell carcinoma; IL-10, interleukin 10; OEA, *N*-oleoylethanolamide; PBMC, peripheral blood mononuclear cell; PEA, *N*-palmitoylethanolamide; qRT-PCR, quantitative reverse-transcription polymerase chain reaction; SCFA, short-chain fatty acid; THC, delta-9-tetrahydrocannabinol.

mechanistically through the activation of CB2 cannabinoid receptors on the gastrointestinal epithelium [73]. Overall, these findings underscore the intricate relationship between cannabis use, the ECS, alterations in gut microbial community structure and their complex interplay with pain perception. This area warrants significant further investigation.

4.3. Oro-pharyngeal microbiota after use of marijuana

Frequent and long-term marijuana use is associated with an increased risk of head and neck squamous cell carcinoma (HNSCC), exacerbated by smoking of tobacco [76]. Oral microbial dysbiosis is observed in HNSCC patients, with increased abundance seen in *Fusobacterium, Peptostreptococcus, Alloprevotella, Capnocytophaga, Catonella* and *Prevotella* genera, and significant depletion in abundance of *Streptococcus, Actinomyces, Veillonella*, and *Rothia* [77,78]. The study identified by Newman and colleagues [42], examining the oral microbiota of marijuana users and nonusers, sampled at two key mucosal sites relevant to head and neck cancer (the lateral tongue and oro-pharynx), identified marijuana-specific mucosal differences in genera. This included lower abundance of *Capnocytophaga*, *Fusobacterium* and *Porphyromonas* on the lateral tongue of marijuana users, whereas *Rothia* was found in greater abundance at this site - an organism identified as being in low abundance on HNSCC mucosae [42]. At the oropharyngeal site, differences observed in mucosa-associated bacterial genera with marijuana use were also distinct, with higher levels of *Selenomonas* and lower levels of *Streptococcus* seen - microbiota community/biofilm changes that were more consistent with that observed in malignant mucosae [42]. These findings indicate that daily/almost daily marijuana inhalation can significantly alter the oral microbiota, potentially impacting the microbial environment in ways that could influence HNSCC development [42]. This work highlights unique interactions between marijuana use and oral microbial communities, potentially mediated by direct effects of marijuana smoke on oral mucosal tissue, but also impacted by other factors such as alterations in oral hygiene practices, and/or changes in host immune response. Further research is clearly needed to elucidate the mechanisms by which marijuana use influences oral microbiota and to understand how these microbial changes might contribute to the pathogenesis of cancer at this site.

Moreover, a clinical study examining the impact of medical cannabis consumption on the oral microbiota cultured from the saliva identified increased levels of *S. mutans* and *Lactobacillus* spp. in those individuals using cannabis [39]. Of note, high oral abundance of *S. mutans* and Lactobacilli is associated with tooth decay/dental caries in adults [79]. Cannabis use has consistently been linked to an increased risk and severity of periodontal disease, with long-term use associated with poor periodontal health in young adults, and a higher prevalence of severe periodontitis in younger age groups [80]. These findings emphasise the importance of addressing cannabis use in oral health interventions. To fully understand the possible oral health effects of medical cannabis usage, additional study and interventions are clearly needed, including those that capture oral health behaviour and hygiene changes.

4.4. Gut microbiota alterations, poor cognition and chronic marijuana use

Marijuana use has been linked to cognitive impairment [81,82]. The recent study by Panee *et al.* [43] examined for associations between microbiota, peripheral blood mononuclear cell (PBMC) mitochondrial function and cognition in chronic users of marijuana. The study identified changes of *Prevotella* and *Bacteriodes* in terms of cognitive functioning, revealing that extensive lifetime levels of marijuana use was associated with a lower *Prevotella:Bacteriodes* ratio, while non-users had a ~13-fold higher ratio within their faecal bacteriome [43]. In addition, changes observed in the gut microbiota among marijuana users was associated with alterations in PBMC mitochondrial function [43]. Gut dysbiosis, and the consequential alteration of SCFA levels, impact to impair mitochondrial function and this is linked to neurological problems [83]. *Prevotella* and *Bacteroides* are two dominant, antagonistic genera, with abundance of the former associated with individuals consuming a diet rich in fruit and vegetable fibre, and the latter with intake of animal protein/fat-rich diets [84,85]. Higher antioxidant content found in plant-based foods may also contribute to increased mitochondrial adenosine tri-phosphate (ATP) production and basal respiration, providing defense against oxidative stress and potentially enhancing mitochondrial function [86]. In contrast, the lower levels of antioxidants in animal protein/fat-rich diets associated with *Bacteroides*, may explain the inverse correlations observed between *Bacteroides* abundance and mitochondrial activity. Overall, the data available implies that use of marijuana can result in changes in gut microbiota that impacts on systemic mitochrondrial function, with the potential to drive cognitive impairment.

4.5. Effect of cannabinoids in obesity in terms of microbiome

Obesity, the excessive buildup of fat or adipose tissue in the body, is characterised by chronic low-level systemic inflammation, intestinal microbiota dysbiosis and gut epithelial barrier disruption [87]. Use of cannabis/marijuana, and its derivative phytocannabinoids THC and CBD, is gaining popularity for the treatment of obesity and its significant co-morbidities [88]. Cannabis use is associated with improved metabolic parameters, such as better insulin sensitivity and lower fasting insulin levels, which would benefit obese patients [89,90]. Studies have also implicated that there may be dysregulation of the ECS in diet-induced obesity and metabolic disorders [13]. *Akkermansia muciniphila* is a key saccharolyte of the intestinal microbiota, which ferments dietary fibre to generate SCFAs that have the potential to modulate GPCR's such as cannabinoid receptors, and is found in lower abundance in the gut microbiota of obese patients compared to healthy individuals [91]. *A. muciniphila* inversely correlates with the onset of inflammation and altered adipose tissue metabolism [92], and with an increase in endocannabinoid-like molecules within the distal intestine [93] in animal models of diet-induced obesity. The randomised clinical trial of Payahoo et al. [38] identified within this systematic review, examined the action OEA supplementation in an obese population and highlighted

significant elevation of *A. muciniphila* levels that correlated to reduced energy and carbohydrate intake, suggesting OEA may be a potential anti-obesity intervention. OEA, expressed in both adipose tissue and neurons, is anti-inflammatory, decreasing serum pro-inflammatory cytokines, and in addition is known to enhance appetite and satiation regulating hormones to support weight loss in obese individuals [94]. However, OEA does not appear to interact with CB receptors [71], so it actions are most likely through modulation of gut microbiota and gut microbiota-derived SCFAs, indirectly activating the ECS.

5. Conclusions

This systematic review consolidates existing knowledge of how marijuana/cannabis, cannabinoids and endocannabinoid analogues impact on host microbial ecosystems, including oral, gastrointestinal, faecal and vaginal microbiomes. Outcomes of the review illustrated both positive and negative impacts of cannabis use, and cannabinoid actions, on microbiota abundance and diversity in adults across a range of clinical conditions, including cognitive deficit, depression, HIV infection, inflammation/pain, obesity and oral disease. A positive association between serum endocannabinoids and gut microbiota mediates elevation of SCFAs (particularly, but not exclusively, butyrate) producing anti-inflammatory actions and being beneficial for pain relief. Furthermore, significant elevation of *A. muciniphila* abundance following supplementation in obese patients with OEA, showed that endocannabinoid-like analogues have significant clinical potential as anti-obesity/metabolic disorder interventions, acting via modulation of beneficial intestinal bacteria. Of note, moderate marijuana use appears to have clinical benefit in those infected with HIV, demonstrating a key protective effect in reducing infection-induced, intestinal inflammation-associated, abundance of *Prevotella* seen in patients. However, chronic/problematic consumption of marijuana may adversely impact on the gut microbiota, leading a decrease in bacterial richness and diversity, and an increase in systemic inflammation. Moreover, lower abundance of *Prevotella* in those individuals with extensive marijuana use over their lifetime, may result in alterations of mitochondrial function and aberrant levels of SCFAs, resulting in neurological problems and potential to drive cognitive impairment. Similarly, long-term smoking of marijuana can lead to an imbalance of the oro-pharyngeal microbiota, with increased levels of *S. mutans* and *Lactobacillus* spp. observed that likely impact on oral health dental decay and periodontal disease, and the potential to increase risk of HNSCC and oral cancer. Correct dosing, routes of administration and duration of medicinal cannabis treatment all need to be carefully considered in individual patient populations.

Overall, our findings highlight that use of marijuana/cannabis, interventions with cannabinoids and cannabinoid-like molecules in adults, significantly impact on composition and metabolic activities of the microbiome and the systemic metabolism of the host. Our study provides a current resource for researchers and policymakers, facilitating insight into potential therapeutic implications, and influencing the development of focused cannabis/cannabinoid interventions across a wide range of clinical disorders. Despite the limited literature identified to understand these key interactions with host metabolic pathways and the immune system, further exploration in this research field is anticipated. Indeed, detailed within the Cochrane Central Register of Controlled Trials (www.cochranelibrary.com/), there are 5 such clinical trials investigating the efficacy and safety of medicinal cannabis products that include an assessment of impact of the interventions on the microbiome. These include a pilot randomised trial (registered, and a protocol published, in 2019 [95]) studying the impact of oral cannabinoids on inflammation, gut microbiome and immune response in individuals living with HIV on effective antiretroviral therapy (NCT03550352). Similarly, another study (recruiting since registration in 2022) is examining the action of CBD and THC on microbiome and endocannabinoids and their impact on neuroinflammation and blood-brain barrier function in people with HIV (NCT05514899). Our own ongoing randomised controlled trials (both registered in 2024) are examining the efficacy of cannabis products to alleviate side effects of breast cancer chemotherapy (TCTR20220809001) and psoriasis symptoms (TCTR20220518004). Outcome measures in both studies include impact of the interventions on gut, oral and skin microbiota. A fifth study that has yet to start patient recruitment, will examine effectiveness of medicinal cannabis oils (a CBD full spectrum oil and a THC:CBD balanced oil) to treat endometriosis-associated symptoms in adults (ACTRN12624000828527). This will also examine changes in gut microbiota and vaginal microbiota.

The complex nature of cannabis/cannabinoid-host microbiota and immune dynamics should be carefully considered for all future longitudinal studies, clinical trials and individualised interventions that seek to better understand the causal relationships, and the potential for health benefits and any adverse actions, of medicinal cannabis and cannabinoid interventions. Regular assessment of microbiota profiles is also needed as a part of these future studies, to identify for potential shifts in beneficial and harmful microbiota populations, as this will be essential to guide appropriate clinical management strategies. Likewise, comprehensive in-depth analysis of cannabis/cannabinoid alterations in bacterial metabolites and their interactions with host systems biology is also warranted.

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CRediT authorship contribution statement

Szaye Rawicha Hall: Writing – review & editing, Visualization, Formal analysis, Data curation, Conceptualization. **Thunnicha Ondee:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Joanne Fothergill:** Writing – review & editing, Validation, Supervision, Formal analysis. **Ananya Jagota:** Writing – review & editing, Data curation. **Krit Pongpirul:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization. **Barry Campbell:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Formal analysis, Data curation. **May Soe Thu:** Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tanawin Nopsopon:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Nattiya Hirankarn:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. Barry J. Campbell and Joanne L. Fothergill report a relationship with University of Liverpool that includes: employment.

Nattiya Hirankarn and Krit Pongpirul report a relationship with Chulalongkorn University that includes: employment.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2024.117764.

Data Availability

The original contributions presented in the study are included within the article and the Supplementary materials.

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