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REVIEW

The impact of cannabis on immune checkpoint inhibitor therapy: a systematic review of immunomodulatory effects of cannabis in patients with and without cancer

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Abstract

Purpose Cannabis is commonly used among patients with cancer for palliative benefit. As the use of immune checkpoint inhibitors (ICIs) for cancer therapy increases, there is concern about potential interactions between ICIs and cannabis. Preclinical studies suggest that cannabis leads to immunosuppression, which could impair the function of ICIs. However, only a few clinical studies have investigated this relationship. The goal of this review is to synthesize reported immunomodulatory effects of cannabis in patients with and without cancer in order to better understand whether these preclinical findings translate to the clinical space.

Methods A database search was conducted through Ovid Medline to identify relevant articles. Clinical studies investigating cannabis use in humans and the immune system were included. Preclinical studies and case studies were excluded. Information pertaining to immune changes with cannabis exposure was abstracted.

Results Forty studies met inclusion criteria, including 9 randomized, placebo-controlled clinical trials. Analysis of immune-related markers demonstrated no change in cytokines, T-cell counts, and CRP in most studies with cannabis exposure. Among patients with autoimmune diseases, cannabis use showed improvements in clinical symptoms even while objective laboratory immune markers remained unchanged.

Conclusion We did not find evidence of meaningful changes in immune parameters with cannabis use in the clinical setting across multiple diseases. In particular, immune markers relevant to ICI function did not appear to be associated with cannabis use. This evidence may provide some reassurance to patients and oncologists contemplating concomitant cannabis use with ICIs; however, additional well-controlled prospective studies are warranted in this setting.

Keywords Cannabis · Marijuana · Immune system · Cancer · Immune checkpoint inhibitors

Introduction

Immunomodulatory therapies including immune checkpoint inhibitors (ICI) have come to occupy a key place in the landscape of modern medical oncology. These therapies have a broad range of actions which are described elsewhere [1], but generally exert an antineoplastic effect via the engagement of a patient's own immune system in recognizing and destroying cancer cells. Concomitant use of medications or supplements that interfere with the immune response to cancer cells thus represents a potential challenge for clinicians and patients seeking to improve outcomes with immunotherapy.

Cannabis has been shown in several preclinical studies to exert effects on the immune system, largely through activation of the CB2 receptor on immune cells [2, 3].

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Most studies suggest an immunosuppressive effect, including decreased proliferation and increased apoptosis of T-cells (Fig. 1) [4–6]. Cannabis in both medical and recreational forms is used in the US by almost a third of patients with cancer seeking to alleviate the symptoms of cancer itself and side effects of therapy [7–9]. For clinicians seeking to counsel patients regarding cannabis use while receiving immunotherapy, further guidance is needed.

A handful of small observational cohort studies assessing the concomitant use of cannabis and immunotherapy have shown mixed results [10–13]. However, the immunosuppressive effect of cannabis has been explored in the context of several other diseases, including HIV, inflammatory bowel disease (IBD), multiple sclerosis (MS), and transplantation. Findings from clinical studies in these various immune-related fields can shed light on how cannabis interacts with the immune system, which can in turn be used to inform our understanding of potential interactions between cannabis and immune checkpoint inhibitors.

Our goal was to determine if the purported immunosuppressive effects of cannabis demonstrated in the preclinical space translate to measurable changes in clinical parameters of the immune system which could influence immunotherapy outcomes. Our intent was to conduct a broad analysis across disease types to determine what clinical studies to date have shown concerning cannabis and the immune system, providing a more comprehensive understanding of this relationship as a foundation for future research. We thus designed a search strategy to capture any clinical data regarding cannabis use and immune function in patients with and without cancer.

Methods

Database searches

Our database search was conducted on 11/12/23 through the Ovid Medline database in two parts (supplementary 1). The initial search was broad, selecting items containing cannabis-related terms in the subject, title, abstract, or keywords alongside terms related to the immune system, listed in supplementary 1. This was then restricted to human studies. 'Focus' was added in Ovid with cannab- and immun- terms, and dates were limited on this initial search to 2010 to current. This same search was then conducted without Ovid 'focus' with 'neoplasms' added. After key articles were pulled and identified as relevant, these were used to inform the second iteration of the search, conducted on 01/04/24. Criteria were further broadened by date (1970 to current) and re-conducted with neoplasm restriction and without, with duplicates removed. This search was repeated on 05/10/24 to identify any publications since 01/04/24. Search results were generated as abstracts, which were compiled and screened for potential eligibility by two authors (CBH and DZ).

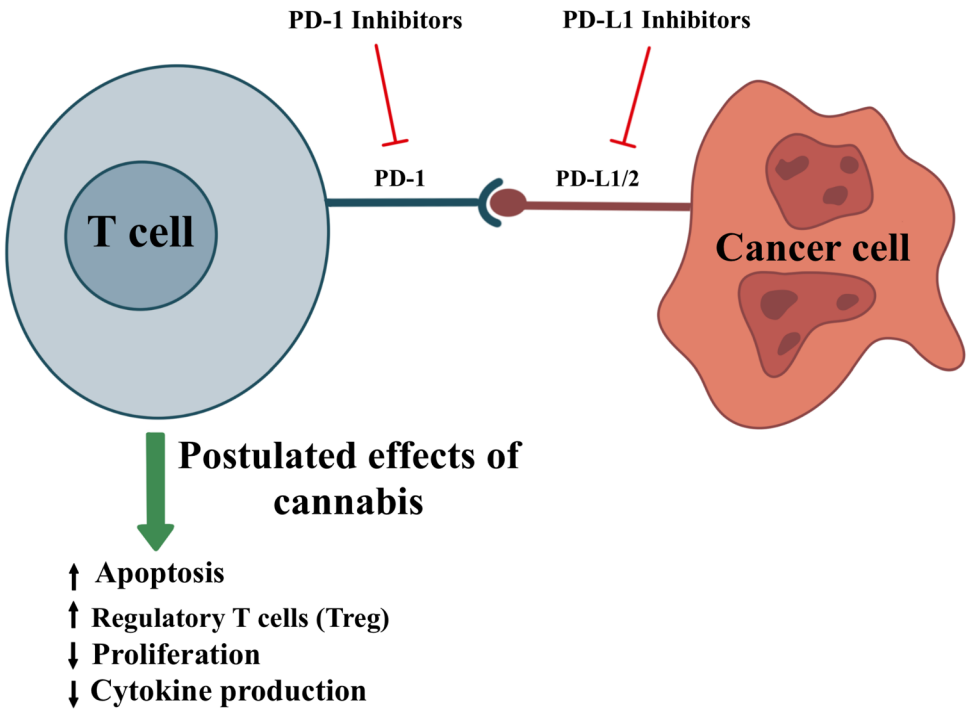

Fig. 1 Postulated interactions between ICIs and cannabis. Cancer cell expression of PD-L1/2 has an inhibitory effect on a T-cell's ability to recognize and destroy neoplastic cells. Immune checkpoint inhibitors block this inhibitory signal and allow for unrestrained T-cell action. Postulated interactions between cannabis and ICIs center around globally decreased T-cell activity rather than direct interaction between the two drugs

Selection criteria

Inclusion criteria were defined as clinical studies of any design with human subjects investigating cannabis use with a measurable relation to the immune system. A measurable relation was defined as either an objective measure (e.g., a laboratory assessment) or a symptomatic change in an immunological disease (e.g., clinical improvement in degree of inflammation in a patient with inflammatory bowel disease). Review articles were included in the initial database screening and used for relevant cited articles, but were not included in the final selected group. Exclusion criteria were defined as any pre-clinical study (in vitro or animal model) and case reports. Studies solely investigating the use of cannabis to manage toxicities related to cancer therapy were excluded, as the goal of this review was to ascertain the impact of cannabis on immune-specific effects. Criteria were applied during review of abstracts pulled during the database search; studies that met inclusion criteria were read in their entirety and placed in our final group (Fig. 2) [10–12, 14–50].

Article analysis

Three authors (CB, DZ, and GS) independently read the final 40 articles selected. Our objective in our article analysis was to determine what, if any, immunomodulatory effects of cannabis were demonstrated across disease types. Therefore, for each article, data were abstracted regarding study design, disease investigated, immune-related parameters investigated, measurement or dosing of cannabis products including tetrahydrocannabinol (THC) and/or cannabidiol (CBD) dose, time on treatment, and potential sources of bias as recorded in supplementary table 2. Unavailable data were coded as 'unknown.' As a method to indicate each study's relative value to our paper's objective, articles were then rated out of 3 'stars' based upon relevant criteria: 1) whether the study design was randomized/controlled, 2) whether cannabis dosing was controlled and/or objectively measured (vs. by clinician or patient report), and 3) whether an objective laboratory immune-related marker was measured. If cannabis dosing was not controlled but was measured via blood testing or verified with purchase data, a full star was given for category 2. Studies where C-reactive protein was the only immunologically-related test conducted were not given a star for category 3 due to the nonspecific nature of this test alone as a measure of immune function.

A more focused analysis was conducted on studies where inflammatory markers were measured in relation to cannabis exposure. Inflammatory markers were selected if they were measured by > 3 total studies. Results were collected on whether these markers significantly ($p < 0.05$) increased, decreased, or stayed the same with cannabis exposure. For reported changes that are more disease-specific and/or less objective, such as symptomatic changes, studies were compiled based on direction of change reported and disease of interest.

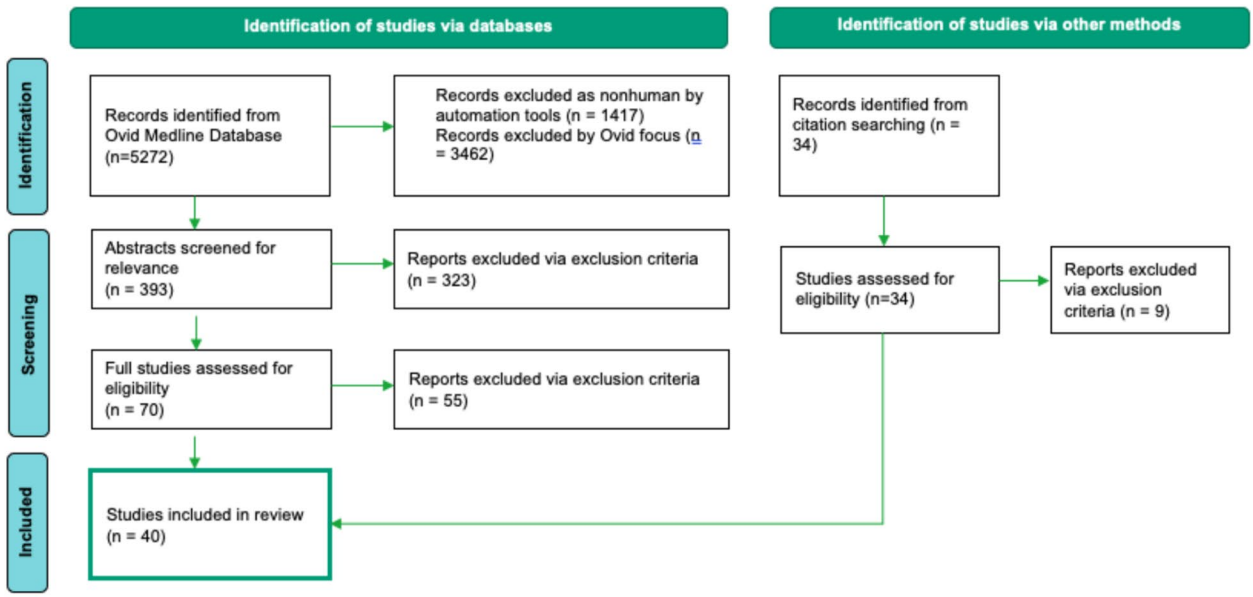

Fig. 2 Study selection process

Results

Characteristics of included studies

Of the 40 analyzed clinical studies, 10 (25%) were randomized, placebo-controlled clinical trials comparing cannabis use to non-use. An additional 3 studies (7%) were not randomized but were controlled, and one was a placebo-controlled crossover study. The remainder included retrospective cohort studies ($n=10$), prospective cohort studies ($n=5$), cross-sectional studies ($n=9$), case–control studies ($n=1$), and one case series study. Sample size ranged from $N=5$ to $N=9156$. Diseases investigated included IBD ($n=6$), MS ($n=4$), cancer ($n=3$), HIV ($n=8$), organ transplant ($n=3$), and other miscellaneous conditions ($n=6$). Ten studies directly investigated cannabis use alone (i.e., in healthy subjects). Only 7 studies met our criteria for 3 stars.

Studies measuring immune-related laboratory markers

Objective systemic immune-related markers were measured by 23 of 40 selected studies (56%). Immune changes reported are summarized in Fig. 3 and Table 1. Most studies (69%) found no change in cytokines, T-cell count, or CRP with cannabis exposure. CRP was the most commonly measured inflammatory marker across all studies, and varied the most in relation to the other immune markers, though the majority ($n=8$, 61%) still showed no change with cannabis exposure. IL-6 and TNF-α were the next most commonly measured immune markers, both with the majority (86% and 71%, respectively) demonstrating lack of change with

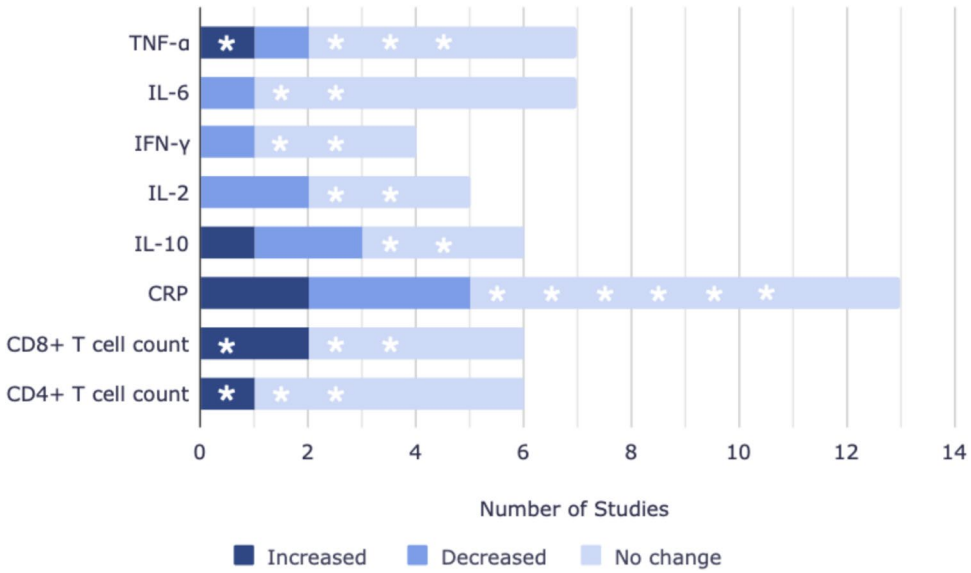

Fig. 3 Reported changes in immune-related markers. Asterisks indicate a study with ≥ 2 stars by our rating criteria as specified under "article analysis" of "Methods." Abbreviations are as follows: TNF-α = tumor necrosis factor alpha, IL-6 = interleukin 6, IFN-γ = interferon-gamma, IL-2 = interleukin 2, IL-10 = interleukin 10, CRP = C-reactive protein

Table 1 Changes in disease progression and symptoms by study. "Disease-specific symptom" refers to a symptom characteristic of an immune-related illness studied in relation to cannabis exposure

Investigated effect of cannabis exposure	Result	Disease/area of investigation	Citation
Disease-specific symptom	Symptomatic improvement	GI (IBD) ($n=5$), autoimmune hepatitis ($n=1$), cancer ($n=1$)	[11, 24, 34–37, 47]
	Symptomatic worsening	Rheumatologic	[29]
	No change	ID (COVID-19) ($n=1$), cancer ($n=1$)	[10, 20]
Overall survival	Decreased overall survival	Cancer	[11]
	No change	Transplant ($n=3$), cancer ($n=2$)	[10, 12, 23, 44, 50]
Transplant complications	Decreased complications	Transplant	[50]
	No change	Transplant ($n=2$)	[23, 44]
Time to tumor progression (TTP)	Decreased TTP	Cancer	[11]
	No change	Cancer	[12]
Response rate	Decreased	Cancer	[10]

cannabis exposure. CD4 + and CD8 + T-cell counts did not change with cannabis use in the majority of studies.

Studies measuring change in immune-related symptoms and clinical outcomes

The most commonly reported non-laboratory change with cannabis exposure was symptomatic improvement ($n = 6$), particularly in studies investigating inflammatory bowel disease ($n = 5$). Kotschenreuther et al. reported worse disease activity scores in a very small sample of 5 patients with rheumatoid arthritis using CBD oil over 4–8 weeks [29]. All studies showing symptomatic change with cannabis exposure were investigating autoimmune diseases; Crippa et al., by contrast, examined symptomatic change in COVID-19 patients randomized to cannabis and non-cannabis arms and showed no significant change between groups [20]. This was conducted alongside a thorough immune marker analysis that also demonstrated no variation between groups.

Among patients with cancer using both cannabis and ICIs, a decrease in progression-free survival (PFS) and overall survival (OS) was reported by Bar-Sela et al. [11]. In a similar cohort, Taha et al. showed no change in PFS or OS, but demonstrated decreased tumor response rates among cannabis users [10]. Waissengren et al. showed no change in PFS in a uniform group of advanced non-small-cell lung cancer patients receiving first line ICIs but did report a nearly 30-month improvement in median overall survival amongst non-cannabis users. However, cannabis was not found to be significant on multivariate analysis ($p = 0.08$) [12]. The authors stated "patients in need of cannabis for symptomatic disease may have higher disease burden and, therefore, reduced survival but similar activity of ICI."

In trials investigating organ transplant complications and graft rejection, all studies showed no change in overall survival, overall mortality, and non-relapse mortality in patients with cannabis exposure. Yeshurun et al. conducted a phase II clinical trial investigating pre- and post-transplant CBD use and showed significantly decreased levels of GVHD in the CBD cohort vs. historical controls [50]. Two studies that did not control cannabis dosing showed no change in transplant complications or outcomes among patients reporting regular cannabis use [23, 44].

Discussion

While preclinical evidence suggests cannabis acts largely as a suppressive immunomodulator, our review did not find evidence of meaningful change in immune parameters with cannabis use in patients with and without cancer. Cannabis use did not appear to impact immune markers relevant to the cytotoxic branch of the immune system necessary for ICI benefit, and clinical studies suggesting a potential immunosuppressive effect of cannabis were mostly related to improved symptom control.

This review was conducted to summarize the current state of clinical research investigating cannabis and the immune system, with the goal of informing a more specific understanding of potential interactions between cancer immunotherapy and cannabis use among cancer patients. Two cohort studies of patients with non-small-cell lung cancer, renal cancer, and melanoma treated with a variety of ICIs showed a potential decline in tumor response rates, progression-free survival (PFS), and overall survival (OS) in cannabis users [10, 11]. However, the cannabis users in both studies appeared to have higher disease burden (e.g., more brain and liver metastases) and were more likely to have received ICIs as a second- or third-line treatment, suggesting more advanced disease. An updated study assessing the same ICI (pembrolizumab) as first-line treatment in NSCLC patients showed no difference in PFS in cannabis users vs. non-users and no association of cannabis and OS when brain and liver metastases were included in multivariable analyses. Therefore, it is difficult to isolate the potential effects of cannabis alone from non-randomized, cohort studies of patients taking multiple palliative medications.

Patients with cancer may use many palliative medications in addition to cannabis that may have immunomodulatory effects. Steroids are well-understood to mitigate the effectiveness of ICIs, yet other medications commonly prescribed alongside ICIs may also confound analyses of concomitant cannabis and ICI use. Opioids have been shown to have both immunosuppressive and immunostimulatory properties that vary across type of opioid and duration of administration [51]. Studies investigating concomitant opioid and ICI use have noted decreased overall survival and progression-free survival among ICI patients with higher opioid intake [52, 53]. NSAIDs, by contrast, have been shown to be correlated with improved OS in patients taking ICIs vs. ICIs alone [54]. Against this backdrop of several other potentially anti- or pro-inflammatory medications, it is difficult to isolate the effects of cannabis alone. This points to the needs for randomized, controlled trials directly investigating this relationship.

From a pathophysiologic perspective, lack of change in CD8 + T-cell counts is of particular interest in relation to immune checkpoint inhibitors. PD-1, PD-L1, and CTLA-4 inhibitors act primarily via CD8 + T-cells and the cytotoxic branch of the immune system. Increased levels of CD8 + 28 + T-cells with ICI treatment have been shown to be predictive of increased immunotherapy response [55]. In this context, the findings by Abrams et al. demonstrating increased CD8 + T-cell counts with cannabis exposure in a randomized, placebo-controlled trial are especially intriguing, though the HIV + status of patients in this trial may

limit generalizability [14]. Pro-inflammatory cytokines produced by CD8 + T-cells, such as IFN-γ, have also been suggested as potential markers of ICI response [56]. IFN-γ promotes chemotaxis and immune cell recruitment and has been shown to increase expression of PD-L1 in the tumor microenvironment [57]. TNF-α and IL-6 are likewise under investigation as predictive biomarkers for ICI response and adverse events, though there is conflicting evidence on the relative levels and directions of change that are most strongly correlated with response rates and OS [56]. The overall lack of change in these cytokines with cannabis treatment identified in this review suggests a less potent systemic effect than might be expected from preclinical studies. Certainly, these results stand in contrast to the cytokine profile that would be expected with exposure to medications well-understood as inhibitors of immunotherapy, such as the suppression of cytokine production seen with steroid treatment [58].

It is possible that the lack of immunosuppressive effects of cannabis in these studies expected from the overall conclusions in the preclinical space is partly due to differences between real-world cannabis exposure and levels of exposure achievable in a laboratory setting. Cannabis is known to have comparatively low bioavailability, particularly when ingested orally—a means of exposure that is growing in favor among patients [59]. Some early studies specifically investigating dose-dependent effects of THC and CBD demonstrated biphasic effects on immune cells [60, 61]. Doses that resemble physiologically available levels (in the nM range) have been shown to metabolically stimulate lymphocytes in vitro and increase pro-inflammatory cytokine production while much higher doses (at the mM range) resulted in more overtly immunosuppressive effects. Indeed, other authors have noted that concentrations used in many in vitro studies are at least tenfold higher than what is found on blood analysis of cannabis users [62]. It is possible that this postulated biphasic effect on the immune system is contributing to the lack of change in inflammatory markers demonstrated across the majority of studies in a dose-dependent manner.

Symptomatic improvement was a commonly reported outcome following cannabis treatment, particularly in studies investigating inflammatory bowel diseases [35, 36, 38]. However, despite statistically significant changes in symptom burden, disease and immune-specific markers did not appreciably vary with cannabis exposure. This delineation between immunological markers and symptomatic severity in IBD suggests that the main benefit of cannabis in these patients is via a non-immunological process. Cannabis has well-established effects on GI motility, nausea, and pain that are thought to be modulated via non-immunosuppressive mechanisms [63]. It is possible that the decreased abdominal pain, number of stools, arthralgias, and improved well-being demonstrated in these studies is the result of cannabis acting directly upon these symptomatic complaints rather than via a broadly immunosuppressive mechanism.

Our review and analysis had some limitations. First, there is no clear standardized protocol for cannabis dosing in clinical trials, reflected in these studies with a marked variation in both reported and controlled cannabis exposure. Among the 13 studies where cannabis dosing was directly controlled, doses of THC ranged from 1.5 mg/day to an upper limit of 210 mg/day. CBD dosing—perhaps due to the lack of psychoactive side effects—was even more varied, ranging from 1 mg/day to maximum doses of 500 mg/day. Diversity in methods of exposure—oral, smoked, or sublingual administration—contributes an added layer of variation. In studies where cannabis exposure was established by report rather than controlled, there is a similar lack of standardization as to what constitutes heavy, low, or occasional use. For example, Rachelefsky et al. defined 'heavy' cannabis use as > 1x/day and 'moderate' use as 3–6x/week [41]. However, Rajavashisth et al. would have included the latter as 'heavy' users by their criteria of > 5 days/month [42], while Ellis et al. would include all of the above in their category of 'ever' cannabis users vs. 'never users' [22]. This variation in cannabis exposure classification across studies likely contributes to the variation in data relating to immune function and adds to the difficulty of extrapolating cannabis' effects on the immune system from any single study. Additionally, it could contribute to the lack of change in objective immune markers demonstrated in the majority of studies, though these findings were replicated even among the randomized, controlled trials with the highest doses of THC and/or CBD per day [20, 24, 36]. As the cannabis landscape in the United States rapidly changes both clinically and commercially, establishment of standard doses alongside understanding of standard bioavailabilities is needed in future clinical trials.

Second, due to the heterogeneity of diseases investigated, study design, and measurements, there was a challenge in comparing results. We developed our rating criteria to indicate which results could be most reasonably extrapolated to our study question about ICIs. For example, Pacifici et al. measured CD8+ T-cell counts in healthy volunteers who self-reported cannabis use and found that daily users did not have CD8+ T-cell counts that differed from normal levels [40]. Bredt et al., by contrast, conducted a randomized, controlled trial where HIV + patients were administered either cannabis cigarettes, dronabinol, or placebo control and CD8+ T-cell counts were found to be unchanged after a 21-day period of regular, controlled use [18]. This variation in quality of evidence is reflected in our rating system: Bredt et al. have three stars by our criteria while Pacifici et al. have one. When our analysis of immune markers is limited only to studies with a higher quality of evidence (≥ 2 stars), there is a higher proportion of studies showing no change in immune markers. The only statistically significant changes

demonstrated in ≥ 2 star studies were increased CD4 + and CD8 + T-cell counts [14] and increased TNF-α [28].

Lastly, symptomatic changes were separated from more objective immune markers in our rating system due to the disease specificity of some symptoms and the possibility that these changes were not the result of immune interactions but of other processes (i.e., cannabis effects on GI motility, nausea, etc.). Measures that were clearly related to immune processes were therefore rated higher. However, this means that symptomatic changes that may have been the result of immune interaction were rated lower unless they were paired with a more specific immune marker.

Conclusion

Our broad review of clinical studies found little evidence to support a clinically meaningful immunosuppressive effect of cannabis use in patients with and without cancer. This provides some reassurance for patients and oncologists considering cannabis use with immune checkpoint inhibitors as the clinical studies reviewed do not demonstrate suppression of the branches of the immune system that ICIs rely upon for efficacy. However, further controlled clinical studies with standardized cannabis dosing and rigorous outcome ascertainment are necessary to fully determine the impact of cannabis on the immune system.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-025-09218-x.

Author contribution CBH and DZ conceptualized the review topic. CBH, DZ, NF, and TS contributed to project direction and results analysis. CBH, DZ, and GS analyzed selected studies. CBH and GS wrote the main manuscript draft. CBH prepared Figs. 1, 2, and 3, Table 1, and supplementary tables 1 and 2. All authors revised and edited the manuscript draft.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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