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Scoping Review

Cannabis Use and Its Multifaceted Impact on the Genitourinary System: A Scoping Review of the Literature

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Abstract

Background and objectives: Cannabis is a commonly used recreational and therapeutic substance in our society. There are a variety of established physical, social, and mental health impacts associated with cannabis use. However, there is no overview of the impact cannabis use has on the genitourinary system. Thus, this scoping review aims to present data on the impact of cannabis on the genitourinary system.

Methods: A scoping review search was undertaken on Embase, Medline, and Web of Science. There were no date restrictions applied. Studies that included data from humans, exposure to cannabis, and outcomes related to the genitourinary system were included. Opinion pieces, commentaries, perspectives, and studies not available in English were excluded.

Results: A total of 50 articles met this review's inclusion criteria. The various studies were thematically organized into four themes: adverse outcomes related to cancer (n = 4), non-cancerous urogenital illness (n = 31), kidney transplant (n = 4), and therapeutic use of cannabis (n = 11). There were several non-cancerous urogenital illnesses associated with cannabis use, including acute kidney injury, urinary retention, rhabdomyolysis, and renal infarcts. The data found in this review suggest that cannabis use may not be a contraindication to receiving a kidney transplant. Finally, several studies highlighted some of the therapeutic applications cannabis may have on the genitourinary system.

Conclusions: This review brings forward conflicting findings on the association between cannabis use and genitourinary malignancies. Moving forward, data from well-designed long-term research studies are needed to understand the impact cannabis use has on the genitourinary system.

Keywords: Cannabis; Genitourinary health; Adverse effects; Therapeutics; Transplant; Scoping review.

Abbreviations: AKI, acute kidney injury; ARI, acute renal infarction; ATI, acute tubular injury; ATN, acute tubular necrosis; CB, cannabinoid; CBD, cannabidiol; CHS, cannabinoid hyperemesis syndrome; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GU, genitourinary; RCC, renal cell carcinoma.

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Introduction

In the USA, cannabis is the most abused federally illegal substance, with nearly one in five Americans using it at least once in 2019.[1] In the global context, cannabis is also the most abused illicit drug, with 2.5% of the global population using cannabis based on annual prevalence data.[2] Furthermore, in recent years, it appears that cannabis use has increased rapidly, even more than the use of cocaine or opioids.[2] A common, growing misconception is that using marijuana does not lead to addiction or marijuana use disorder;[3] however, Hasin *et al*.'s.[4] research suggests that about three in ten people who use marijuana have an underlying

Table 1. Terms used in the literature search

Row	Search terms
1.	Cannabis
2.	Electronic nicotine delivery system
3.	Marijuana vaping or smoking
4.	Cannabis or marijuana or e-cig or electronic cig or vaping or vape
5.	1 or 2 or 3 or 4
6.	Exp urinary tract
7.	Urinary system or urinary tract or urological system or urological tract or kidney or urethra or ureter or bladder
8.	6 or 7
9.	5 and 8
10.	Limit 9 to the English language

marijuana use disorder. Thus, it is necessary to acknowledge that the use of marijuana has the potential to result in marijuana use disorder.

While the *Cannabis sativa* plant does contain well-known cannabinoids such as tetrahydrocannabinol and cannabidiol (CBD), it is important to note there are over 550 chemical compounds that have been identified in the plant, and more than 100 of these compounds are classified as cannabinoids.[5] These natural compounds have been shown to have many therapeutic effects that are used in pain, anxiety, and appetite stimulation, just to name a few.[5,6] However, their synthetic counterparts have many undesirable side effects, believed to be caused by a higher binding potency to the cannabinoid (CB) receptors.[6] Additionally, these synthetic variants may contain several ingredients, such as benzodiazepines, O-desmethyltramadol, and more that can induce a greater psychoactive effect.[6] Since synthetic CBs act as complete agonists of the CB receptors, this leads to a stronger and more potent effect than naturally occurring CB compounds.[7]

Cannabis use affects all biopsychosocial aspects of health. Considering the social impact of cannabis, Fergusson and Boden[8] accounted for various socio-economic factors and found that increasing levels of cannabis were associated with lower degree attainment and lower income at 25 years of age, lower levels of relationship and life satisfaction, greater dependence on welfare programs, and higher unemployment levels. The use of marijuana is associated with short-term (i.e., mood changes, memory difficulties, and possibly delusions) and long-term effects (brain development).[9] Furthermore, marijuana use is associated with impacts on mental health, such as depression, paranoia, and, in some psychiatric patients, worsening psychiatric symptoms.[9] Moreover, marijuana use can impact the cardiovascular, gastrointestinal, reproductive, and respiratory systems.[9] Mehrnoush *et al*.'s[10] systematic review highlights that there is a data gap specific to research on the impact cannabis has on urological health, specifically, bladder cancer. In a recent study involving over 200,000 participants, including individuals who reported using cannabis on a monthly basis or less frequently and controls, a statistically significant association was observed between daily and weekly cannabis consumption and the development of chronic kidney disease (CKD).[11] In the USA, about 33% of patients with CKD reported cannabis use.[12] The multivariable-adjusted hazard ratios for chronic marijuana use and the progression of CKD and all-cause mortality were 0.94 and 1.11, respectively, when contrasted with no marijuana use.[12]

Also, emerging evidence suggests that the impact of cannabis use on the genitourinary (GU) system may be influenced by sex. Various physiological and hormonal differences between males and females may contribute to differential susceptibility to the effects of cannabis.

Furthermore, societal and behavioral aspects related to sex can significantly shape patterns of cannabis use[13] and, subsequently, its impact on the GU system. In males, studies have reported cannabis-associated changes in sperm morphology, reduced sperm count, and altered hormone levels, potentially contributing to fertility issues.[14] Females, on the other hand, may experience irregular menstrual cycles, potential impact on fertility, and possible effects on urinary symptoms related to cannabis use.[15]

The GU system plays a vital role in our overall health and well-being. Conceptually, the GU system includes the kidneys, ureters, bladder, and urethra.[16] This system has endocrine and exocrine functions to maintain homeostasis. Given the prevalence and the multitude of impacts associated with cannabis, coupled with the knowledge gap on its effect on the GU system, our scoping review aims to present research that highlights the impacts of cannabis on the GU system.

Materials and methods

We undertook a scoping review of the scientific literature on how cannabis is associated with urological health using Arksey and O'Malley's[17] five-stage scoping review framework.

Stage 1: Identify the research question

According to Arksey and O'Malley,[17] the very first step in conducting a scoping review is to identify the question of interest. Therefore, to collect existing data on the topic, the search was conducted to address the following research question:

What is the current state of knowledge regarding the effects of cannabis use on the GU system?

Stage 2: Identify the recent findings

Our search strategy was developed using a preliminary search, which allowed us to better grasp the understanding of search terms and keywords, and with the support of a subject expert librarian (Table 1). We searched the Embase, Medline, and Web of Science databases (Fig. S1. shows the exact terms used for the Medline database).

Stage 3: Selecting literature: inclusion criteria

A total of 2,167 articles selected using our search criteria were imported into the review software Covidence (https://www.covidence.org/) for screening.[18] Of them, 674 duplicates were removed, leaving 1,493 papers for screening. We conducted title and abstract screening following the search criteria outlined below.

Type and scope of review

The review included qualitative, quantitative, and mixed-methods studies retrieved from all the search settings and various geographical locations that discussed the implications of cannabis use on urological health. We sought to choose studies that discuss cannabis use on the GU system. The papers selected have analyzed the impact on urological health of the use of cannabis or cannabis-containing products.

Key concepts

This review covers material related to urological health, specifically, adverse outcomes related to cancer (i.e., bladder cancer or kidney cancer), non-cancerous urogenital illness (i.e., acute kidney infarction and negative impacts on kidney function), implications related to kidney transplant (critical considerations for patients who require a kidney transplant and use cannabis) and the therapeutic use of cannabis (i.e., role in the treatment of neurogenic bladder and treatment of other urogenital conditions).

Participants

The review focused on participants of any age, including all sex identities in any given geographic location, published in any year and data only from human participants.

Following this, 167 full-text reviews were assessed, and 117 additional studies were excluded because the papers discussed the wrong patient population (n = 21), wrong intervention (n = 25), wrong outcomes (n = 36), and wrong study design (n = 35). We provide a Preferred Reporting Instrument for Systematic Reviews and a Meta-Analysis (commonly known as PRISMA) flow chart delineating these steps in Figure 1. To capture as much data as possible and to account for diversity, our review did not apply any date or geographic restrictions. We included data from most published studies except opinion pieces (perspectives, non-research-focused letters, or comments). We focused on including peer-reviewed publications discussing the use of cannabis and its impact on the GU system. We excluded all articles not written in English, non-human studies, and studies irrelevant to the key concepts above.

Stage 4: Data extraction

A data charting tool was co-developed by the team of reviewers to capture essential data to answer this review's research question. We created an extraction tool using Covidence to record the author, publication year, country, study aims, study design, and participant characteristics (types of people included in the study, i.e., CKD patients, youth, and patients who had kidney transplant procedures), cannabis exposure (type of cannabis use, frequency of use, duration of use), inclusion and exclusion criteria, and outcomes related to GU health (related to the risk of bladder cancer, fertility, pain management, and kidney stones), and a notes section for additional points. Two independent investigators reviewed each article, extracted relevant data, and inputted the data into the Covidence data extraction tool. In case of conflict or disagreement in the data extracted by the two reviewers, a third independent reviewer evaluated the article for consensus.

Stage 5: Collating, summarizing, and reporting the results

The data were summarized using the number of publications each year, the geographical region, and the study design. Our findings are presented under four major themes, determined by our focus on studies included in the review: (1) the adverse outcomes of marijuana related to cancer; (2) the presence of non-cancerous urogenital illness; (3) the use of cannabis and its related implications on kidney transplant; (4) the therapeutic outcomes of cannabis. Each article was coded based on its content and relevance to the major theme(s). After the final analysis stage, the key findings and existing data gaps were identified.

Results

Characteristics of identified studies

Of the 50 studies included, 90% (n = 45) were published within the last 10 years (Fig. 2). The majority of papers (n = 36; 72%) were from the USA, followed by Canada (n = 5; 10%). There were a few countries where only a single study originated from (Table 2). The most common study design was case reports, which comprised 42% of included studies (n = 21). This was followed by cross-sectional studies, which made up 18% of the studies included (n = 9) (Fig. 3).

Frequency of themes

Figure 4 highlights the number of studies that discussed information relevant to the key themes of this study. Of the studies included in this review, four articles discussed adverse outcomes associated with cannabis use related to cancer. Thirty-one discussed non-cancerous urogenital illness. Implications of cannabis use in relation to kidney transplantation were discussed in four articles. Eleven articles discussed the therapeutic use of cannabis for various conditions related to the GU system.

Frequency of reported cannabis usage

Figure 5 provides insight into reported patterns of cannabis usage across the studies in the results section, along with the corresponding outcomes. For this study, regular usage is categorized as chronic (consuming cannabis once or more a week), while occasional usage is cannabis consumption less than once a week. Instances where the usage frequency was not specified are grouped under the unreported frequency. Kidney-related injuries encompass acute kidney injury (AKI), acute renal infarction (ARI), acute tubular necrosis (ATN), and acute tubular injury (ATI).

Adverse outcomes related to cancer

It has been observed that there are mixed relationships between cancer and cannabis use. Chacko *et al*.[19] conducted a case-control study in the USA that discussed 52 men less than 60 years of age presenting consecutively with urothelial carcinoma and 104 age-matched controls (defined by having no history of urothelial carcinoma, hematuria, or irritative voiding symptoms, as well as unremarkable results on urinalysis and urine cytology) with 88% of patients reporting history with habitual cannabis use. Through this study, it was found that marijuana smoking may have a causal relationship with the development of urothelial carcinoma of the bladder.[19] Although one of the key limitations of the Chacko *et al*.[19] study is that the use of marijuana among the study's population of Vietnam-era veterans, who were less than 60 years of age, is not representative of the typical marijuana use of patients generally seen in urology. On the other hand, a cohort study conducted

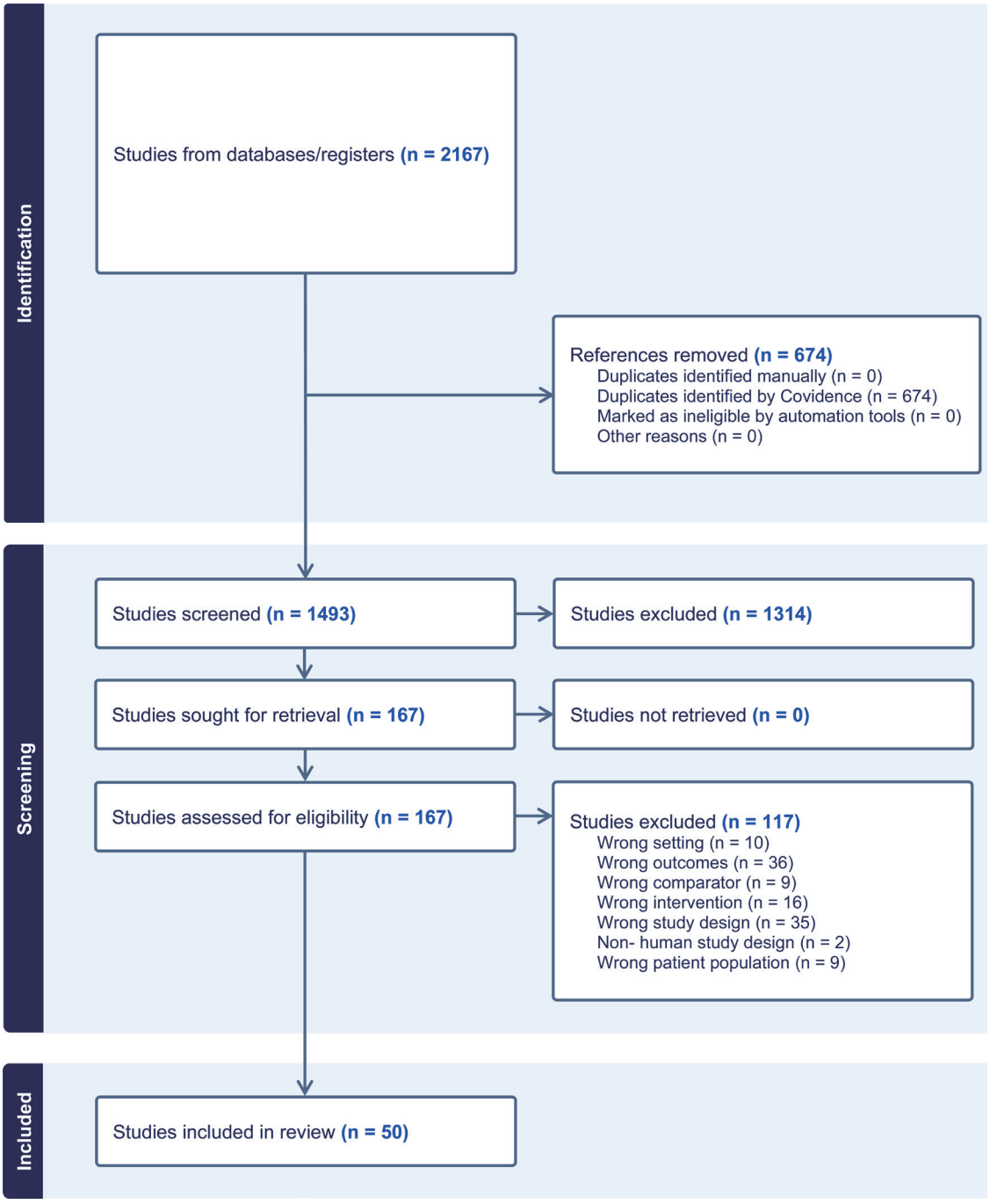

Fig. 1. Preferred Reporting Instrument for Systematic Reviews and Meta-Analysis flow diagram.

in the USA by Thomas *et al*.[20] studied 39,222 participants with histories of cannabis, tobacco smoking, or both, which illustrated an inverse relationship between cannabis use and bladder cancer. The participants in the study reported having consumed cannabis more than 500 times each.[20]

A more recent cohort study conducted by Huang *et al*.[21] studied 151,945 UK participants aged between 40 and 69 years who used marijuana and found that a history of cannabis use correlated with a lower risk of bladder cancer, prostate cancer, and renal cell carcinoma (RCC). Study participants were divided into two groups: one group had never been exposed to cannabis, and the other group had varying degrees of cannabis exposure, ranging from using it once to over a hundred times.[21] In particular, cannabis use has been shown to have a potential causal effect on a lower incidence of either RCC or bladder cancer, which was significant in females but not in males.[21] Mehrnoush *et al*.'s[10] systematic review looked at 84,295 patients with bladder cancer that had varying cannabis exposure. The participants across the three studies exhibited varying

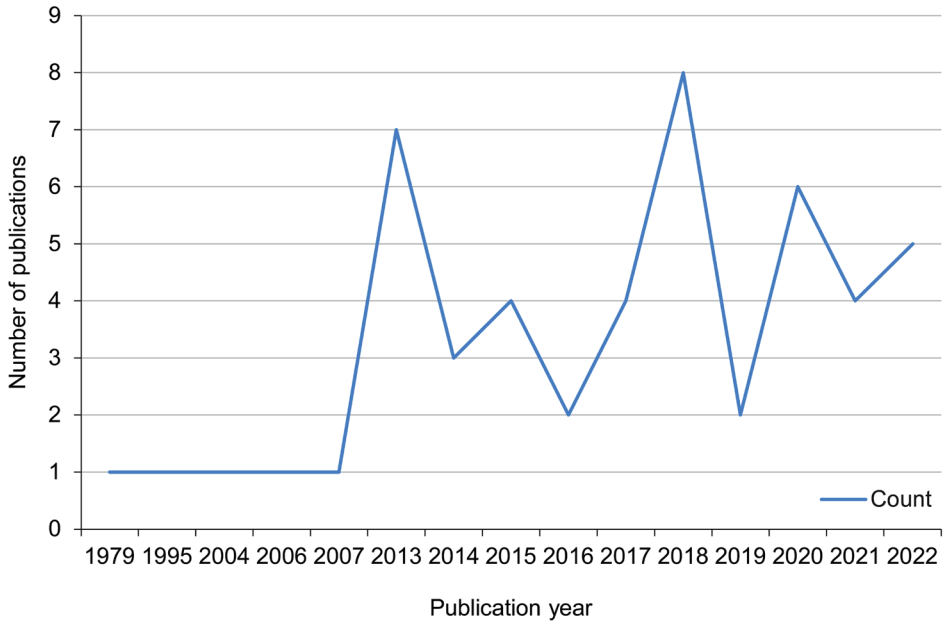

Fig. 2. Number of publications per year from 1979 to 2022.

levels of cannabis usage.[10] In the first study, participants reported engaging in habitual daily cannabis use, while the second study did not provide specific details.[10] In the third study of the review, participants indicated smoking five marijuana cigarettes every day for 30 days.[10] The outcomes of this review indicated contradictory findings between carcinogenic and protective effects.[10]

Non-cancerous urogenital illness

Several studies suggested synthetic CB use may be linked to the development of AKI and other non-cancerous urogenital illnesses.[22–24] Bhanushali *et al*.[22] presented a case series of four young men who were reported to have taken synthetic CBs known as SPICE or K2 over a few weeks with unspecified frequency before admission to the hospital. The researchers found that three patients developed ATN while the fourth patient had pre-renal AKI.[22] All patients in this case series were from the same community and were admitted to the same healthcare facility within a 9-week window.[23] A case study conducted by Srihari *et al*.[23] on a 43-year-old male with a history of cannabis use over some time between 1 to 5 years (at least once a week), along with tobacco, opioid, and cocaine abuse. The study documented that the patient was diagnosed with CB hyperemesis syndrome (CHS), which subsequently resulted in an AKI.[23] In a recent case study, Curtis *et al*.[24] reported a 29-year-old male with a history of poly-substance abuse and was also reported to have ingested K2. The authors concluded that the most probable cause of the patient's AKI was the ingestion of K2.[24] In 2013, a case series was reported by Murphy *et al*.[25] which involved 16 individuals aged between 15 and 33 years who routinely consumed synthetic CBs regularly over a few days. The findings of the report revealed that all 16 patients had developed an AKI.[25] Another case series report by Murphy *et al*.[25] on 15 to 33-year-old marijuana users who smoked synthetic marijuana for days or hours before symptoms onset found that cannabis could have had an impact on developing AKI. A case report by Berry *et al*.[26] on patients with no prior kidney injury found that abusive use of synthetic CBs over short periods is a risk factor for developing AKI.[27]

Another case report by Habboushe *et al*.[27] on a healthy 25-year-old male with 8 years of daily marijuana use (two grams to a quarter ounce) found the patient to have an elevated serum creatinine of 3.21 and was admitted for AKI secondary to CHS. Karass *et al*.[28] reported on a case study of a 20-year-old man who used synthetic CBs daily for a few weeks before presenting at the emergency department. The authors proposed that the use of CBs caused thrombotic microangiopathy, ultimately leading to the patient's AKI.[28] Lambrecht *et al*.[29] reported on a previously healthy 26-year-old male who was said to have smoked cannabis for the last 10 years regularly before he visited the emergency department. The authors strongly considered the AKI developed from exposure to synthetic CBs.[29]

A case study presented by Kazory and Aiyer[30] detailed a 22-year-old man with AKI who reportedly smoked synthetic CBs occasionally for 3 days before presenting to the hospital. The authors suggested that synthetic CBs may be the ultimate culprit for

Table 2. Number of studies from different countries and regions

Country	Count
Belgium	1
Canada	5
Germany	1
India	2
Italy	1
Poland	1
Saudi Arabia	1
Taiwan	1
UK	1
USA	36

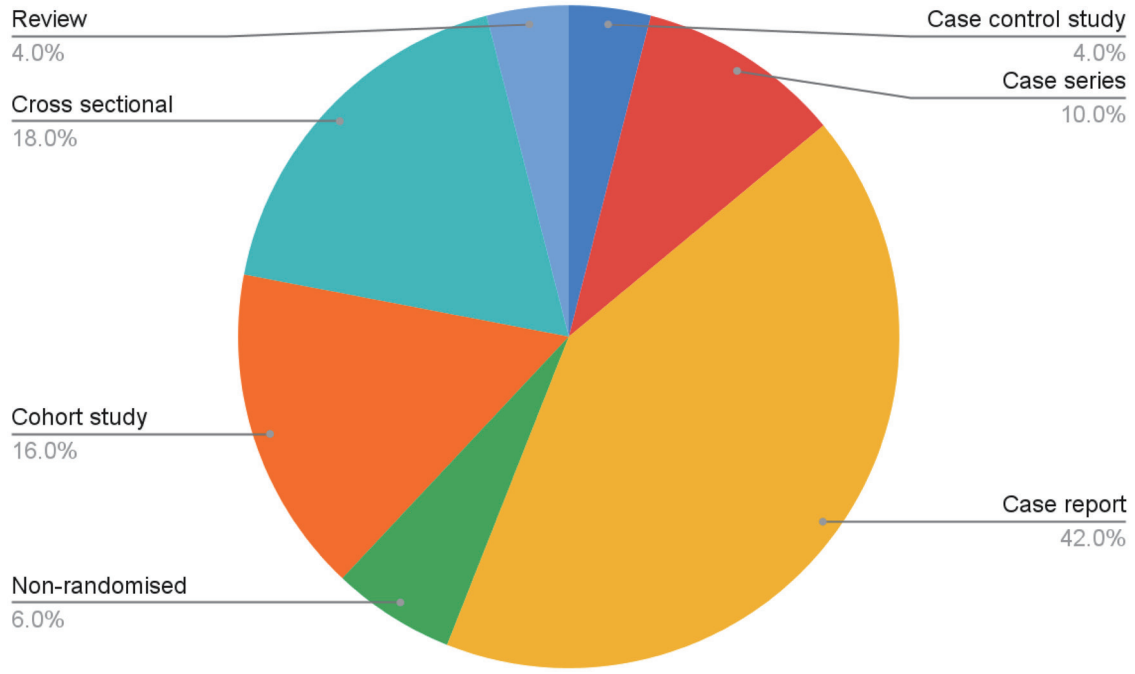

Fig. 3. Percentage of study designs included in the review.

the development of AKI because of their toxic components not naturally found in plant CBs.[30] Thornton *et al*.[31] presented a case study of a healthy 26-year-old male who was reported to have an AKI likely due to synthetic cannabis use frequency of 2 to 3 times daily for over a year. Fernandez *et al*.[32] published a case report on a 19-year-old male with no prior medical problems who used synthetic cannabis with no specified time frame and experienced an AKI. They reported that the AKI could have happened due to an overdose.[32] A case series presented by Buser *et al*.[33] on patients aged 13–40 with no known renal disease found these patients with AKI all had a history of habitual smoking history of synthetic cannabis over 2 weeks. Argamany *et al*.[34] presented a case study of a 27-year-old man with no prior medical history but reported to have smoked marijuana for 1 week (unknown frequency) before his admission to the emergency department. The authors suggest that exposure to synthetic CB products led to rhabdomyolysis and AKI.[34]

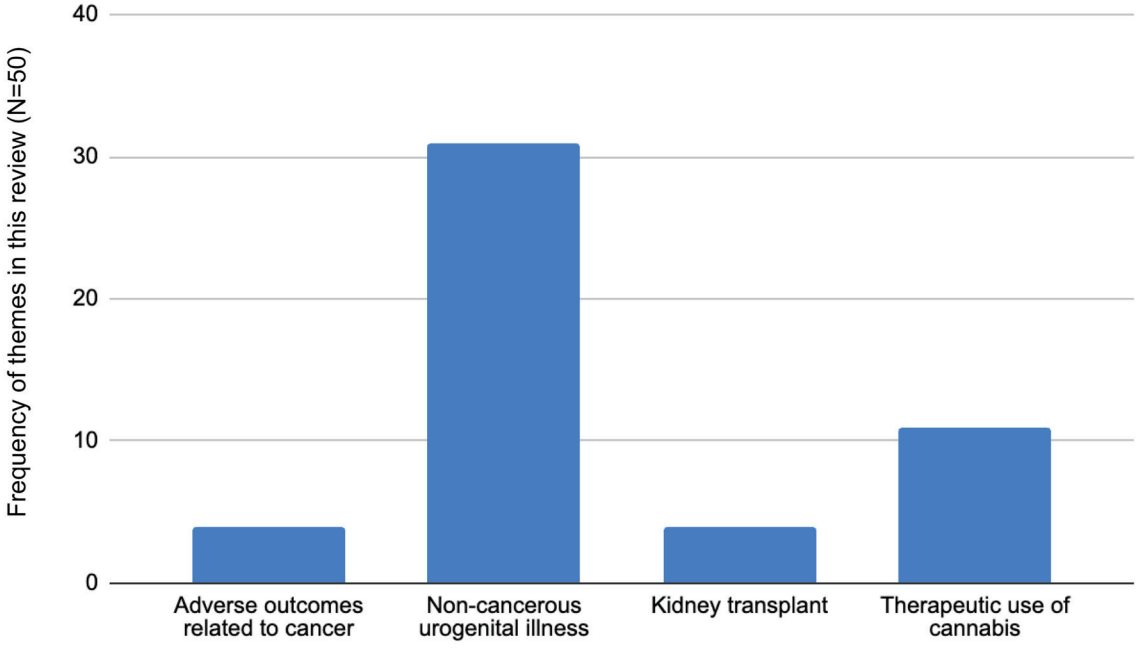

Fig. 4. Frequency of themes in this review (*n* = 50).

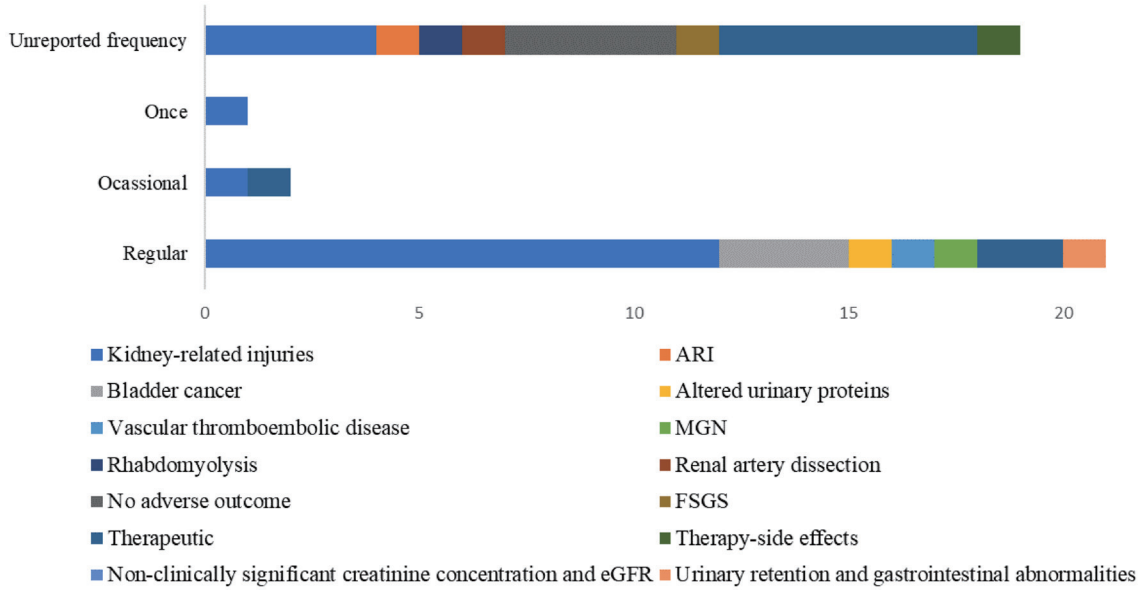

Fig. 5. Reported frequency of cannabis usage and the resulting outcomes in each study. ARI, acute renal infarction; FSGS, focal segmental glomerulosclerosis; MGN, membranous glomerulonephritis.

Another case report by El Zahran *et al*.[35] of a 29-year-old male concluded that the use of synthetic CBs can result in hyperthermia, rhabdomyolysis, and renal failure. Jindal *et al*.[36] brought forward a case of a 21-year-old male who consumed synthetic cannabis and experienced mild renal dysfunction. El Zahran *et al*.[35] highlighted the case of a 29-year-old patient who experienced rhabdomyolysis and renal failure following the use of a synthetic CB roughly anywhere between 3 weeks, with missing information on use frequency before showing up in the hospital.

Other case reports have stated that any form of CB intake would increase one's risk of kidney-related illnesses.[29,37–39] A case report on a 31-year-old healthy patient by Esprit *et al*.[37] inferred that using cannabis pills with unreported frequency can be associated with a risk of developing ATI. Lambrecht *et al*.[29] reported on a case study of a 29-year-old man who reported being a regular smoker of marijuana for the last 10 years. The authors suggested that constant exposure to marijuana led to the development of ARI.[29] Al-Hwiesh *et al*.[38] presented a case report of a 34-year-old male who reported using marijuana roughly 4 times a week, and it was found that using cannabis regularly can be related to the risk of ARI. Lou *et al*.[39] highlighted a case of a 32-year-old heavy daily cannabis user with unspecified frequency of cannabis use who experienced a spontaneous renal artery dissection.

A case study by Chang *et al*.[40] presented a 50-year-old man who was reported to have smoked cannabis regularly with unreported frequency for the last 3 years before his first emergency department visit. The authors noted that regular exposure to cannabis may have been attributed to severe AKI and metabolic alkalosis.[40] A case report by Patil *et al*.[41] on an 18-year-old male who was experiencing marijuana addiction suggested that single use of synthetic marijuana use could have led to AKI. Nedumaran *et al*.[42] compared the urine of cannabis users who smoked cannabis at a frequency of 5 times daily over the past 12 months and healthy controls; a total of 19 urinary proteins were found to be significantly altered in cannabis users. These proteins have a variety of roles, including tumor suppression, immune response, and metabolism.[42] In a study conducted by Lu *et al*.,[43] the researchers assessed adults who smoked marijuana once in the past 30 days from the National Health and Nutrition Examination Survey data and found an association between marijuana use and serum creatinine concentration and estimated glomerular filtration rate (eGFR). However, this was not clinically significant. A cohort study by Alvarado *et al*.[44] evaluated the longitudinal association of marijuana users with unreported frequency and adverse kidney outcomes and found that there was no adverse effect between cannabis use and reduced kidney function. Ishida *et al*.[45] assessed the long-term use of marijuana. They found that the use of marijuana was not significantly associated with a change in eGFR, swift eGFR decline, or albuminuria.

A case study reported by Farouji *et al*.[46] described a 44-year-old female who reported using cannabis actively and also reported having used it 1 day before the onset of symptoms. She was already at risk of vascular thromboembolic disease, and it was suggested that cannabis use could have led to a rare ascending aorta thrombosis complicated with stroke and bilateral renal infarcts.[46]

Burton *et al*.[47] presented a case study of a 55-year-old man with lower back pain who was reported to have smoked cannabis daily with unreported frequency for at least 5 years, in addition, he also reported using cannabis butts 6 times in the past 2 years. The authors strongly suggested a correlation between the inhalation of cannabis and the development of urinary retention and gastrointestinal abnormalities.

However, some studies found no association between cannabis use and AKI risk or any negative impact on kidney function. A study on the impact of cannabis use in patients with CKD by Potukuchi *et al*.[48] found that cannabis use with no specific frequency was not associated with AKI risk. A similar study carried out by Rein *et al*.[49] with patients who consumed cannabis with no reported frequency, with and without CKD, found that in patients without CKD, cannabis consumption did not have a negative impact on kidney function; however, for those with CKD, cannabis consumption was associated with a faster annual eGFR decline.[49] A case report by Hernandez *et al*.[50] of a 59-year-old patient highlights that recreational cannabis use—without mentioning frequency—may be an important factor in the development of secondary focal seg-

mental glomerulosclerosis in CKD patients. However, Bonnet *et al*.[51] assessed the long-term frequent cannabis use with a median consumption rate of 2.5 g daily for the past 36 months and its relationship to serum CB levels. Their study found no statistically significant association between the participants' GFR and cannabis use.[51]

Implications related to kidney transplant

Ruckle *et al*.[52] studied the impact that marijuana use has on living kidney donors and their recipients. Participants self-reported marijuana use, and to be considered a user, participants could not have just sampled or had a CB-positive drug screen. It was found that there were no differences in peri- or post-operative characteristics of outcomes based on the donor's marijuana use.[52] Fabbri *et al*.[53] assessed if marijuana use should be a factor involved in the consideration of kidney transplantation. Marijuana use was conceptualized as any self-reported marijuana use within 5 years before transplant. Their study found that dual marijuana and tobacco users and tobacco-only users had a significant risk of graft loss; however, isolated users of marijuana did not face the same risk for graft loss.[53] Shrivastava *et al*.[54] evaluated people who were in the process of undergoing kidney transplants; they found that people with kidney transplants who use marijuana do not face additional risks of morbidity or mortality. It was unclear how this study defined marijuana users.

Bohatyrewicz *et al*.[55] presented a case report of a man with a kidney transplant who developed *de novo* post-transplant membranous glomerulonephritis. The man had experienced marijuana use disorder for 10 years. They suggested this patient's membranous glomerulonephritis may have been associated with his extensive marijuana use.[55]

Therapeutic use of cannabis

Brady *et al*.[56] conducted an experimental study on the use of cannabis-based extract sprays for bladder dysfunction in advanced multiple sclerosis. A dosage of 2.5 mg of CBD per spray was used for 8 weeks, followed by 2.5 mg of tetrahydrocannabinol-only per spray was used for another 8 weeks. It was concluded through patient self-assessments of pain, that spasticity and quality of sleep improved significantly.[56] Similarly, Kim-Fine *et al*.[57] evaluated multiple sclerosis patients with bladder symptoms and found various modes of cannabis consumption to improve bladder frequency, urgency, incontinence, and emptying. The frequency of cannabis consumption was not specified. Torri Clerici *et al*.[58] assessed the use of tetrahydrocannabinol and CBD oromucosal spray on patients with multiple sclerosis dysfunction in a non-randomized experimental study. Duration and use of the sprays were not provided in the study. Specifically, they used the overactive bladder symptom score and a variety of objective parameters, such as bladder compliance and maximum detrusor pressure.[58] The spray was discovered to show significant improvements in subjective urinary urgency and objective urodynamic parameters.[58] Anderson *et al*.[59] researched patient perspectives on CBs for interstitial cystitis/bladder pain syndrome and noted that respondents found them beneficial for their symptoms with mild side effects. Information on frequency use was not presented in the study. Mathur *et al*.[60] studied the use of cannabis sativa for 1 week, 3 times a day, as a homeopathic treatment in the management of recurrent urinary tract infections for males and females. They found it to be an effective treatment for the infections. Kasman *et al*.[61] found that cannabis use improved sexual function among females. The majority of the sample population reported cannabis use 6 or more times per week. Samaha *et al*.[62] investigated the use of cannabis among adult patients with a history of end-stage kidney disease treated with hemodialysis, peritoneal dialysis, or a combination of both. Half of the patients noted an improvement in their restless leg syndrome and uremic pruritus symptoms.[62] Dosage and frequency used were not provided.[62] Desai *et al*.[63] researched cannabis use in geriatric patients with CKD and its association with septic shock and mortality. It was found that cannabis use, although frequency was not reported, did not affect the risk of developing septic shock but was associated with a significantly lower inpatient mortality rate.[63] Surveys conducted by Collister *et al*.[64] on Canadian adults with CKD and kidney failure found that smoking, consuming edibles, and oil treatments alleviated their symptoms, such as pain, sleep, and restless leg syndrome. Once again, the frequency of use of cannabis products was not reported in the study.

Battle *et al*.[65] highlighted that patients with RCC who were undergoing systemic therapy and used marijuana or CBD oil (unknown frequency) had a higher likelihood of experiencing therapy side effects that were bothersome. Moreover, these patients were less likely to discuss the after-treatment effect of cannabis situation with their doctor.

Capodice and Caplan[66] studied the human endoCB system, cannabis, and CBD, and their implications in urology and men's health in various health-related case studies. Through various reviews, they concluded cannabis to be a potential treatment for urinary tract symptoms. Still, cannabis may have implications on the male reproductive system, including being a risk factor for testicular germ cell tumors.[66] Frequency of use varied among participants, including weekly or more than weekly, chronic, and frequent use.

Discussion

This scoping review has outlined some impacts that cannabis use can have on the GU system; many of studies analyzed were case reports. There are a variety of hypothesized acute and chronic GU system impacts associated with cannabis use. For example, some of the acute health impacts include AKI and urinary retention. Interestingly, the effect on urinary retention and improvement in lower urinary tract symptoms indicates the normal duality of the medications we use to treat these symptoms and is encouraging for a possible therapeutic benefit in further testing. Spontaneous renal artery dissection, CHS, and potentially increased risk of urothelial carcinoma of the bladder may be associated with chronic use of cannabis. However, there are certainly confounding variables, such as the type of cannabis and other health conditions, that are important factors to consider. Furthermore, in certain populations with CKD, cannabis use was associated with secondary focal segmental glomerulosclerosis and a rapid decline in kidney function. It is important for us to understand better the broad impact cannabis use has on the GU system, especially because the use of cannabis is now becoming legalized in various countries, such as Canada, Uruguay, and some USA states.[67] As cannabis consumption continues to become legalized, it is necessary for policy around cannabis use to be on the same page as the established GU health impacts of cannabis consumption.

Our review underlines the diverse implications of cannabis use on the GU system, emphasizing the need for more proactive measures in clinical settings. Based on our findings, we suggest the following potential guidelines:

1. Regular screening for cannabis use as part of history-taking may be beneficial;

2. Clinicians should consider cannabis use as a potential factor in unexplained GU symptoms or conditions;
3. Regular monitoring of cannabis users, particularly those with underlying GU conditions, may be beneficial;
4. Tailored advice and interventions may be needed for patients. Specifically, urologists may consider establishing regular screening to understand if patients are actively using cannabis and to provide evidence-based guidance. Urologists may consider asking patients directly about cannabis use when taking a lifestyle history. Regular monitoring of kidney function may be warranted through assessing eGFR and microalbuminuria and may be beneficial for users of cannabis, specifically those with CKD. Furthermore, if a patient discloses cannabis use, urologists can provide guidance on the risks associated with cannabis use. For example, urologists can suggest that the current evidence highlights mixed findings on the association of cannabis use with cancer. However, there is some limited evidence that suggests cannabis use is associated with urogenital illnesses such as AKI and CHS. It is important to note that these claims have no biological plausibility.

One particular type of cannabis that has arisen in popularity in recent years is synthetic cannabis. Our scoping review has highlighted some of the negative impacts associated with the consumption of synthetic cannabis. Specifically, our review brings forward several reports that found the consumption of synthetic cannabis was associated with ATN, ATI, AKI, and rhabdomyolysis. This is of concern, especially because synthetic cannabis is often marketed to young people as natural and harmless.[9] Hence, users may not fully understand the harms that can be associated with synthetic cannabis products. Therefore, urologists must have direct discussions with their patients who use cannabis and clarify the type of cannabis products their patients use. If it is discovered that patients are using synthetic cannabis, a collaborative discussion around the established harms associated with synthetic cannabis on the GU system should take place.

The majority of participants involved in the studies reported chronic cannabis usage was associated with the emergence of AKI. Additionally, regular consumption has been linked to the occurrence of ATN and ARI. Notably, certain studies observed that even occasional or isolated instances of cannabis use resulted in kidney-related injuries as highlighted in Figure 5. However, these occasional uses were also noted to have therapeutic benefits (Fig. 5).

Considering kidney transplants in relation to cannabis use, the findings from this review suggest that cannabis use may not be a contraindication to receiving a kidney transplant. Our findings highlight that isolated marijuana use was not associated with an increased risk of graft loss in kidney transplant recipients.[52–54] Many healthcare professionals may be exposed to misinformation regarding cannabis use and receiving an organ transplant.[68] Moreover, the literature highlights that patients have been denied receiving an organ transplant because of their cannabis use.[68] Ultimately, our findings suggest that isolated cannabis should likely not be a contraindication for receiving a kidney transplant.

While it was previously believed that the CB_1 and CB_2 receptors are mainly distributed in the central nervous system and immune system, recent research indicates that these receptors may play a significant role in the GU system, including renal homeostasis and function.[69,70] *In vitro* and *in vivo* studies have provided evidence that CB_1 and CB_2 receptors are located throughout the kidneys and involved in renal hemodynamics, tubular sodium reabsorption, and protein extraction in urine.[69] This occurs through the binding of two important CB_1 and CB_2 endogenous ligands, anandamide and 2-arachidonoyl-sn-glycerol.[69] In murine models, the binding has been shown to decrease glomerular filtration rates, and inhibit Na+/K+ transporters and Na+/K+/2Cl- co-transporters.[69] Although these ligands are found in normal amounts in the body, the high-affinity binding of synthetic CBs to CB_1 receptors has been shown to increase the activation of mitogen-activated protein kinase, leading to cell death, inflammation, and oxidative/nitrosative stress.[71] While these mechanisms are believed to contribute to the development of various renal diseases, this review also aims to highlight the potential therapeutic uses of cannabis. For example, the specific constituents of cannabis may play a role in the treatment of urinary tract infections, improvements in interstitial cystitis, bladder pain syndrome, urinary dysfunction, sleep, pain, sexual function, restless leg syndrome, and uremic pruritus. This new understanding suggests that these receptors may have the potential to be therapeutic targets, which warrants further investigation in the future. The presence of CB_1 and CB_2 receptors in the lower urinary tract has helped us to understand the effect of cannabis in treating dysfunctional voiding. Case reports suggesting urinary retention provide corollary support for this hypothesis, as this is seen with other medications that reduce detrusor overactivity (anticholinergics and beta-3 agonists). Moving forward, further research is necessary to understand the pharmacology behind the CB receptors and how the distribution of these receptors within the GU system can be utilized by various therapeutic agents while also minimizing any adverse side effects that patients can experience. Specifically, research on pharmacological agents that bind selectively to the CB_1 and CB_2 receptors within the GU system may have applications in treating various GU diseases.

In the future, longitudinal studies are needed to better understand the long-term impacts of cannabis use on the GU system. Data from these long-term studies may help provide more clear data on cancers associated with cannabis use. These data may also provide a more holistic perspective on chronic urogenital illnesses associated with cannabis use. In addition, long-term data can also be useful for patients who receive renal transplants, as we can better understand the long-term impacts of cannabis use for these patients. Furthermore, as suggested, data on the potential of cannabis-based pharmacological agents collected through randomized control trials can help assess therapeutic impacts and adverse effects.

There are several limitations to this scoping review. First, the majority of data are from case reports and case series (52%). Thus, the quality of evidence we are including is generally low compared to studies looking exclusively at high-quality randomized control trials. Research on the GU impacts of cannabis is unraveling and this may contribute to the lack of available data. Inherent to the design of a scoping review, we did not conduct a quality assessment; therefore, the quality of many studies varied, and many potential confounding variables were not controlled for. Some of these case reports, or series included more participant information than others, and factors such as family history, medication use or history of medication use, comorbidities, relevant previous illnesses, or current underlying illness could all potentially contribute to the patient's visit and influence the diagnosis by their health provider. In several cases, patients consumed tobacco in addition to cannabis, and tobacco use has also been shown to impact the GU system negatively. There were also some inconsistencies in the findings of different studies on the same topic. In regards to the impact of cannabis use on eGFR, some studies found cannabis use had a negative impact on lowering eGFR in patients with CKD[49] while others found no association between the two.[51] It is important to note the distinction between synthetic CB use

and natural cannabis use, as the existing literature seems to suggest that synthetic CB has a more significant negative impact on kidney and reproductive health, but some studies do not specify the type of cannabis used which may have resulted in an inconsistency in findings. Also, many of the studies (n = 20) did not report on the frequency of cannabis use. Therefore, future studies should aim to describe the frequency of marijuana use, so that associated health outcomes can be discussed. Data sources were limited to the databases we searched, namely Embase, Medline, and Web of Science. Thus, data outside of these databases were not included in this review. We also did not look for any unpublished research that could potentially be useful in our study. Also, there is no evidence regarding which routes of administration may be associated with positive or negative GU effects, as one would hypothesize smoking would have the highest risk of negative effects. Thus, research on different administration routes and GU outcomes is needed. Finally, while we propose potential clinical guidelines, further evidence is required before the creation as no strong correlations can be drawn from current evidence, and their applicability needs further validation through rigorous experimental studies and trials.

Future directions

Moving forward, future studies evaluating the long-term GU health outcomes associated with cannabis use are needed. Moreover, there is a need to determine if there is an association between cannabis use and GU malignancies. This is essential as the current data highlight conflicting perspectives. Finally, although there are potential therapeutic applications of cannabis for various GU health conditions, well-designed randomized control trial data are needed to evaluate the efficacy and safety of these potential therapeutics.

Conclusions

In conclusion, this scoping review has synthesized data on the impact that cannabis use has on the GU system. Synthetic CBs may be linked to AKI and other urogenital illnesses, highlighting potential health risks. However, the impact of cannabis on urogenital health is complex, with emerging evidence indicating a therapeutic role in certain urological conditions. Data from this review supports the notion that cannabis use should not be a contraindication for receiving a kidney transplant. Moving forward, additional rigorous, long-term research is needed to understand the true impact that cannabis has on the GU system.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/JERP.2023.00057.

Fig. S1. Search strategy on Medline.

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Conflict of interest

Dr. Lea Lough is a consultant with GeneCentrix, Inc. Otherwise, the authors declare they have no conflict of interest to disclose relevant to the content of this paper.

Author contributions

Contributed to study concept and design (NB and JH), acquisition of the data (NB, DL, RV, QT, SR, MA, PK, LL, AN, MR, XRZ, DH, MM, VM, and JH), data analysis (NB, DL, RV, QT, SR, MA, PK, LL, AN, MR, XRZ, DH, MM, VM, and JH), drafting of the manuscript (NB, DL, RV, QT, SR, MA, PK, LL, AN, MR, XRZ, DH, MM, VM, and JH), critical revision of the manuscript (NB, DL, RV, QT, SR, MA, PK, LL, AN, MR, XRZ, DH, MM, VM, and JH), and supervision (LL, DH, MM, VM, and JH). All authors have contributed significantly to this study and approved the final manuscript.

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