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The evolution of recommendations for cranberry use in recurrent urinary tract infections: A systematic review

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Abstract. *Urinary tract infections (UTI) constitute a major complaint in medical offices worldwide, especially concerning women. Although the efficacy of cranberry in UTI prevention is still controversial it has long been recommended for use in clinical practice. Based on the recommendation evaluation, the present study aimed to conduct a systematic review to assess the efficacy of cranberry prophylaxis in recurrent UTIs in women. Main changes among reviewed publications revolved around the mechanism by which cranberry produce the results observed and once it was established that it relates to bacterial fimbriae-mediated adhesion, most authors now struggle to establish accurate measures to come up with a protocol for its use. Many studies compared cranberry effects to placebo and traditional antibiotic treatment and showed promising results about effectiveness, as well as economic drawbacks. Altogether, cranberries could help to delay ecological resistance to antibiotics as well as protect patients from infections. Further investigation, mainly regarding dosage, is needed to formulate protocols and safely introduce cranberries to clinical practice*

Key words: *cranberry, prophylaxis, recommendations, urinary tract infection.*

Conflict of interest statement. The authors declare no competing interest.

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Еволюція рекомендацій щодо використання журавлини у жінок з рецидивуючою інфекцією сечової системи: систематичний огляд

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Резюме. Інфекції сечової системи (ИСС) є основною скаргою в медичних установах усього світу. Хоча ефективність журавлини для профілактики ИСС все ще викликає суперечки, її вже давно рекомендують для використання в клінічній практиці. На основі оцінки рекомендацій це дослідження було спрямоване на проведення систематичного огляду для визначення ефективності профілактики журавлиною у хворих на рецидивуючі ИСС. Основні зміни серед розглянутих публікацій стосувались механізму, за допомогою якого журавлина дає спостережувані результати, і як тільки було встановлено, що це стосується бактеріальної адгезії, опосередкованої фімбріями, більшість авторів зараз намагаються розробити протокол її використання. Багато досліджень порівнювали ефект журавлини з плацебо та традиційним лікуванням антибіотиками та продемонстрували багатообіцяючі результати щодо ефективності та економічної обґрунтованості. Загалом, журавлина може допомогти відстрочити резистентність до антибіотиків та захистити пацієнтів від інфекцій. Проте, щоб сформулювати протоколи та безпечно запровадити журавлину в клінічну практику, необхідні подальші дослідження, головним чином щодо дозування.

Ключові слова: журавлина, профілактика, рекомендації, інфекція сечової системи.

Introduction. Currently, urinary tract infections (UTI) constitute a major complaint in medical offices all around the world especially concerning women [1], more specifically the elderly, disregarding the presence or absence of structural alterations [2]. It is estimated that 10% of women will have at least one UTI episode per year and around 50-70% have had or will have at least one episode in their lifetime [1, 2] being 20% the chance they will have at least one recurrent episode within a month of the previous [2-4]. Classically, UTIs are differentiated between those acquired in the community and those acquired in hospital facilities (nosocomial), being *Escherichia coli* the most important pathogen, responsible for approximately 85-95% of uncomplicated cystitis cases and more than 90% of uncomplicated pyelonephritis in post-menopause women [5]. It is not only prevalent but also expensive since estimates point out that the spending due to UTIs reached 2.3 billion dollars in the US, making it an important public health issue [2, 3].

A patient is defined as having recurrent UTI when two episodes happen within 6 months, or three episodes happen within a year [6]. Numerous factors are correlated to the recurrence of UTI, the most noticeable being: frequent sexual relations, spermicide use, previous

episodes of UTI when the younger, maternal history of UTI and recent antimicrobial use [2]. Although two episodes in 6 months are enough to establish the recurrent UTI diagnosis, it is usual for these recurrences to happen after two weeks from the first symptom outbreak, being much more common than two chronologically unrelated episodes within 6 months [2, 5, 7]. It is also well-known that a woman who has had at least two UTI episodes within 6 months has as little as a 33% chance of remaining infection-free in the following 6 months [3, 8].

Concerning UTI treatment, antibiotic therapy is traditionally recommended, more specifically nitrofurantoin for 5 days and sulfamethoxazole-trimethoprim for 3 days [9]. Fluoroquinolone for 3 days tends to present more often adverse effects but could be used as an alternative to the mainline drugs [10]. Furthermore, there are other treatment options from the association of drugs to extending the therapy span depending on the patient's condition and medical policy [3]. In recurrent cases, the prescription of other classes of antimicrobial drugs is usual in prolonged use, lifestyle changes, oral and vaginal estrogen reposition for peri-menopause women [11]. Among all these usual alternatives the most efficient is antimicrobial drugs [2]. Despite its efficiency, it is crucial to note possible adverse effects of drug use, such as antibiotic resistance, which seems to raise demand for new preventive solutions [2, 6].

Amidst the main problems associated with the prolonged use of antibiotics, we could enumerate bacterial resistance and native bacterial flora destruction [12, 13]. A key issue with traditional treatment relies on the increased prevalence of isolated antibiotic-resistant *Esch-*

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erichia coli, the most prevalent uropathogen [12, 14]. Empirically or prophylactically prescribed antibiotics are currently regarded as the economically better means to control these infections, although the prescription without the lab diagnosis confirmation or pathogen culture isolation contributes to the bacterial resistance issue, which is a major problem in primary care [15]. It is shown that the use of antibiotics is directly correlated with uropathogen resistance, which corroborates the importance of new preventive and curative methods in UTI [5].

To minimize long-term antibiotic-related damage to the patients under this regimen, a new prophylactic treatment was created. At first, therapy consisted of 2mg trimethoprim for 12 months, usually associated with 10mg sulfamethoxazole [9]. The problems of long-term antibiotic use - as efficient as it was - outnumbered the benefits [16, 17]. From 1998 on, the first recent studies regarding Cranberry (*Vaccinium macrocarpon*) as a prophylaxis agent for recurrent infections were conducted [18]. Initially, the studies were seen as controversial, but further investigation and new hypotheses were followed by favorable recommendations for its efficiency and use as prophylactic therapy for recurrent UTI [9].

Because of the recent discoveries on the subject and its relevance to medical practice worldwide, we conducted a systematic literature review to analyze the development of understanding and recommendations that followed cranberry's role as recurrent UTI prophylactic agent, from the beginning of cranberry therapy up until the articles that suggested the current recommendation and its theoretical basis.

The following review considered population as women with recurrent UTI episodes, control as usual therapy without cranberry or placebo and the outcome as presence or absence of reinfection. Article research was conducted on PubMed, Scielo, Science Direct and Medline bases. The following keywords were used: "urinary tract infection", "cranberry", "prevention", as well as its equivalents in Portuguese. Boxes "AND" and "OR" were selected when they were present.

Enters and records identified in the electronic data banks were exported to the platform Rayaan, used in selection. Studies were initially filtered by title and abstract independently by two reviewers of our researchers. Those selected on a first filtration were evaluated regarding eligibility and inclusion in this review by full-text analysis.

Articles reviewed by two researchers which presented adult women cases of uncomplicated recurrent UTI and used cranberry as prophylaxis or not were included. Articles of opinion and reviews, observational studies, case reports, complicated UTI studies and isolated episodes were all excluded, as well as those who related the infection with any prosthesis presence. Articles were not excluded based on language, date, or place of conduction.

Eligible studies were again evaluated based on the recurrence of symptoms, prophylactic therapy use with or without cranberry and outcomes with new episodes.

Urinary tract infection and women susceptibility.

Women seem to be more susceptible to urinary tract infection due to a relative shortening of the urethra [3], the proximity of the urethral meatus to the anus and a moist peripheral ambient comparatively to masculine anatomy [4, 5].

Other than female sex as a risk factor for the infection development, there is a higher incidence related to genetic patterns, old age, menopause, urogenital dysfunction and pelvic surgery, which are individually investigated [10].

Children's prevalence rate varies from 2.1% to 8.7%, on account of age, sex and circumcision. Uncircumcised men aged 53 weeks old have an overall higher prevalence of UTI (20.1%) but the prevalence among men rapidly decreases after the first year of life, whereas there is a notably high feminine rate [2, 3]. Excluding the first 8-12 weeks when infections could be secondary to a hematogenic condition, UTI result from ascending infections and are usually mono-microbial, often due to Gram-negatives, such as *Klebsiella*, *Proteus*, *Enterobacter*, *Pseudomonas* and *Serratia species*.

Concerning menopause, the feminine genital tract, the urinary tract and perineal support tissue share an embryologic origin and that should explain why those tissues are usually sensitive to steroid sex hormones. Consequent to the estrogen privation, reduced tissue resistance develops atrophy of the urogenital tract during menopause, which results in a predisposition to trauma and infection from previously better-isolated microbes.

The main procedures correlated to urogynecological infections are sling and auto catheterization [6]. Up to 90% of gynecological surgery patients have indwelling catheters during the postoperative period, and up to 20% have postoperative UTI, majorly due to *Escherichia coli* as the main isolated pathogen [7, 8].

Non-antibiotic prophylaxis is even more important in such groups, given the high recurrence rates and to which recurrent antibiotic use tends to develop the adverse effects previously indicated.

Bacteria and UTI. Various virulence factors allow *E. coli* cells to colonize urothelial mucosa selectively, producing inflammatory reactions that could eventually lead to infection spread towards cavities and renal tissue [2]. Among the factors, colonization ones called adhesins are crucial for the infection's success. *E. coli* adhesins are mainly fimbriae-mediated, capable of adhering to allow colony growth of epithelium surface. Practically all uropathogenic *E. coli* (UPEC) are capable of expressing a specific lectin-associated mannose, which is by its turn associated with type 1 fimbriae and constitutes the main mechanism by which bacteria colonize uroepithelial cells [2].

Cranberry mechanism hypothesis and results.

Diet consumption of Cranberries has long been associated with urinary tract health promotion [19]. The first record of a hypothesis as to why those factors are related is commonly attributed to a 1914 study by Dr.

Blatherwick, who stated that cranberries, as well as prunes, are rich in benzoic acid, which is combined with glycine in urine resulting in hippuric acid formation, which acidity could prevent infections [20, 21]. Corroborating Blatherwick's hypothesis, studies published between 1920 to 1970 suggested that urine acidification was the mechanism by which cranberry juice produces bacteriostatic effects *in vitro* [22, 23] while further investigations in 1975 and 1978 showed inconclusive results about urine acidification secondary to cranberry ingestion [24, 25].

The controversy brought up by these studies' results compelled authors to suggest that cranberry products' role was not evidence-based and were obscure in comparison with antibiotics [26]. Even in essays where cranberries lead to lower infection establishment rates than placebos, the concentration, dose, use span and many other intervention parameters were not clear [12].

However, recent studies explored an alternative mechanism by which cranberry could protect the urinary tract from infection focused on bacterial adhesion inhibition on the mucous surface, instead of pH variation [27]. As stated, almost all uropathogenic *E. coli* are capable of expressing a fimbriae-1 lectin-associated mannose, which consists of its main colonizing factor called 'fimbrial adhesins', pili mediated cell-anchoring proteins capable of adhering and growing on the epithelial surface [28, 29].

Zafiri et al. found two components of cranberry juice capable of inhibiting this molecular base for adhesion in *E. coli* cells: fructose and proanthocyanidin [15], which corroborates the Sobota and Schmidt previous study that not only states cranberry juice effectiveness but found that the urine of rats fed with cranberry replenished *E. coli*'s uroepithelium adhesion rates up to 80% [27].

Fructose is a component of many juices that shows type I pili-mediated adhesion inhibition and anti-adherence properties of proanthocyanidin was demonstrated in human erythrocytes and suppression of P-receptor resin granules agglutination when incubated with P-fimbriated *E. coli* [30].

Current prophylaxis. Prophylaxis is currently prescribed to recurrent UTI (rUTI), prevalent in women, as Nitrofurantoin, trimethoprim (or cotrimoxazole) and fosfomicin trometamol as first-line drugs. Oral cephalosporins and quinolones should be restricted to specific indications. Antibiotic prophylaxis reduces the number of uropathogens in the gut and/or vaginal flora and reduces bacterial "fitness". Given the correct indication, the recurrence rate of rUTI can be reduced by about 90% [31].

Cranberry vs. standard drugs. A study published in 2007 conducted a meta-analysis of randomized controlled trials and found that cranberry products importantly reduced the incidence of symptomatic UTI over a year (RR 0.66, 95% CI 0.47-0.92) in comparison with placebo or control, particularly in women with rUTI [32-35].

Other studies concerning cranberry prophylactic effects by Kontiokari [35] showed a 22% reduction of rUTI episodes following cranberry use, while Bailey [36] found no patient presenting UTI after 12 weeks of cranberry prophylactic use. McMurdo [34] also concluded that the hypothesis of cranberry as a symptomatic UTI reduction agent was reasonable in elderly patients. Stapleton [29] showed a 68% reduction in UTI on a case-control study of cranberry vs. placebo. Foxman [16] explored a double-blind placebo with a UTI risk group of patients consisting of women who have had scheduled gynecological procedures with catheter use and found 50% fewer cases on patients who used cranberry capsules. Hess [37] found UTI reduction on another cranberry versus placebo among 47 patients presenting spinal damage and neurogenic bladder after 6 months of therapy with cranberry.

There was also an inconclusive study conducted by Barbosa-Cesnik [16], where 31 out of 155 patients presented UTI even after cranberry use versus 23/164 on the control group, suggesting cranberry wouldn't have such an impact on UTI prevention as previously thought. A methodological limitation found on the majority of the studies we compiled consisted of high remission rates, which were above 50% on some studies [38], mainly on those which lasted between 6 and 12 months. The reason claimed by researchers is that women who had recurrent episodes were less likely to continue their participation. Stothers reported that the concentrated cranberry capsule could present favorable results on patient remission instead of cranberry juice, reaching the same prophylactic effect [32]. In spite of dosage establishment limitations, posological form and case-control grouping methods, it seems reasonable to admit that many studies' results point to a beneficial effect of cranberry as a prophylactic diet supplement in uncomplicated recurrent UTI patients [39].

Cochrane database and SIGN guideline 88 stated that a head-to-head trial of cranberry versus low-dose antibiotic prevention of recurrent UTI was required because the previous placebo-controlled trials had demonstrated effectiveness for both, and the effectiveness of antibiotic therapy being considerably superior [40]. To meet that demand, McMurdo [34] conducted the head-to-head trial with predominantly elderly women and concluded that the chance of UTI recurrence while using cranberry versus low prophylactic trimethoprim doses was around 60%, which is not statistically significant. Antibiotic treatment assured less than 7 days (mean) without UTI manifestation. Recurrence was very similar in incidence with cranberry (16%) and trimethoprim (12%). That study concluded that trimethoprim had a very limited advantage over cranberry extract in the prevention of recurrent UTIs in older women and had more adverse effects, as in the risk of antimicrobial resistance or superinfection with *C. difficile* or fungi.

Beerepoot's [11] study also compared the effect of cranberry as opposed to TMP-SMX as prophylaxis

to UTI, measuring bacteriuria periodically. After one month, 22 of the 83 women in the TMP-SMX group (26.5%) and 32 of the 89 women in the cranberry group (36.0%) had asymptomatic bacteriuria. At 12 months, these percentages were 30.2% (16 of 53) and 37.0% (17 of 46), respectively.

But even more important than the similar results found, high resistance rates were noted as soon as 1 month after TMP-SMX prophylaxis use. In addition to TMP-SMX resistance, there was also an increase in resistance to amoxicillin and quinolone during the use of TMP-SMX prophylaxis. Thus, it seemed reasonable to conclude from the trial group that TMP-SMX (480 mg once daily) is more effective than cranberry capsules (500 mg twice daily) for the prevention of rUTIs. However, this should be weighed against the greater development of antibiotic resistance.

An economic analysis of the issue, also conducted by Stothers [32] showed that the cost of cranberry therapy is extraordinarily high so there is no cost/benefit advantage in comparison with TMP-SMX prophylaxis since cranberry was less effective and more expensive. Cranberry dosage seems to be the most obscure topic concerning the theme. Only Howell's [38] study, a multi-center randomized paper conducted on sexually active women was conclusive on the matter. It points towards ≥ 36 mg daily dose as sufficient to produce an ideal antibacterial effect on urine analysis. One other study compared doses inconclusively [41].

Changes in knowledge and recommendations on the use of cranberry for prophylaxis of repeat UTI among the years are presented in Table 1.

Table 1

Changes in knowledge and recommendations on the use of cranberry for prophylaxis of repeat UTI among the years

Time	Recommendations
1914 - 1978	Empirical knowledge stated that cranberry could act as prophylaxis to recurrent UTI through urine acidification.
1978	First refutation was published to the acidification hypothesis.
1989	Cranberry effect was first described as an inhibitor of bacterial uroepithelium adhesion. From this date, such hypotheses have been considered truthful with further discoveries adding information to why that is, concerning protein receptors and biochemical interaction of bacterial adhesion and cranberry compounds.
2006	Cranberry's adhesion inhibition was tested a few times, mostly in vitro. From this year on, studies began exploring cranberry's effects on human urine after fruit consumption and some hypotheses suggested the result to be dose-dependent. Clinical prophylactic use of cranberry on recurrent UTI patients was not recommended and subject to controversy.
2007	Clinical trials were conducted showing a significant reduction of UTI incidence in women after twelve months of treatment in comparison to placebo (RR 0,61; IC 95%: 0,40–0,91). The study that compiled the clinical findings was the first record of an alternative to fruit consumption, suggesting results could be different using cranberry pills and cranberry juice, but those proved to be insignificant.
2008	New studies' results were similar to the ones from the previous year. Cranberry products reduced significantly symptomatic UTI incidence in twelve months in comparison to placebo or control (RR 0,66, IC 95% 0,47-0,92). A new study brought light upon administration mean comparison, but efficacy was inconclusive due to treatment discontinuity. Regarding treatment adhesion, pills showed better prospects than juice. The minimum dose value for efficiency was still unclear despite prior claims to its importance to protocol establishment. A breakthrough concerning dosage was reached by discovering anti-adhesion activity of cranberry juice ingestion against fimbriated E. coli lasting up to 10 hours, suggesting a reasonable trial should consider juice consumption at least twice a day.
2009	Cranberry was usually tested against control or placebo, but then trials began comparing cranberry to antibiotic therapy with trimethoprim. These studies showed the drug to be more efficient in absolute numbers to cranberry in preventing UTI, although the results were not statistically significant. Drawbacks in long-term drug use were listed extensively, mainly regarding adverse reactions, ecological bacterial resistance and price of treatment.
2010	Studies were published investigating whether other natural substances similar to cranberry substances could have the same effect on UTI prophylaxis. Vitamin C and other oxycoccus were tested, but other fruit showed virtually no effect. One substance was confirmed to be important in cranberry's effect: proanthocyanidin. Cranberry was also associated with many products endeavoring to find synergy, and a relevant finding was published associating oral cranberry with vaginal probiotics, resulting in better efficiency than placebo as well as the two isolated mono-therapies.

Continuation of Table 1

Time	Recommendations
2011	Some studies published in 2011 further investigated whether cranberry or antibiotic had a better prophylactic action regarding many factors. The most prominent studies concluded trimethoprim was more effective, although the difference between them was not expressive, the numbers being 20.2% of women on trimethoprim presenting asymptomatic bacteriuria against 37% of women on cranberry therapy.
2012	Beyond efficacy, studies discussed collateral effects of cranberry treatment, ranging from nausea, reflux, frequent evacuation, cephalgia, bloodstream glucose levels increased and cutaneous reactions. There was also a hypothesis that suggested potential thrombocytopenia and nephrolithiasis due to regular cranberry use.
2013	The year was noticeable due to thorough research of methodological and practical fails that could have led prior publications to error or at least explain data disparity found amidst the articles. An interesting study showed a correlation between result disparity and bacterial species to infect patients and discovered that cranberry did not cause a significant variation on infection rate in different species, those being <i>Enterococcus</i> sp. ($p = 0,315$), <i>Klebsiella</i> sp. ($p = 0,734$), <i>S. Saprophyticus</i> ($p = 0,875$), <i>Lactobacillus</i> sp. ($p = 0,600$), <i>S. aureus</i> e <i>Proteus</i> sp. (no data). <i>E. coli</i> was the only species that showed significant global number reduction throughout the trial. The investigation conducted upon prophylactic result disparity was correlated to age by one study, showing that children, young women, and peri-menopause women presented better responses to treatment than elderly women. Another important analysis was conducted on the different commercial formulas of products used in trials, which resulted in production method diversity increase in the next few years.
2014	Studies were conducted regarding trimethoprim efficacy comparison again. Due to a demand increase, despite new cranberry products released on the market, several trials started to list natural treatment as more expensive than antibiotics even in the long term, contrary to what prior studies stated in 2009.
2015	The scientific community seemed to be concerned in comparing means of administration to their respective effectiveness in preventing recurrent UTI. Although many studies concluded that 500mg cranberry powder containing 2.8mg CAPs per day for six months were effective in reducing UTI incidence, data also suggested that the whole cranberry fruit (seeds included) would have a better protective effect than supplements and other processed products, probably due to synergy of gathered components or even metabolites, instead of only CAPs. Further studies were suggested to confirm such claims.
2016	A relevant study conducted on dogs showed cranberry and its extract ingestion to be an option in preventing UTI on the species (<i>Canis familiaris</i>), data proving the extract efficacy statistically equal to cephalexin, with the bonus of lower chance of producing bacterial resistance or superinfection. Another study conducted on women reported a 39% reduction of clinical UTI presentation and a 37% reduction of pyuria. Despite promising results, no difference was observed among UTI microbiologically positive patients. Many hypotheses were brought up to try and explain why that is, showing the results to be inconclusive. Again studies to scrutiny data disparity were conducted, suggesting diagnosis error, a possible unknown effect that produced asymptomatic infections, and differential diagnosis considering many women had perineal irritation, who could simulate UTI while being something else. Altogether, the new effect seemed reasonable and authors assumed cranberry had the potential of diminishing bacterial propagation subsequently reducing infection hazard, as well as chronic development tendency.
2017	Studies seemed to be past effectiveness and data disparity, endeavoring to investigate bacterial subgroups on which cranberry would be effective. It was also questioned whether or not cranberry could be a good strategy on patients with high risk for UTI, such as urinary tract malformation patients or post invasive procedure patients.
2018	Trials were conducted to measure more accurately synergy phenomena observed with cranberry-associated substances on UTI prevention, the most successful one regarding propolis extract. It was found a great reduction in cystite frequency in the first 3 months of treatment on the propolis + cranberry trial group compared to placebo but the reduction did not last the next 3 months. This reduction corresponded to almost half the frequency of the active period (46.2%) and 0.59 incidence rate, compared to placebo. It was also reported that there was an increase of period between the first cystitis recurrence of almost 4 weeks ($69,9 \pm 45,8$ days on propolis + cranberry group vs. $43,3 \pm 45,9$ days on placebo group; $p = 0,0258$) which represented an infection-less period increase of 61%. Trial success was attributed to the synergy of propolis known bacteriostatic effect and proanthocyanidins anti-adherent effect, and their important urinary tropism. This important study claimed the association to be able to reduce antibiotic consumption on recurrent cystitis women due to reduction of recurrent symptomatic bacteriuria in the long term.

Continuation of Table 1

Time	Recommendations
2019	New in vitro studies was conducted. Now clinical effectiveness was extensively inspected. Promising results followed the trials, though described as improvable. A great number of researches were carried out endeavoring to develop new prophylaxis approaches and microbiome-based treatment. Several trials associated cranberry and probiotics again, though in a much more robust study. For the first time, a study could suggest a positive clinical effect on the association. These studies also claimed that the synergy of cranberries with anti-inflammatory agents should be an interesting trial to take place in the future, such as D-mannose, Boswellia and Curcuma.
2020	No study was found that would suffice inclusion criteria.
2021	No study was found that would suffice inclusion criteria.

Conclusions. Considering all the compiled studies, it is evident that many alterations on Cranberry use as prophylaxis to recurrent UTI were made throughout time since the start of the 20th century. These alterations ranged from new information on cranberry mechanisms to the effectiveness of such treatment.

Current studies on cranberry UTI prophylaxis seem to be promising, although treatment doses are not yet well-established in the literature. It is also known that other natural substances such as propolis, could also potentialize its action. Considering our research, one could infer that new studies are much needed to establish protocols with the clinical application for cranberry prophylactic treatment, considering the possibility of breakthroughs that could again alter the rec-

ommendation on the use or not of a certain substance, drug, and its mechanisms.

Conflict of interest The authors declare that they have no conflict of interest.

Authors' contributions. All the authors conceived and designed the review, collected and interpreted the data, and drafted the manuscript. Souza, Silva and Souza were mainly concerned with data extraction and review for inclusion in the manuscript. Leite and Carvalho were responsible for organizing the filtered articles and were assisted by De Faria in planning chapters and writing the final version.

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