Acta Scientiarum
http://periodicos.uem.br/ojs
ISSN on-line: 1807-8648
https://doi.org/10.4025/actascihealthsci.v48i1.74281
CC BY

Analysis of regulatory guidelines and their impacts on *Cannabis*-based formulation market in Brazil

Fabricio Felippe dos Santos[1], Gabrielle Silva de Campos Lazzarini[2], Kattya Gyselle de Holanda e Silva[3], Júlia Scherer Santos[4] and Thaís Nogueira Barradas[5*]

[1]Programa de Pós-Graduação em Ciências Farmacêuticas, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brasil. [2]Programa de Pós-Graduação em Ciências Farmacêuticas, Faculdade de Farmácia, Universidade Federal de Juiz de Fora, Juiz de Fora, Minas Gerais, Brasil. [3]Programa de Pós-Graduação em Nanobiossistemas, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brasil. [4]Departamento de Farmacologia, Universidade Federal de Juiz de Fora, Juiz de Fora, Minas Gerais, Brasil. [5]Departamento de Fármacos e Medicamentos, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, Avenida Carlos Chagas Filho, 373, Cidade Universitária, 21941-170, Rio de Janeiro, Rio de Janeiro, Brasil. *Corresponding author. E-mail: thaisbarradas@ima.ufrj.br

ABSTRACT. *Cannabis sativa* has gained notoriety regarding its medicinal applicability. The free-of-charge offer of products containing cannabinoids in the state of São Paulo (Brazil) emerges as a significant milestone in Brazil's public health history. Although other Brazilian states have not yet foreseen the provision through the Brazilian Public Health System, there is an expectation that they will establish their own respective regulations. An effective national sanitary regulation is crucial to enable the marketing of cannabinoids-containing products with suitable quality, safety and efficacy both the private and public health system. Hence, this review provides a historical analysis of the Brazilian regulations about cannabinoids commercialization, highlighting current regulatory and pharmaceutical development limitations. The commercialization of these products began due to population demand, which led the Brazilian regulatory agency to approve a resolution authorizing the importation of *Cannabis*-based products. The current national regulatory framework impacts the pharmaceutical development of these products as it limits administration routes and the use of new pharmaceutical technologies. Furthermore, there is also a commercial impact, considering that manufacturers must comply with the requirements of the Pharmaceutical Inspection Cooperation Scheme. Currently, two main resolutions guide the marketing flow of these products in Brazil and further advances are needed to achieve products with quality, efficacy, and safety, which will enable a free public supply to the Brazilian population.

Keywords: Pharmaceutical formulation; pharmaceutical industry; *Cannabis;* Agência Nacional de Vigilância Sanitária.

Received on August 23, 2024.
Accepted on December 02, 2024.

Introduction

Cannabis sativa is a plant with a history of global use with significant pharmacological potential. The extract from *Cannabis sativa*is mainly composed of phytocannabinoids, which cannabidiol (CBD) and tetrahydrocannabinol (THC) are the major components. Among physiological effects, these compounds promote a homeostatic modulation of brain, skin, digestive, hepatic, cardiovascular, genitourinary, and even bone functions (Battista et al., 2012; Gupta & Talukder, 2021; Russo, 2016). However, the application of *Cannabis* extracts or their major components is a significant pharmaceutical challenge. For example, CBD demonstrates low bioavailability, extensive first-pass metabolism, instability in gastric pH, and low solubility (Cherniakov et al., 2017).

In this context, aiming to reduce these drawbacks, some formulations containing those phytocannabinoids, have been developed in the literature. These formulations were not only simple preparations, such as oil-based solutions (Leibtag & Peshkovsky, 2020), but also complex nanosystems (Banerjee et al., 2021; Caggiano et al., 2022; Fu et al., 2022). However, some limitations of administration routes are imposed by the pharmaceutical regulatory guidelines which restrict the use of high technology in the formulation design.

Based on the increased disclosure of *Cannabis* treatments, the Brazilian national regulatory agency, Agência Nacional de Vigilância Sanitária [ANVISA] has promoted discussions about this scenario, leading to innovative regulatory solutions for the marketing of *Cannabis*-based products in Brazil. Currently, the flow of these products includes registered medicines, *Cannabis* Products with a Sanitary Authorization and products imported personally.

The distinct commercialization profile of *Cannabis*-based products is motivated by the reversed history related with the use of these products in Brazil. The Brazilian resolution – entitled RDC – No. 17/2015 marked the beginning of importing *Cannabis*-based products to attend to a populational demand for refractory epilepsy children treatment (de Souza et al., 2022).

Recently, São Paulo – a Brazilian state – had authorized the provision of *Cannabis*-based products through the public health system (Sistema Único de Saúde – SUS). The decree establishes the criteria for supplying CBD isolated or in synergy with other cannabinoids and terpene products. The patient can apply for all Dravet and Lennox-Gastaut syndromes as well as for tuberous sclerosis treatments upon medical prescription. Patients diagnosed with these conditions commonly do not respond to conventional medicines, justifying the distribution of these alternative treatments. Although rare, those conditions significantly impact the patients' lives, reinforcing the importance of alternative treatments to improve their quality of life (Northrup et al., 2021; Sullivan et al., 2024). The high cost of *Cannabis* treatments for the patient, whose commonly would not be able to finance the treatment, has inspired the pioneering initiative of São Paulo state. This initiative may serve as an example for other Brazilian states to establish their regulations, incorporating *Cannabis*-based products into their public policies.

The present study aimed to develop an analysis of the current Brazilian regulatory landscape of *Cannabis*-based products. Besides, the impacts of the regulatory guidelines on medicine registration, importing and manufacturing flows, and in pharmaceutical formulation design.

Methods

The regulatory analysis was performed using an adapted methodology from de Souza et al., (2022). The following keywords: '*Cannabis*', '*Cannabis sativa*,' and '*Cannabidiol*' were search in the subject field of Brazilian regulatory agency (https://www.gov.br/anvisa/pt-br) until February 2024. Those keywords were also searched on *'general search'* into controlled section of Brazilian regulatory agency website. The analysis also considered the aspects established in the Technical Regulation on substances and medicines subject to special control (Brasil, 1998). The data were collected, and the technical requirements were described and analyzed regarding their regulatory impact.

Results and discussions

Analysis of Brazilian Regulatory Landscape

The main regulations governing *Cannabis*-based products are the following resolution: RDC No. 660, from March 30, 2022 (Agência Nacional de Vigilância Sanitária, 2022b), and RDC 327, dated from December 11, 2019 (Agência Nacional de Vigilância Sanitária, 2019). Mevatyl® is the only registered medicine, and it is in accordance with its guidelines of specific medicines registration (Agência Nacional de Vigilância Sanitária [ANVISA], 2011). Moreover, technical notes, normative instructions, and other regulations compose the historical and current regulatory landscape for *Cannabis*-based products in Brazil: Medicines, *Cannabis* Products and Imported *Cannabis*-based products (Figure 1).

Historically, in 2015, the first resolution about imported *Cannabis*-based products was released (Agência Nacional de Vigilância Sanitária, 2015), which was later revoked by the currently available RDC No. 660/2022. It addresses the procedures for ANVISA obtaining authorization for the importation of industrialized *Cannabis*-based products, as well as the customs clearance processes.

Personal use importation requires a prescription and can be performed by legally constituted third parties. Consequently, a legal representation service emerged: companies with expertise in foreign markets offering services to solve all procedures related to the personal importation of *Cannabis*-based products, from the medical consultation, customs clearance and the products receipt by the user. These companies are not considered importers by ANVISA, as the current regulation does not foresee this kind of service, establishing a gap that needs to be addressed by futures guidelines. In fact,it is characterized as a consultancy which makes easier the access to *Cannabis*-based products. Among the many products available in foreign markets, the most part are not registered as medicines and, therefore, do not undergo rigorous quality control measures. This results in products with questionable efficacy, safety, and quality (de Souza et al., 2022). In this way, the mentioned service aims to analyze products that meet the criteria of the efficacy-safety-quality pharmaceutical triad.

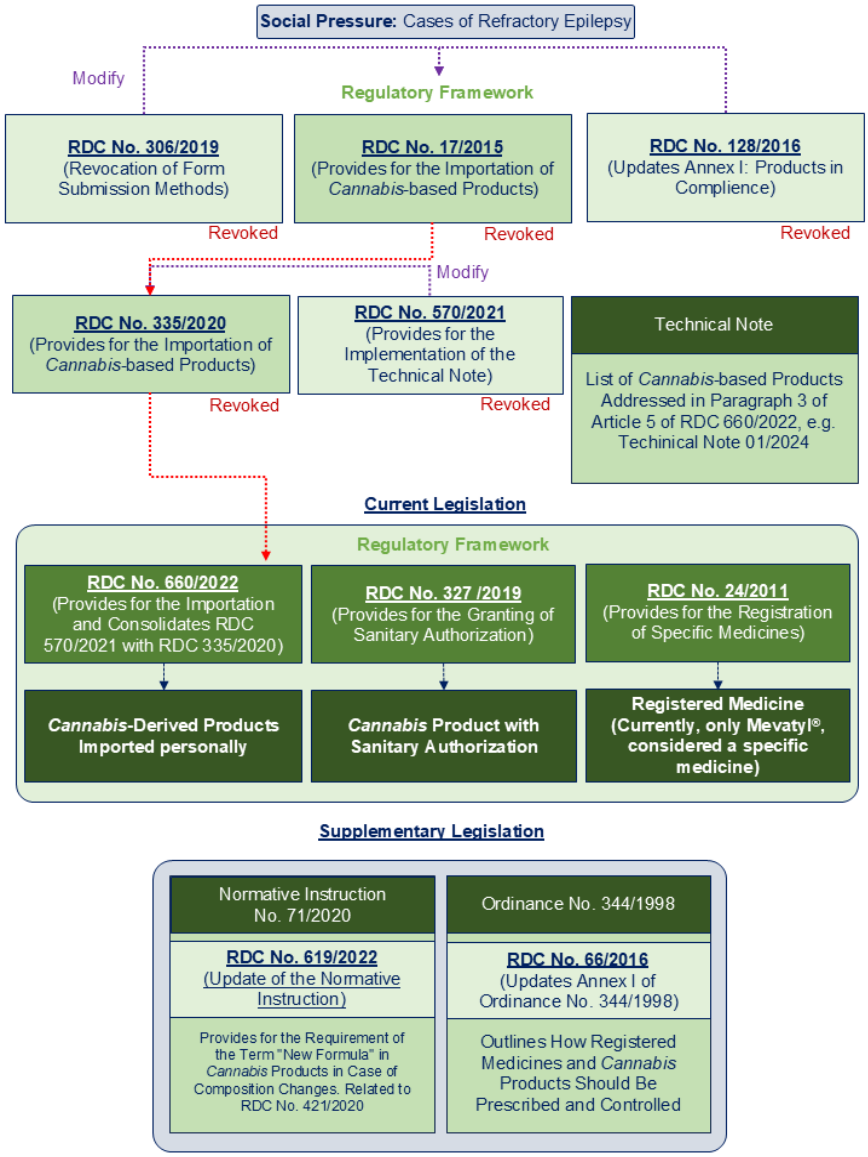

Figure 1. Infographic of the Brazilian Regulatory landscape for *Cannabis*-Based medicines and Products.

It is undeniable that resolution No. 660/2022 (Agência Nacional de Vigilância Sanitária, 2022b) allowed broad flow of a large variety of imported *Cannabis*-based products in the country. Nonetheless, it is important to emphasize that the products do not require any registration on ANVISA. In that regard, previously evaluated products listed in the technical notes, such as 01/2024, may have an easier authorization process, favoring the prescription of them.

Besides, RDC No. 327/2019 regulates the procedures for granting Sanitary Authorization for the manufacture and importation of *Cannabis* products for medicinal purposes (ANVISA, 2019). To summarize, this resolution addresses regulatory aspects related to commercialization, dispensing, monitoring, and inspection of *Cannabis* products. One important concept of this resolution is that *Cannabis*formulations are considered products instead of medicines – *Cannabis* products – and, therefore, they are not subjected to the same commercial authorization and requirements as medicines. Additionally, the Sanitary Authorization is a new regulatory model granted for 5 years and non-renewable. Products whose marketing is permitted under this 5-year authorization can be stored and sold in pharmacies. Nevertheless, they must be designed exclusively for oral or nasal administration. Another important point regarding of the Sanitary Authorization is that bioavailability assays or clinical trials are not mandatory, clearly distinguishing *Cannabis* products from medicines (ANVISA, 2019).

Efficacy and safety assurance is guaranteed only for registered medicines, since bioavailability assays and clinical trials are required. The resolution No. 327/2019 requires: Good Manufacturing Practice (GMP) and Good Agriculture and Collection Practice (GACP) certificate from the manufacturers and a stability study in

Zone IV (ANVISA, 2019), aiming to ensure a minimum product quality. Therefore, since clinical trials and bioavailability assays are optional, it is hard to ensure safety and efficacy of these products just with the requiring of quality documents and the formulation scientific rationale. In addition, this resolution highlights the importance of ANVISA's participation as a member of the Pharmaceutical Inspection Cooperation Scheme (PIC/S), demonstrating that Brazil follows global technical requirements, and has high manufacturing standards. In this context, a documentation flow between PIC/S member countries is established, facilitating the Sanitary Authorization process and avoiding duplicate inspections.

To summarize, this scenario highlights the challenge of balancing: access to medicines/products and the inherent risk of formulations that don't have clinical trials. As ANVISA is responsible for granting approvals for medicines, cosmetics, and food products, it is crucial to update the *Cannabis* resolution, mainly to provide products with quality, efficacy and safety in the public health system

Regulatory impacts in Cannabis-based products formulations commercialized in Brazil

One of the major features in RDC No. 327/2019 ([ANVISA], 2019) is that manufacturers of *Cannabis* products which aim to obtain a Sanitary Authorization must have their production line certified by a PIC/S member agency. In Brazil, there are several products sold manufactured by Colombia industries, and the regulatory agency of Colombia is not a member of PIC/S. Diversely, products manufactured by United States and Switzerland industries, countries which the regulatory agency is member of PIC/S, have fewer products authorized to be commercialized in Brazil. In this scenario, to be marketed in Brazil, Colombian formulations are approved by other international agencies, once their own regulatory agency does not have expertise to certify *Cannabis* production lines following the PIC/S requirements. One justification for this is that Colombia as well as Canada, have historical policies for providing officinal formulations or even the *Cannabis* raw material. Moreover, the distance between Brazil and Colombia, combined with Colombia's favorable conditions for *Cannabis* cultivation, results in a greater number of formulations being marketed in Brazil compared to other countries, such as Canada, which has a similar production capacity to Colombia (Cubillos Sánchez, 2020). Beyond that, the low cost of Colombian *Cannabis*-based formulations production may be an advantage and a possible explanation for the higher numbers of marked products compared to other countries located farther from Brazil. Further, the absence of following PIC/S guidelines, could hinder Colombian export market rising. Just as RDC No. 327/2019 restricts manufacturing line inspections to be carried out by a PIC/S member, the increase in Colombian export flows could lead other regulatory agencies to establish more restrictive regulations. In this context, these agencies could require that the exporting country have a regulatory agency overseeing the quality of the entire process based on PIC/S guidelines. This quality practice throughout the product's lifecycle is already a reality in current manufacturing regulations for pharmaceuticals in Brazil, as required by RDC No. 658/2022 (ANVISA, 2022a).

Concerning the concepts and the limitations of the Sanitary Authorizations, it is important to mention that this regulatory classification for *Cannabis* products is valid and allows its commercialization only for five years. During this period, the industry should conduct a clinical trial to apply for a medicine registration. However, there is a regulatory gap within RDC No. 327/2019 that allows, in practice, the extension of the non-renewable five-year commercialization period. A single formulation, produced by the same manufacturer, may receive a new Sanitary Authorization when submitted by a different marketing authorization holder. Consequently, identical products can remain on the market for a period longer than the five years established by the resolution, even in the absence of clinical trials.

Resolution RDC No. 327/2019 plays a key role in the advent and encouragement of *Cannabis*-based products commercialization in Brazil, with a promising future for this new pharmacological therapy, due to its facilitating role in ensuring access to these products (Gregorio & Mascarenhas, 2022). This resolution is a very important regulatory framework not only because its impacts on expanding access to products containing cannabinoids (Villas Bôas & Rezende, 2020; Gregorio & Mascarenhas, 2022), but also because it brings to focus the discussion about the balance between access and quality-safety-efficacy.

Regarding regulatory impacts on formulation compositions, phytocannabinoids are classified as biopharmaceutical class II, therefore they have low solubility and high permeability besides their physical-chemical instabilities (Cherniakov et al., 2017). Therefore, it is important to define the appropriate technology for those molecules, including designing modified drug delivery systems in pharmaceutical forms which could optimize cannabinoids clinical effect. Nevertheless, resolution No. 327/2019 prohibits using modified drug release systems and prevents using alternative routes, such as transdermal one (ANVISA, 2019). The current

available market formulations employ relatively simple technology to ensure maximum safety and optimize bioavailability. There is a higher frequency of medium-chain triglycerides as excipient in oily solutions, which allows to improve phytocannabinoids bioavailability (Izgelov et al., 2020). Furthermore, the use of antioxidants is essential to prevent CBD oxidation. Hence, isomers of Vitamin E and butyl hydroxyanisole may be employed for this purpose.

In short, resolution No. 327/2019 shows regulatory gaps allowing the prolonged marketing devoid of any clinical trials. Dueto the guideline's restrictions, the formulations are all designed for oral or nasal administration and have a limited number of excipients allowed. The development of formulation with low complexity is a requirement for commercialization authorization even though it does not ensure a satisfactory pharmaceutical development.

Future regulatory changes about the use of modified-release technologies are expected. These changes will impact in the use of new technologies that could increase the stability of formulations (Rebibo et al., 2022) and improve cannabidiol solubility (Hossain et al., 2023) resulting in formulations with better performance. For example, transdermal route would be a promising route due to ease of application and increased bioavailability as the systemic pre-metabolism is avoided (Mishra et al., 2019). Despite that, manufacturers must provide evidence of an appropriate rationale development for safety modified release and non-oral/nasal formulations.

Conclusion

The Brazilian regulatory landscape allows the importation of *Cannabis*-based formulations and the sale of *Cannabis* products with Sanitary Authorization. Sanitary Authorization is addressed in RDC No. 327/2019, which ensures the market of limited-composition formulations in Brazil. Nevertheless, there is a gap in the current regulation allowing identical formulations to be marketed extending the non-renewable 5-year without clinical trials. Therefore, the regulatory scenario is directed towards meeting growing public demand. However, there are still significant areas for improvement, such as the expansion of free distribution in other Brazilian states besides São Paulo by the public health system.

References

Agência Nacional de Vigilância Sanitária. (2011). RDC n.º 24, de 14 de junho de 2011. *Diário Oficial da União*, seção 1, p. 22.

Agência Nacional de Vigilância Sanitária. (2015). RDC n.º 17, de maio de 2015. *Diário Oficial da União*, seção 1, p. 8.

Agência Nacional de Vigilância Sanitária. (2019). RDC n.º 327 de 11 de dezembro de 2019. *Diário Oficial da União*, seção 1.

Agência Nacional de Vigilância Sanitária. (2022a). RDC n.º 658, de 30 de março de 2022. *Diário Oficial da União*, seção 1, p. 77.

Agência Nacional de Vigilância Sanitária. (2022b). RDC n.º 660 de 30 de março de 2022. *Diário Oficial da União*, seção 1.

Banerjee, A., Binder, J., Salama, R., & Trant, J. F. (2021). Synthesis, characterization and stress-testing of a robust quillaja saponin stabilized oil-in-water phytocannabinoid nanoemulsion. *Journal of Cannabis Research*, *3*(1), 43. https://doi.org/10.1186/s42238-021-00094-w

Battista, N., Di Tommaso, M., Bari, M., & Maccarrone, M. (2012). The endocannabinoid system: An overview. *Frontiers in Behavioral Neuroscience*, *6*. https://doi.org/10.3389/fnbeh.2012.00009

Brasil. (1998). Portaria n. 344, de 12 de maio de 1998. *Diário Oficial da União*, seção 1, p. 20.

Caggiano, N. J., Wilson, B. K., Priestley, R. D., & Prud'Homme, R. K. (2022). Development of an in vitro release assay for low-density cannabidiol nanoparticles prepared by flash nanoprecipitation. *Molecular Pharmaceutics*, *19*(5), 1515–1525. https://doi.org/10.1021/acs.molpharmaceut.2c00041

Cherniakov, I., Izgelov, D., Barasch, D., Davidson, E., Domb, A. J., & Hoffman, A. (2017). Piperine-pro-nanolipospheres as a novel oral delivery system of cannabinoids: Pharmacokinetic evaluation in healthy volunteers in comparison to buccal spray administration. *Journal of Controlled Release*, *266*, 1–7. https://doi.org/10.1016/j.jconrel.2017.09.011

Cubillos Sánchez, P. A. (2020). Cannabis for medical and scientific purposes: The Colombian landscape. *Colombian Journal of Anesthesiology*, *49*(2). https://doi.org/10.5554/22562087.e954

de Souza, M. R., Henriques, A. T., & Limberger, R. P. (2022). Medical cannabis regulation: An overview of models around the world with emphasis on the Brazilian scenario. *Journal of Cannabis Research*,*4*(1), 33. https://doi.org/10.1186/s42238-022-00142-z

Fu, X., Xu, S., Li, Z., Chen, K., Fan, H., Wang, Y., Xie, Z., Kou, L., & Zhang, S. (2022). Enhanced intramuscular bioavailability of cannabidiol using nanocrystals: Formulation, in vitro appraisal, and pharmacokinetics. *AAPS PharmSciTech*, *23*(3), 85. https://doi.org/10.1208/s12249-022-02239-3

Gregorio, L. E., & Mascarenhas, N. G. (2022). O uso medicinal da *Cannabis sativa* L.: Regulamentação, desafios e perspectivas no Brasil. *Concilium*, *22*(3), 191–212. https://doi.org/10.53660/CLM-220-230

Gupta, A. K., & Talukder, M. (2021). Cannabinoids for skin diseases and hair regrowth. *Journal of Cosmetic Dermatology*, *20*(9), 2703–2711. https://doi.org/10.1111/jocd.14352

Hossain, K. R., Alghalayini, A., & Valenzuela, S. M. (2023). Current challenges and opportunities for improved cannabidiol solubility. *International Journal of Molecular Sciences*, *24*(19), 14514. https://doi.org/10.3390/ijms241914514

Izgelov, D., Shmoeli, E., Domb, A. J., & Hoffman, A. (2020). The effect of medium chain and long chain triglycerides incorporated in self-nano emulsifying drug delivery systems on oral absorption of cannabinoids in rats. *International Journal of Pharmaceutics*, *580*. https://doi.org/10.1016/j.ijpharm.2020.119201

Leibtag, S., & Peshkovsky, A. (2020). Cannabis extract nanoemulsions produced by high-intensity ultrasound: Formulation development and scale-up. *Journal of Drug Delivery Science and Technology*, *60*, 101953. https://doi.org/10.1016/j.jddst.2020.101953

Mishra, D. K., Pandey, V., Maheshwari, R., Ghode, P., & Tekade, R. K. (2019). Cutaneous and transdermal drug delivery. In *Basic fundamentals of drug delivery* (pp. 595–650). Elsevier. https://doi.org/10.1016/B978-0-12-817909-3.00015-7

Northrup, H., Aronow, M. E., Bebin, E. M., Bissler, J., Darling, T. N., de Vries, P. J., ... Young, L. (2021). Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. *Pediatric Neurology*, *123*, 50–66. https://doi.org/10.1016/j.pediatrneurol.2021.07.011

Rebibo, L., Frušić-Zlotkin, M., Ofri, R., Nassar, T., & Benita, S. (2022). The dose-dependent effect of a stabilized cannabidiol nanoemulsion on ocular surface inflammation and intraocular pressure. *International Journal of Pharmaceutics*, *617*, 121627. https://doi.org/10.1016/j.ijpharm.2022.121627

Russo, E. B. (2016). Beyond cannabis: Plants and the endocannabinoid system. *Trends in Pharmacological Sciences*, *37*(7), 594–605. https://doi.org/10.1016/j.tips.2016.04.005

Sullivan, J., Benítez, A., Roth, J., Andrews, J. S., Shah, D., Butcher, N. J., ... Cross, J. H. (2024). A systematic literature review on the global epidemiology of Dravet syndrome and Lennox–Gastaut syndrome: Prevalence, incidence, diagnosis, and mortality. *Epilepsia*. https://doi.org/10.1111/epi.17866

Villas Bôas, G. de K., & Rezende, M. de A. (2020). Discussão sobre o acesso aos medicamentos derivados da *Cannabis* à luz da inovação em saúde no Brasil. *Revista Fitos*, *14*(2), 259–284. https://doi.org/10.32712/2446-4775.2020.960