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Research Article

Nanocompuestos de cannabis de liberación controlada: una opción terapéutica y transicional

Controlled-Release Cannabis Nanocomposites: A Therapeutic and Transitional Option

Nanocompósitos de cannabis de liberação controlada: uma opção terapêutica e transitória

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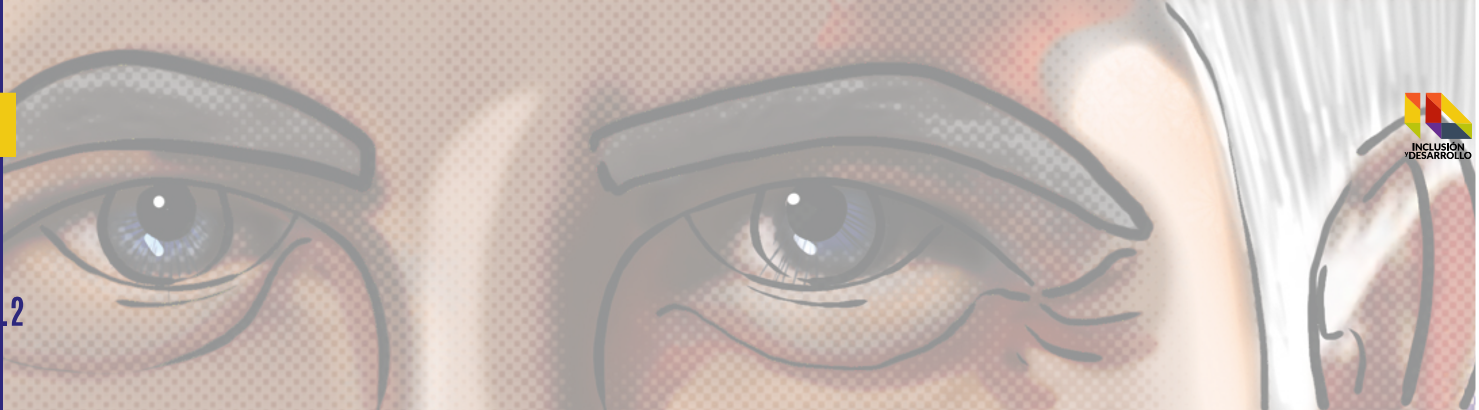

RESUMEN

Esta propuesta tiene por objeto el desarrollo de compositos a partir de cannabinoides (CBD) inmovilizados sobre carbones, como instrumento futuro para la sustitución de cultivos ilícitos y/o la apertura de nuevas líneas económicas en Colombia contribuyendo a modelos de paz. Para esto, se obtuvo carbón activo a partir de la pirolisis de semillas y se funcionalizó con grupos amina (CAN). Los materiales obtenidos se caracterizaron fisicoquímicamente. La carga de CBD se realizó sobre los carbones y se evaluó la liberación a condiciones fisiológicas simuladas, a pH 2.1 (gástrico) y pH 7.4 (intestinal). Los materiales desorbidos se pusieron en contacto con aflatoxinas durante 15 minutos a 37°C en medio intestinal para evaluar el efecto dual de los carbones. La molécula de CBD tuvo una mayor afinidad por los materiales CAN, lo cual se atribuye a interacciones π deslocalizados-catión. Las liberaciones de CBD fueron cercanas al 90% en el medio gástrico, y alcanzaron el 100% en intestino. La remoción de aflatoxinas (AFLAB1) con CAN fue del 100% a partir de concentraciones de 426 µg/L. Los carbones permitieron la liberación controlada de CBD y la remoción subsecuente de aflatoxinas convirtiéndose en alternativas de valor terapéutico, mientras contribuye a la sustitución de cultivos ilícitos.

Palabras clave: canabinoides, carbones, aflatoxinas, liberación.

ABSTRACT

This proposal aims to develop composites from cannabinoids (CBD) immobilized on activated carbons, as a future instrument for the substitution of illicit crops and/or the opening of new economic lines in Colombia, contributing to models of peace. For this, active carbon was obtained from the pyrolysis of seeds and was functionalized with amine groups (CAN). The materials obtained were characterized physicochemically. CBD loading was carried out on the coarbons and the release was evaluated under simulated physiological conditions, at pH 2.1 (gastric) and pH 7.4 (intestinal). The desorbed materials were put in contact with aflatoxins for 15 minutes at 37°C in intestinal medium to evaluate the dual effect of the carbons. The CBD molecule had a higher affinity for CAN materials, which is attributed to delocalized π-cation interactions. CBD releases were close to 90% in the gastric medium and reached 100% in the intestine. The removal of aflatoxins with CAN was 100% from concentrations of 426 µg/L. Carbons allowed the controlled release of CBD and the subsequent removal of aflatoxins, becoming alternatives of therapeutic value, while contributing to the substitution of illicit crops.

Keywords: cannabinoid, carbons, aflatoxins, release.

RESUMO

Esta proposta visa desenvolver compósitos a partir de canabinóides (CBD) imobilizados em carvões, como um futuro instrumento para a substituição de culturas ilícitas e/ou a abertura de novas linhas económicas na Colômbia, contribuindo para modelos de paz. Para isso, o carbono ativo foi obtido a partir da pirólise de sementes e foi funcionalizado com grupos amina (CAN). Os materiais obtidos foram caracterizados físico-quimicamente. A carga de CBD foi realizada nas brasas e a liberação foi avaliada em condições fisiológicas simuladas, em pH 2,1 (gástrico) e pH 7,4 (intestinal). Os materiais dessorvidos foram colocados em contato com aflatoxinas por 15 minutos a 37°C em meio intestinal para avaliar o duplo efeito dos carbonos. A molécula de CBD tinha maior afinidade com materiais CAN, o que é atribuído a interações deslocalizadas de cátions π. As liberações de CBD foram próximas de 90% no meio gástrico e atingiram 100% no intestino. A remoção de aflatoxinas com CAN foi de 100% a partir de concentrações de 426 µg/L. O carvão permitiu a libertação controlada de CBD e a posterior remoção de aflatoxinas, tornando-se alternativas de valor terapêutico, ao mesmo tempo que contribuiu para a substituição de culturas ilícitas.

Palavra-chave: canabinóides, carbonos, aflatoxinas, liberação.

Literature Review

Cannabis is the most widely consumed psychoactive substance in the world, and its psychoactive properties, linked to certain cannabinoids such as tetrahydrocannabinol (THC), have been associated with high dependency rates. Cannabis and its derivatives are currently classified under Schedule I of the 1971 Convention on Psychotropic Substances and are subject to regulation regarding their use, possession, sale, consumption, and production (JIFE 2019). Between 1975 and 1985, large amounts of U.S. dollars flowed into Colombia due to the operations of criminal organizations engaged in the illicit cultivation and export of processed cannabis (marijuana), an activity that had been ongoing since the late 1960s, primarily in the departments of La Guajira, Cesar, and Magdalena. This was a business controlled by clans and families (drug traffickers) who exploited impoverished farmers, generating significant profits for the former.

To date, marijuana, cocaine, and heroin remain the most trafficked psychotropic substances worldwide. Drug trafficking has significantly impacted Colombia's political, social, and economic landscape, serving as a major financial pillar for paramilitary groups, guerrilla factions, and organized crime. Although cannabis cultivation has been criminalized and subject to legal prosecution, from a pharmacological standpoint, this plant species is unique in its diverse array of phytochemical compounds, which have demonstrated clinical benefits in managing symptoms related to general pain, as well as chronic and neuropathic pain in patients with advanced-stage cancer. As a result, cannabis offers additional therapeutic tools to healthcare professionals (Salazar Londoño 2021).

Today, the medical use of cannabinoids is legal in our country, and globally, many have been approved for pharmaceutical applications, including dronabinol, nabilone, nabiximols, and cannabidiol (CBD). In Colombia, for example, the number of potential patients for medicinal cannabis use may be around one million, with projected revenues of approximately USD 480 million by 2032 (Ramírez 2019). This is a conservative estimate of the potential demand in Colombia, based on pathologies for which cannabis could be used for therapeutic purposes through master formulations, consumer products, and chemically synthesized medicines.

This measure considers the scientific evidence on cannabinoid effects compiled by the U.S. National Academies of Sciences, Engineering, and Medicine in 2017. Therefore, it is not unreasonable to consider a medicinal cannabis program for Colombia. Canada and Israel, for example, have 400,000 and 30,000 patients, respectively, enrolled in medicinal cannabis-based treatments, along with the most extensive portfolio of CBD-based products. Currently, Colombia accounts for 0.22% of global medicinal cannabis consumption; (PwC 2000) however, this figure could increase to 0.28% by 2030 through value-driven initiatives. For instance, it is crucial to introduce innovative, high-quality products and services into the market, supported by a mature ecosystem fostering close collaboration between academia, the state, and communities.

Following the approval of Law 1787 of 2016, which established the regulatory framework for access to cannabis for medical and scientific purposes, and its subsequent regulation through Decree 613 of 2017. Beyond significant potential demand for health applications, Colombia also offers favorable conditions for production, including lower production costs—particularly in inputs and labor—optimal light conditions (12 hours per day), robust productive infrastructure, an available skilled workforce, and a well-established agricultural sector, reinforced by the country's strong floriculture tradition. Additionally, historical expertise in cannabis cultivation and vast areas of rural land dedicated to this purpose further support its production potential.

Moreover, medicinal cannabis products available in the country—across cosmetics, pharmaceuticals, and food sectors—face significant technical limitations. Because cannabinoids are lipophilic molecules, they exhibit strong adhesion to products, impeding the migration of these bioactive compounds to biological tissues, which results in bioavailability levels of less than 20% (Nakano et al. 2019). Nanotechnology presents a wide range of possibilities, as its nanoscale properties allow for the precise control and adjustment of surface characteristics.

In a pioneering review conducted by Chandrakala, Aruna, y Angajala (2022), the advancements and solutions offered by nanocarriers to enhance cannabinoid dosage, reduce side effects, and provide alternative transport mechanisms for the treatment of neurodegenerative diseases were compiled. The authors presented various nanoplatforms capable of delivering these compounds to their target sites within the Central Nervous System, highlighting lipid nanoparticles, nanocapsules, dendrimers, nanogels, liposomes, and polymeric nanoparticles as potential candidates for future developments (Begines et al. 2020). The present proposal focuses on the development of intelligent activated carbon nano-intermediates for CBD immobilization, aiming to enhance bioavailability and facilitate the selective release of molecules in target tissues, with the subsequent removal of aflatoxins. This proposal is framed within the development of high-value scientific cannabis-derived products as a future instrument for the substitution of illicit crops and/or the establishment of new economic sectors in Colombia.

Methodology

Initially, carbon was obtained through the pyrolysis of pre-activated seeds. For activation, the seeds were mixed in a 1:2 ratio with a supersaturated potassium hydroxide solution under infrared illumination for 24 hours, following the method suggested by Elmouwahidi et al (2012). Subsequently, the mixture was pyrolyzed at 800°C in an inert nitrogen atmosphere, and once the carbon was obtained, surface modifications were applied to incorporate amino groups with basic characteristics. The unmodified and amine-functionalized materials were labeled CA and CAN, respectively. The materials were then characterized: morphology was analyzed using scanning electron microscopy (SEM) with a LEO GEMINI-1530 microscope (Carl Zeiss, Germany) (Saleh et al. 2022). At the textural level, analyses were conducted via nitrogen (N2) adsorption at -196°C, using a Quadrasorb SI analyzer (Quantachrome, USA). The samples were pre-degassed at 100°C for 24 hours. The Brunauer-Emmett-Teller (BET) equation was applied to the nitrogen adsorption isotherms to determine the specific surface area (SBET), while the Dubinin-Radushkevich equation was used to calculate the micropore volume (Vmic), corresponding to spaces between 0.5 and 2 nm.

Similarly, the Barrett-Joyner-Halenda (BJH) method was applied to calculate the mesopore volume (Vmeso), corresponding to spaces ranging from 6.5 to 50 nm. Mercury porosimetry was performed using an AutoPore IV 9510 (Micromeritics, USA) at pressures of up to 60,000 psi to determine the macropore volume (Vmacro), corresponding to spaces between 50 and 10,000 nm. The total pore volume (TV) was considered the sum of Vmicro, Vmeso, and Vmacro (S. Wang, Shivanna, and Yang 2022). The chemical characterization of the materials was performed by measuring the acidity of the carbons through the isoelectric point (IP), following the methodology previously described by Pérez-Cadenas et al (Pérez-Cadenas, Maldonado-Hódar y Moreno-Castilla 2003).

CBD loading onto the materials was conducted using batch adsorption experiments at different CBD concentrations (10–1000 mg/L) with a fixed amount of carbon (100 mg), maintaining a carbon-to-CBD solution ratio of 1:10. The adsorption curves were adjusted to the Solid-Liquid Equilibrium (SLE) model to interpret the interaction between carbon and CBD (Giraldo et al. 2017). In vitro desorption tests were carried out by measuring release kinetics under simulated physiological conditions of gastric pH = 2.1 and intestinal pH = 7.4 at 37°C for 400 minutes. The physiological media were rigorously prepared using saline, organic, and inorganic solutions (Yilmaz et al. 2020). For aflatoxin removal under intestinal conditions, the desorbed materials were exposed to commercial aflatoxin (AFLA) for 15 minutes at 37°C and pH = 7.4 (S.-Y. Wang et al. 2023). CBD quantification was performed using a previously established calibration curve at 255 nm in a Genesys 20 Thermo Scientific ultraviolet spectrophotometer (Massachusetts, United States), while aflatoxin quantification was conducted using a high-performance liquid chromatography (HPLC) system with a pre-established calibration curve (Keskin y Eyupoglu 2023). Resultados y discusión

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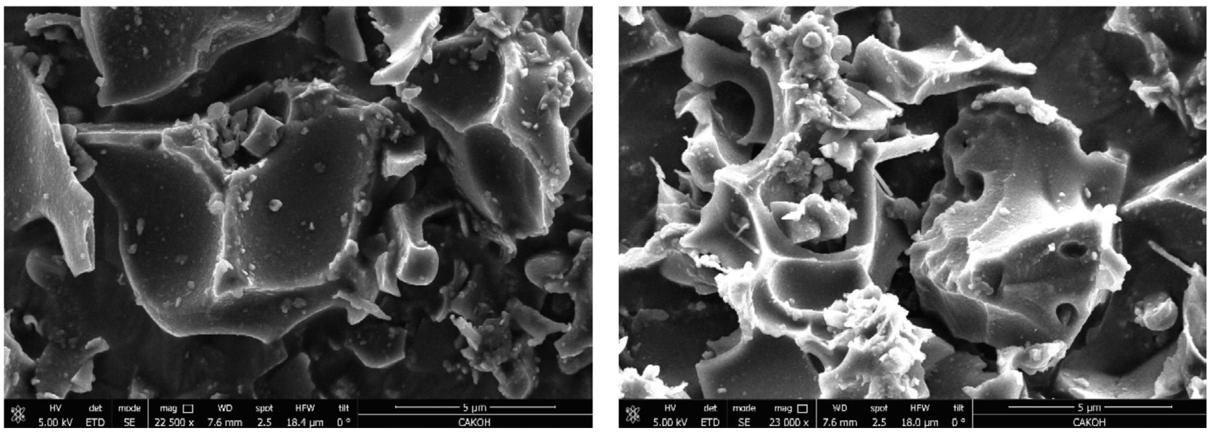
Results and Discussion

Characteristics of Activated Carbons

The morphology of CA and CAN is shown in Figure 1. The carbons exhibited three-dimensional networks with irregular primary particles on a micro- and nanometric scale, with free interparticle spaces at the nanometric level, forming the porous region where CBD and AFLAB1 molecules are retained.

Figure 1. *Scanning electron microscopy (SEM) images of activated carbon (CA) and nitrogen-functionalized activated carbon (CAN).*

A. B.



Note: Prepared by the authors.

Table 1 presents the textural and chemical properties of the obtained carbons. Both materials exhibited high surface areas, reaching up to 600 m^2 of free space per gram of carbon.

Table 1. *Textural properties and isoelectric point of activated carbon (CA) and nitrogen-functionalized activated carbon (CAN).*

Material	S_{BET}	Vmicro	V_{meso}	V_{macro}	V_T	PI
	m^2/g	cm^3/g	cm^3/g	cm^3/g	cm^3/g	
CA	683	0.24	0.91	0.03	1.18	9.0
CAN	608	0.23	0.66	0.03	0.92	7.7

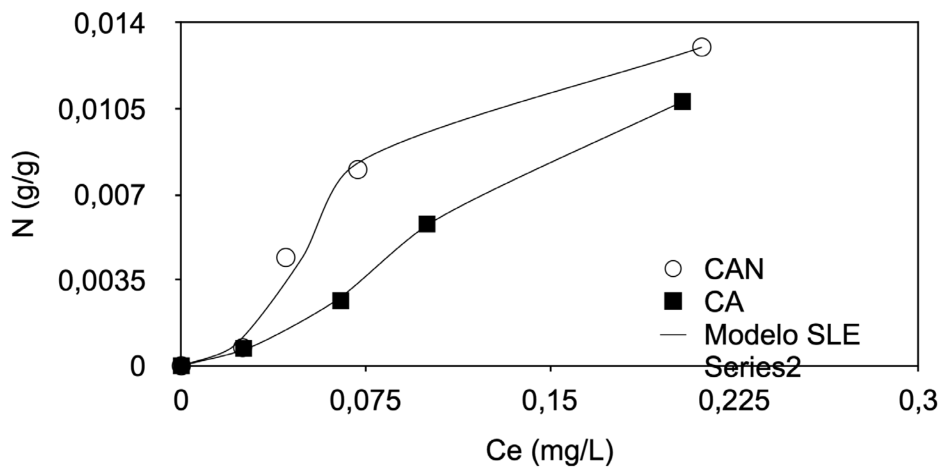
Note: Prepared by the authors.

The CA surface area decreased with surface modification, as nitrogen heteroatoms, introduced to alter the material's chemistry, were deposited in the pores through physisorption, reducing the available free area. The nitrogen atoms and their derivative structures were primarily accommodated in the micro- and mesopores due to their smaller size (0.5 to 50 nm). This explains why CAN exhibited lower Vmicro and Vmeso values but retained the same Vmacro as CA. Finally, the PI values were also included in Table 1. The CA material was neutral, but the addition of nitrogen atoms altered its surface chemistry, making it a basic electrophilic material according to Lewis theory (Bursten 2004). The basic modification aims to enhance interactions between the carbon and the highly nucleophilic CBD and AFLAB1 molecules.

CBD Adsorption on Activated Carbon

The adsorption isotherms of CBD on CA and CAN materials are presented in Figure 2. For the analysis of the adsorption isotherms, the experimental data were adjusted to the Solid-Liquid Equilibrium (SLE) (Montoya et al. 2014) model, which provides insights into the affinity between the adsorbent (carbons) and the adsorbate (CBD molecules) through parameter H, as well as the degree of self-association of the adsorbate on the adsorbent surface (parameter K).

Figure 2. *CBD adsorption isotherms at 25°C in an aqueous solution at pH 7.4 on activated carbon (CA) and nitrogen-functionalized activated carbon (CAN), obtained from chemical activation and seed pyrolysis.*



Note: Prepared by the authors, obtained from chemical activation and seed pyrolysis.

The parameters obtained from the SLE model for each material are presented in Table 2. It can be observed that the adsorption isotherms exhibit a good fit to the SLE model, with a root mean square error (RMSE%) of <1%. The Qmax parameter followed the order CAN>CA, indicating that the functionalized CAN material had a higher affinity for CBD. Additionally, the values of the K parameter suggest a greater self-association of CBD molecules in the presence of CA materials.

Table 2. *Parameters obtained for the Solid-Liquid Equilibrium (SLE) model from the adsorption isotherms of cannabidiol (CBD) on activated carbons CA and CAN.*

	H (mg/g)	K (g/g)	Qmax (g/g)	RMSE (%)
CA	55.4	817.4	0.012	0.123
CAN	52.4	461.5	0.014	0.396

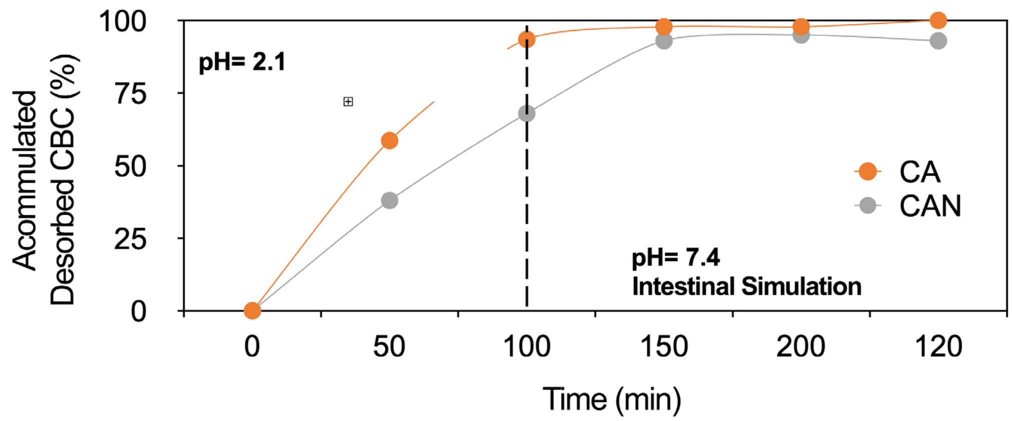
Note: The H parameter is inversely related to adsorption affinity, the K parameter to the self-association of the adsorbate on the adsorbent surface, and Qmax represents the maximum adsorbed quantity. Prepared by the authors

To explain the higher adsorption of CBD on CAN, it is important to note that the adsorption experiments were conducted at pH 7.0, while the isoelectric points of CA and CAN were 7.7 and 9.0, respectively (Table 1). At pH 7.0, CA and CAN were negatively and positively charged, respectively. Specifically, the positively charged CAN materials experience stronger attractions with CBD, which is characterized as an anionic molecule (Nelson et al. 2020) with a high electron density, resulting in physisorption through cation-pi electron interactions (Zhao and Zhu 2020).

CBD Desorption Kinetics from Activated Carbons

The desorption kinetics of CBD under simulated physiological conditions are shown in Figure 3. The results indicated that the strongest complexes, such as CBD on CAN, initially exhibited a lower tendency to desorb due to strong electrostatic cation-pi electron interactions. However, over time (400 min) and under physiological conditions, both carbons desorbed up to 100% of the loaded CBD.

Figure 3. *Desorption kinetics of cannabidiol (CBD) from activated carbons CA and CAN functionalized with nitrogen groups under simulated physiological conditions.*



Note: Prepared by the authors

On the other hand, the desorption process was more efficient under gastric conditions due to the excess hydrogen ions in this medium, which altered all structures, making them cationic and causing electrostatic repulsion between the materials and CBD, leading to its release (Fritz et al. 2021). According to the latest recommendations from the Food Standards Agency (FSA), adults should consume CBD in food products at a dosage of 10 mg per day (Maldonado 2023). Therefore, the use of at least 0.7 to 0.8 grams of CA and CAN would provide the recommended dose. This is advantageous considering that evidence suggests oral administration of pure CBD is highly inefficient due to the molecule's lipophilicity, which results in slow, erratic, and variable absorption among individuals (Fu et al. 2022). Its oral bioavailability ranges between 5% and 10%, and the maximum plasma concentration for a 20 mg dose in men and a 15 mg dose in women is 14.5 ng/mL and 9.4 ng/mL, respectively (Perucca and Bialer 2020). These pioneering findings emphasize the need for careful formulation of CBD-based complexes to enhance solubility, bioavailability, and therapeutic effects, as well as the development of high-value formulations that could compete with the current supply of cannabis-derived products in the medium term.

Elimination of Aflatoxin B1 (AFLAB1) with Activated Carbon

Aflatoxin B1 (AFLAB1) is a toxic secondary metabolite produced by fungi (Kumar et al. 2021). When humidity and temperature conditions are favorable, fungi proliferate and form colonies capable of generating high concentrations of AFLAB1. Cereals, nuts, and fruits are primary sites for fungal growth and subsequent AFLAB1 production (Awuchi et al. 2020). Moreover, given their thermostability and resistance, these toxins persist throughout food processing, ultimately entering the human food chain (Chandra 2021). Exposure to high levels of AFLAB1 can cause acute necrosis, cirrhosis, and liver cancer. In the long term, these compounds exhibit carcinogenic, mutagenic, teratogenic, estrogenic, immunotoxic, nephrotoxic, and neurotoxic properties. Several strategies have been developed to mitigate the negative effects caused by toxin consumption, such as the use of adsorbents (Ma et al. 2021). The present study demonstrated the additional capacity of carbons to act as AFLAB1 binders in the intestine after CBD desorption. Specifically, the evaluated materials achieved aflatoxin removal rates ranging from 13% to 100% within just 15 minutes after the test began, as shown in Figure 4.

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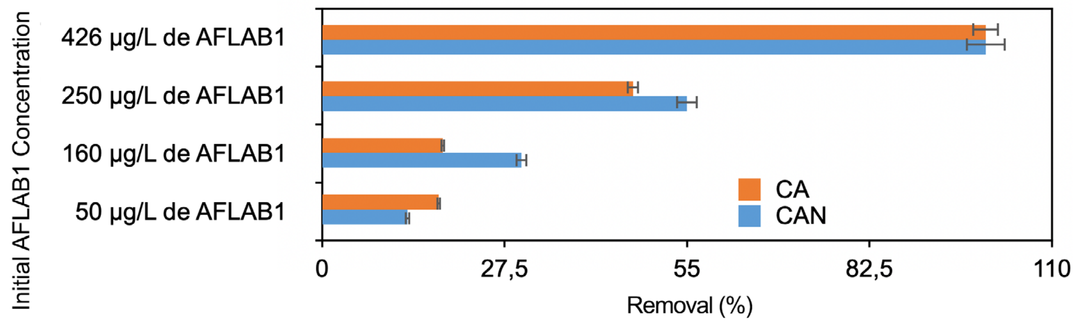
Figura 3. *Eliminación de aflatoxina B1 (AFLAB1)*



Note: Elimination of aflatoxin B1 (AFLAB1) using CA and CAN functionalized activated carbons after 15 minutes of testing at initial AFLA concentrations ranging from 0.05 mg/L to 0.426 mg/L in a pH 7.4 buffer. Prepared by the authors.

The adsorption efficiencies followed the order CAN>CN for most of the AFLAB1 concentrations evaluated. It might be assumed that adsorption is always conditioned by the porous space of the materials, meaning that materials such as CAN, with a smaller micropore space, would exhibit the lowest elimination capacity. However, CAN demonstrated a greater affinity for AFLAB1 despite having an area 11% smaller than its CA analog (Table 1). This same trend was observed during CBD adsorption. This phenomenon could be explained by considering that, although microporous space is reduced when nitrogen is introduced to the surface, this reduction is offset by an increased affinity of the nitrogen groups for CBD and AFLAB1 molecules, both of which are electron-rich anionic structures. The strong affinity between CAN and AFLAB1 compared to unmodified CA is attributed to hydrogen bonding between the electrons of AFLAB1's aromatic rings and the electropositive hydrogens covalently bonded to the nitrogen atom on the CAN surface (Alkorta, Elguero y Frontera 2020). The findings of this study are promising, as the World Health Organization (WHO) recommends the absence of AFLAB1 in living organisms due to its carcinogenic, mutagenic, and teratogenic effects. Aflatoxin removal is often limited by the inability of conventional adsorbent-based methods to eliminate AFLAB1 concentrations in the μg/L range. However, in this study, complete removal was achieved in less than 20 minutes using only 10 mg of carbon.

Conclusions

Throughout this study, carbonaceous materials were successfully developed from agro-industrial waste with tailored chemistry to enhance cannabinoid loading and release under simulated physiological conditions, followed by aflatoxin removal. The results were highly promising, revealing delivery capacities of up to 14 mg of CBD per gram of carbon over 400 minutes through the gastrointestinal tract. Additionally, the same material demonstrated the ability to remove up to 100% of aflatoxin at a concentration of 426 μg/L. The nitrogen group modifications proposed for the carbon material proved beneficial in enhancing CBD immobilization, ensuring gradual release under physiological conditions, and ultimately facilitating AFLAB1 removal through irreversible chemical interactions. Finally, this type of study represents a valuable alternative, as it contributes to the transition from illicit crop cultivation to cultivation for phytotherapeutic purposes.

Acknowledgments

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Origin

This article is the result of the research project “Cannabis Nanocomposites for Controlled Release and Incorporation in Food Supplements,” a study focused on the replacement of illicit crops, the promotion of science for peace in Colombia, and the inclusion of women in science. The project has a one-year implementation period and is still ongoing.

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Availability of Data and Materials

Data and material availability is overseen by Professor Karol Zapata Acosta, who can be contacted at kzapata@unal.edu.co.

Conflict of Interest

The authors declare no conflict of interest.

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