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STUDY OF THE INCORPORATION OF PROPOLIS INTO KOMBUCHA BACTERIAL CELLULOSE MEMBRANE AND ITS RELEASE KINETICS

ESTUDO DA INCORPORAÇÃO DA PRÓPOLIS EM MEMBRANA DE CELULOSE BACTERIANA DA KOMBUCHA E SUA CINÉTICA DE LIBERAÇÃO

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ABSTRACT

Kombucha tea is a beverage obtained from a symbiotic culture of acetic acid bacteria (*Komagataeibacter*, *Gluconobacter*, and *Acetobacter*) and lactic acid bacteria (*Lactobacillus*, *Lactococcus*), which during the fermentation process, produce bacterial cellulose (BC), a biopolymer free from lignin and hemicellulose. BC is biodegradable, non-toxic, and biocompatible, yet it has been underexplored in the literature. The objective of this study was to establish a methodology for incorporating different concentrations of propolis extract and to evaluate its potential for controlled release through in vitro degradation studies, for therapeutic purposes. Studies have shown that propolis exhibits bactericidal, anti-inflammatory, and tissue regenerative properties, and when applied to biological tissues, it does not cause hypersensitivity reactions. Fourier-transform infrared spectroscopy (FTIR) analyses revealed that kombucha bacterial cellulose membranes incorporating propolis showed good physical interaction. Additionally, ultraviolet-visible spectroscopy (UV-Vis) indicated a reduction in the release rate of propolis into the medium.

Keywords: bacteria; incorporation of extracts; Controlled Release System.

RESUMO

O chá de Kombucha é uma bebida obtida a partir de uma cultura simbiótica de bactérias de ácido acético (Komagataeibacter, Gluconobacter e acetobacter) e bactérias de ácido láctico (Lactobacillus, Lactococcus), as quais, durante o período de fermentação, são capazes de produzir a chamada celulose bacteriana (CB), um biopolímero isento de lignina e hemicelulose que, além de ser biodegradável, atóxica e biocompatível, tem sido pouco explorado na literatura. O objetivo deste trabalho consistiu em determinar uma metodologia de incorporação de diferentes concentrações de extrato de própolis e avaliar o potencial para a liberação controlada da própolis por meio de estudo de degradação in vitro, para fins terapêuticos. Estudos demonstram que a própolis apresenta uma ação bactericida, anti-inflamatória e regeneradora tecidual, e que, quando aplicada em tecidos biológicos, não causa reações de hipersensibilidade. Por meio das análises de espectroscopia de infravermelho com transformada de Fourier (FTIR) foi possível observar que as membranas de celulose bacteriana de kombucha com a incorporação da própolis tem uma boa interação física e com as espectroscopias no ultravioleta visível (Uv-Vis), nota-se uma redução da taxa de liberação da própolis no meio.

Palavras-chave: *bactérias; incorporações de extratos; Sistema de Liberação Controlada.*

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INTRODUCTION

Propolis is a resinous material used in folk medicine since ancient times due to its numerous health benefits. Currently, it is a raw material to produce various extracts that can be used as pharmaceutical ingredients (ALVES, 2018; SURAN *et al.,* 2021). The characteristics of each type of propolis depend on factors such as hive, location, and seasons (BRAAKHUIS, 2019).

According to Shahinozzaman *et al.* (2021), propolis is a natural antibiotic, which is why it has been used for many years in the treatment of various diseases such as allergies, diabetes, infections, and it also offers protection against skin diseases and burns. Commercially, it can be found in the form of capsules, throat sprays, and tinctures, and it can be applied to the skin as lotions or ointments. Both types of propolis extract, alcoholic and aqueous, show good results. However, depending on the application medium, such as in the treatment of skin burns where the skin is more sensitive and delicate, the aqueous extract is used. On the other hand, the alcoholic extract exhibits inhibitory activity against strains such as *S. epidermidis* and *S. aureus*, leading to the death of these microorganisms (FRANÇA; NASCIMENTO, 2020; KRUPP *et al.,* 2019).

Several biomaterials have been studied as alternatives in the treatment of lesions (KRUPP *et al.,* 2019), aiming to enhance and improve their therapeutic properties. These biomaterials, such as membranes, can serve as matrices, aiding the action of other active compounds like propolis. Currently, there are several products available on the market that assist in the treatment of lesions, including the development of bacterial cellulose membranes from kombucha, which can be applied to facilitate wound healing and contribute to reducing cellular damage (ANDRADE, 2017).

BACTERIAL CELLULOSE

Cellulose is the most abundant biopolymer in the world, with a production rate exceeding 1000 tons per year, and it can be found in various life forms such as plants, bacteria, and fungi (PEREIRA *et al*., 2014; CÉSAR *et al*., 2015). Bacterial cellulose (BC), also known as biocellulose or microbial cellulose, has a molecular formula like that of plant cellulose (SANTOS *et al.,* 2012). However, BC is considered pure, lacking lignocellulose, lignin, and hemicellulose in its composition, and it differs in its physical, mechanical, and chemical properties. Noteworthy among these properties are its high mechanical strength, water retention capacity, and porosity, in addition to being non-toxic, biodegradable, and highly hydrophilic (SILVA, 2020).

BC is synthesized by the bacterium *Komagataeibacter hansenii* (CACICEDO *et al*., 2016; OLIVEIRA *et al.,* 2022). The yield and properties of BC depend on several factors, including the bacterial strain used, the composition of the culture medium, and the operational conditions applied during the cultivation process. BC can be molded into various shapes and sizes, and it can be

sterilized without altering its structure or properties. It can also be easily modified through in situ and ex situ processes (ROMLING; GALPERIN, 2015; SILVA, 2020).

There are different methods to produce BC, ranging from industrial processes to homemade approaches. One common method involves its production in a fermented beverage called kombucha, which contains symbiotic cultures of bacteria and yeasts (SCOBY).

KOMBUCHA

Kombucha tea is a beverage obtained from a symbiotic culture of acetic acid bacteria *(Komagataeibacter, Gluconobacter*, and *Acetobacter*) and lactic acid bacteria (*Lactobacillus*, *Lactococcus*), historically produced by fermenting *Camellia sinensis* tea and a cellulose biofilm containing the symbiotic culture of bacteria and yeast (SCOBY), native to Southeast Asia. These microorganisms, during the fermentation process lasting 7 to 21 days, form a floating biofilm on the surface of the growth medium (AHMED *et al.,* 2020; MOUSAVI *et al*., 2020; SOTO *et al.,* 2018).

Kombucha is produced by fermenting green or black tea with a sucrose content of 5 to 8%, using a starter culture consortium called SCOBY, capable of inhibiting the growth of potentially contaminating bacteria and other microorganisms (GOES, 2020). Other raw materials can also be used to produce this beverage, such as fruit juice, soy, and orange pulp (MIRANDA *et al.,* 2022).

Therefore, the quality of cellulose and its composition can vary depending on the species used, the time of year, and the climatic conditions (GAGGIA *et al.,* 2018). According to MIRANDA *et al.* (2022), several benefits have been demonstrated due to its ease of use, tangy flavor, and especially its beneficial health properties, including oxidative stress control, antimicrobial activity, diabetes treatment and prevention, reduction in cancer proliferation, and improvement in liver function.

CONTROLLED RELEASE SYSTEM

The Controlled Release System (CRS) has revolutionized the field of drug delivery, aiming to prolong the release time and maintain drug concentration within the therapeutic window, responding directly to physiological stimuli related to the damaged area such as pH, light, ionic strength, magnetic stimuli, and temperature (CAVALCANTI, 2023). Among its main advantages, it should be highlighted the reduction in the number of drug administrations, consequently minimizing costs, lowering risks of adverse effects, maintaining low oscillation of therapeutic levels, increasing plasma drug concentration with a longer half-life, and enhancing safety in the use of highly potent drugs (SILVA *et al*., 2018).

According to Filho (2020) and Saghazadeh *et al*. (2018), CRS allows for controlled dosage at the wound site, preventing metabolic deactivation and maintaining drug concentration over an

extended period. It sequentially and selectively activates antibacterial agents, growth factors, cytokines, and other small molecules in a controlled manner, facilitating the wound healing process and often reducing the number of doses administered.

Polymeric materials have been gaining ground in the development of new devices, as highlighted by Rabello (2017). Some studies have focused on incorporating bioactive compounds such as synthetic drugs or natural products into implantable biomaterials. One alternative under study is the use of transdermal systems that utilize the skin surface as a platform for drug delivery. The drug may be contained in a reservoir or dispersed in a matrix system, with controlled release occurring through drug diffusion across the inner membrane, and the device is affixed to the skin using an adhesive (FILHO, 2020).

Therefore, the development of a CRS in wound dressings is not only interesting but also extremely relevant, as it allows the drug to act specifically on the wound site, avoiding high-dose oral medications and potential systemic side effects.

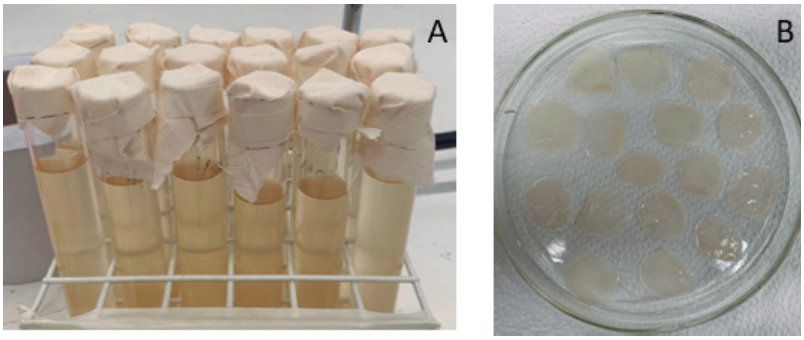
MATERIALS AND METHODS

The membrane of Kombucha Bacterial Cellulose (MCKB) produced in the Fatec Sorocaba Laboratory was used, prepared from a medium consisting of black tea leaves, sucrose, and 1 liter of water. Commercially obtained materials included dry extract of green propolis (PDE) from Henrifarma Chemical and Pharmaceutical Products LTDA, as well as aqueous extracts of propolis (EEP) and etanolic extracts of propolis (AEP) with a minimum of 11% dry extract, both from Ecoas brand, available in pharmacies.

METHODS OF PRODUCING BACTERIAL CELLULOSE FROM KOMBUCHA

Using the adapted methodology from Gomes (2020) and Amorin (2020), initially, 50 g of sucrose were dissolved at 80 °C in 1000 mL of distilled water in a beaker, to which 5 g of green tea was added. The system was left to infuse for 10 to 15 minutes, after which the tea was filtered and allowed to cool to room temperature. For inoculation, 250 mL of previously fermented tea for 21 days was used, and the Kombucha SCOBY was employed as a pre-inoculum, transferred to test tubes covered with cloth, and kept at room temperature for 14 days for fermentation (Fig. 1A) and subsequent formation of new membranes (Fig. 1B).

Figure 1 - Production of MCBK (A) and Membranes after 14 days of fermentation (B).



Source: Own elaboration.

PURIFICATION OF BACTERIAL CELLULOSE MEMBRANES IN NaOH

For the purification of bacterial cellulose membranes from Kombucha, they were immersed in a 0.1 M sodium hydroxide (NaOH) solution and maintained in a water bath at 80 °C for 1 hour. Subsequently, the membranes were washed repeatedly with distilled water until the medium reached a neutral pH (pH 7.0).

METHODS OF INCORPORATING PROPOLIS INTO BACTERIAL CELLULOSE MEMBRANES FROM KOMBUCHA

After purifying the bacterial cellulose membranes from Kombucha (BCMK), they were transferred to Eppendorf tubes, to which different concentrations of propolis were added in mass and volume (5%, 10%, and 20%), as shown in Table 1.

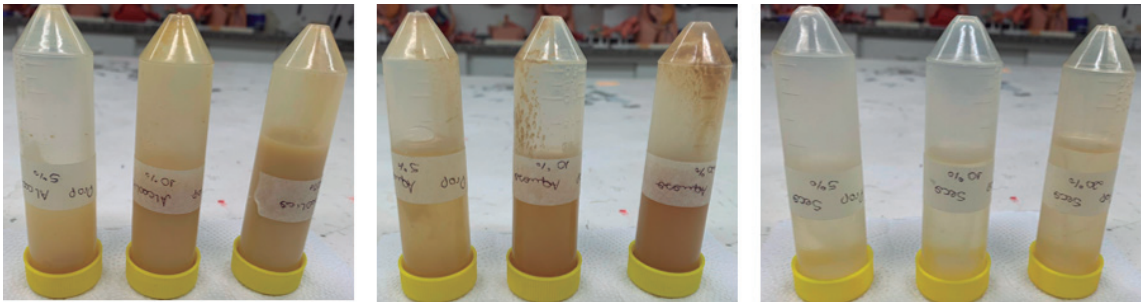
Table 1 - Composition of bacterial cellulose membranes from Kombucha with different types and concentrations of propolis.

Membranes	PDE (g)	AEP in Volume (µL)	AEE in Volume (µL)
MCBK	0	0	0
BCMK + PDE 5%	0,09	0	0
BCMK + PDE 10%	0,18	0	0
BCMK + PDE 20%	0,36	0	0
BCMK + AEP 5%	0	900	0
BCMK + AEP 10%	0	1800	0
BCMK + AEP 20%	0	3600	0
BCMK + EEP 5%	0	0	900
BCMK + EEP. 10%	0	0	1800
BCMK + EEP. 20%	0	0	3600

***BCMK** (bacterial cellulose membranes from Kombucha); **PDE** (propolis dry extract); **AEP** (Aqueous extract of propolis); **AEE** (Etanolic extract of propolis).
Source: Own elaboration.

Thus, as illustrated in Figure 2, the membranes were kept immersed in their respective solutions for 72 hours at room temperature.

Figure 2 - Membranes immersed in different concentrations of propolis.



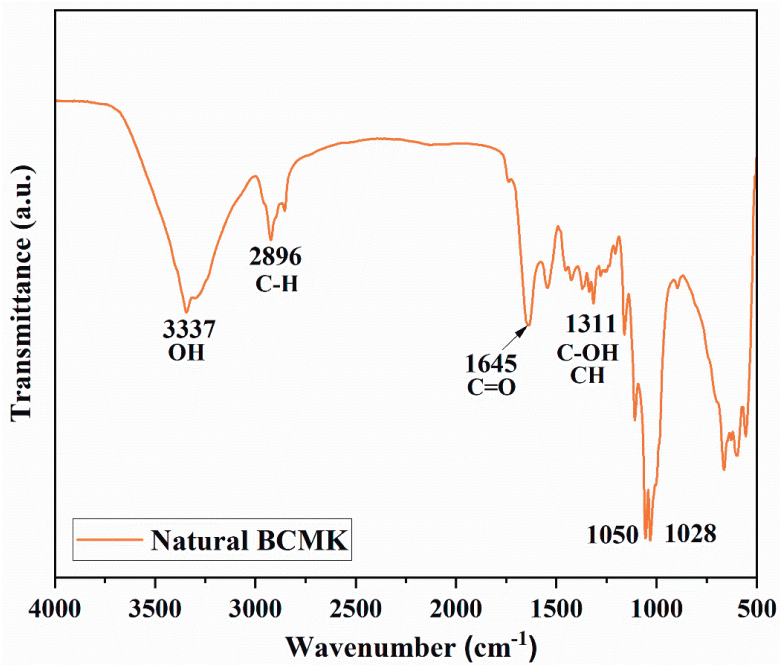
*Although some residues inherent to the solubilization of propolis can be observed, they do not interfere with the obtained membrane
Source: Own elaboration.

RESULTS AND DISCUSSION

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

The samples were submitted to FTIR analysis to verify the physicochemical interaction between both analyzed constituents. Therefore, according to Fig. 3 and Fig. 4A, 4B, and 4C, it is possible to evaluate the main bands of the analyzed samples and the physicochemical interaction of the different concentrations of PDE, AEP and EEP with BCMK.

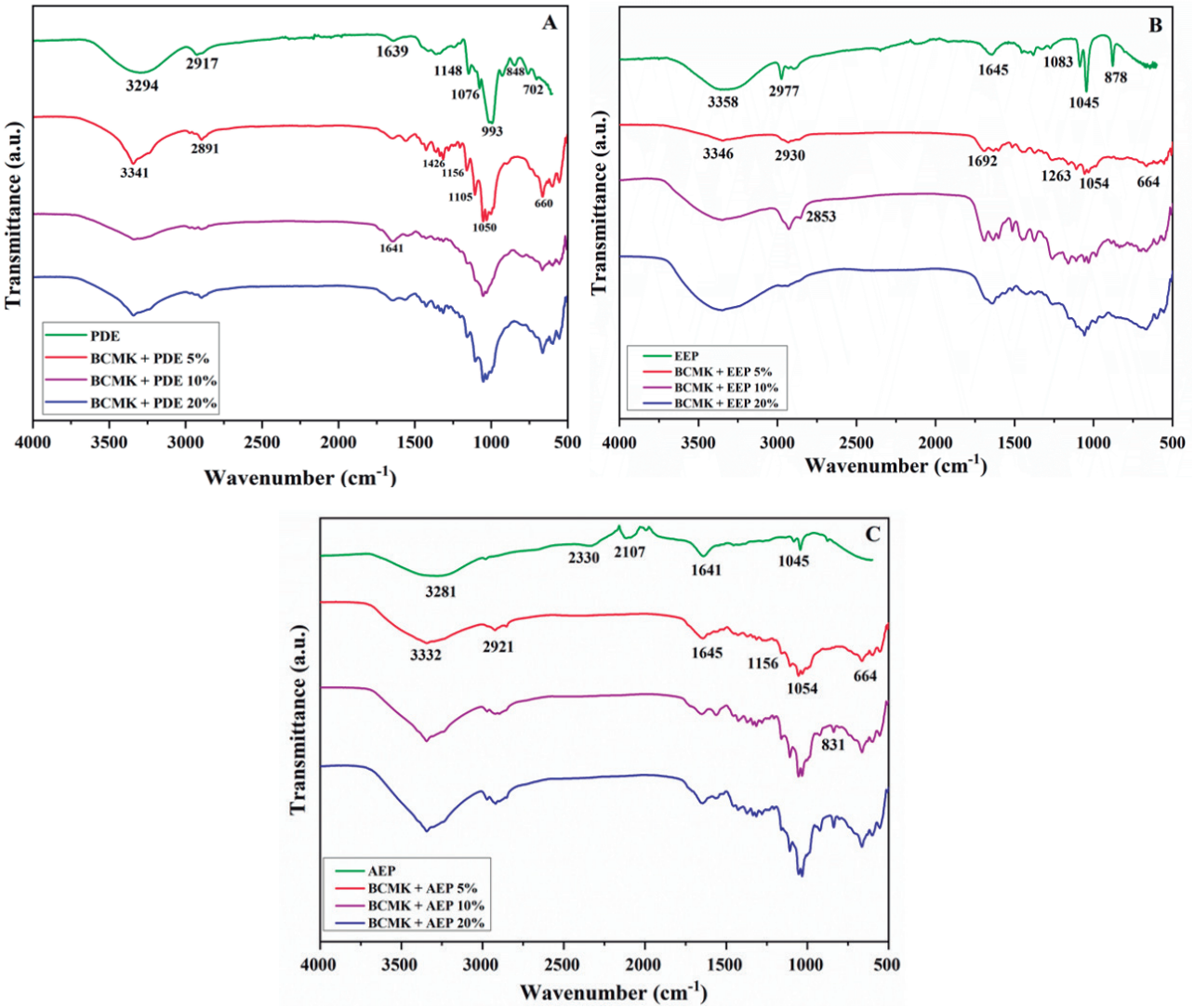
Figure 3 - FTIR of natural BCMK.



It is possible to observe that BCMK presented characteristic bands around 3337 cm^{-1}, which can be attributed to the stretching vibration of the OH group, at 2896 cm^{-1} indicating the presence of C-H stretching vibration, as well as absorption band at 1645 cm^{-1} corresponding to the specific vibration of the C=O group, and at 1311 cm^{-1}, which can be attributed to C-OH and CH deformation, and bands at 1050 cm^{-1} and 1028 cm^{-1}. Indicating the presence of proteins from Kombucha membranes, these being the main attributions that characterize pure BCMK (GOES, 2020; AMORIN, 2020).

Figures 4A, 4B, and 4C present the spectra obtained from BCMK with different types and concentrations of propolis.

Figure 4 - FTIR of BCMK with different concentrations of propolis (5%, 10%, and 20%).



There was no observation of a new band emerging in the BCMK with propolis, although the gradual increase in propolis concentrations in the membranes leads to a broadening of the bands, which is evident in the membranes with EEP and AEP propolis and is mainly associated with the formation of hydrogen bonds between cellulose and propolis. The presence of propolis can be confirmed

through the bands described below (BANKOVA *et al*, 1998 *apud* PICCHI, 2010). It is possible to verify that PDE presented characteristic bands at 3294 cm^{-1}, related to OH stretching of the hydroxyl group associated with polyphenols, at 2917 cm^{-1} axial deformation of C-H for aromatics. The spectra at 1148, 1076, and 993 cm^{-1} were attributed to the stretching vibration of the C-O ester group, at 848 cm^{-1} to angular deformation out of plane for C-H, possibly associated with vibration of the aromatic ring, and at 702 cm^{-1} to the phenyl group (SCATOLINE, 2017; CORCIOVA *et al.,* 2019; PERES *et al.,* 2018).

The EEP showed characteristic bands around 3358 cm^{-1}, corresponding to the characteristic stretching of hydrogen bonded to the hydroxyl group (O-H), typical of phenolic compounds. Additionally, bands were observed at 2977, 2930, and 2853 cm^{-1} corresponding to symmetric stretching of CH_3 and asymmetric stretching of CH_2, which are associated with remnants of waxes according to visual inspection of the alcoholic extract. The bands at 1645 and 1692 cm^{-1} correspond to stretching vibrations of C=C in the aromatic ring, while bands at 1083 and 1054 cm^{-1} were attributed to stretching of the C-O-C bond in aromatic ether, and the presence of bands at 878 cm^{-1} was related to functional groups characteristic of primary and secondary alcohols (REDONDO, 2018; GOMES,2019).

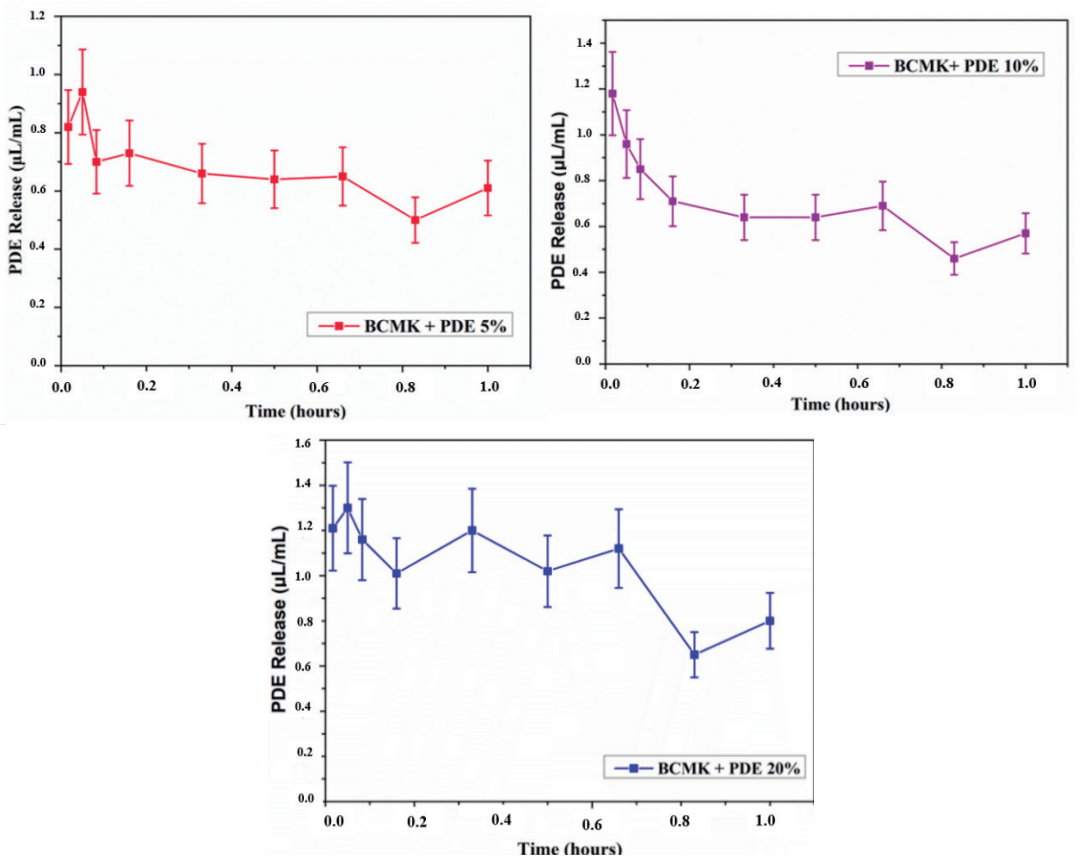
The AEP showed bands around 3281 cm^{-1} corresponding to stretching of -OH or N-H, at 2921cm^{-1} axial stretching of C-H, at 1641 cm^{-1} attributed to angular deformation of C=C in the aromatic ring or bending of $N\text{-}H_2$, at 1645 cm^{-1} corresponding to stretching of C=O, and at 1045, 1054 cm^{-1} referring to stretching of C-O-C and C-O bonds. The bands at 831cm^{-1} correspond to out-of-plane angular deformation of aromatic C-H, indicating a possible physical interaction between Kombucha bacterial cellulose membranes and different concentrations of propolis. Since pure propolis consists of an organic mixture with varied composition, it is important to note that several of the mentioned bands may correspond to vibrations of other unidentified compounds present in its composition (CAMPOS, 2017; BASÍLIO, 2018).

The other extracts, although they show similar vibrations, indicate an increase in alcohol content, evidenced by the elongation of some bands. The alcohol concentration influences a greater extraction of flavonoids, while more aqueous solutions result in a higher extraction of phenolic compounds (CAMPOS, 2021).

Ultraviolet-Visible Spectroscopy (UV-VIS)

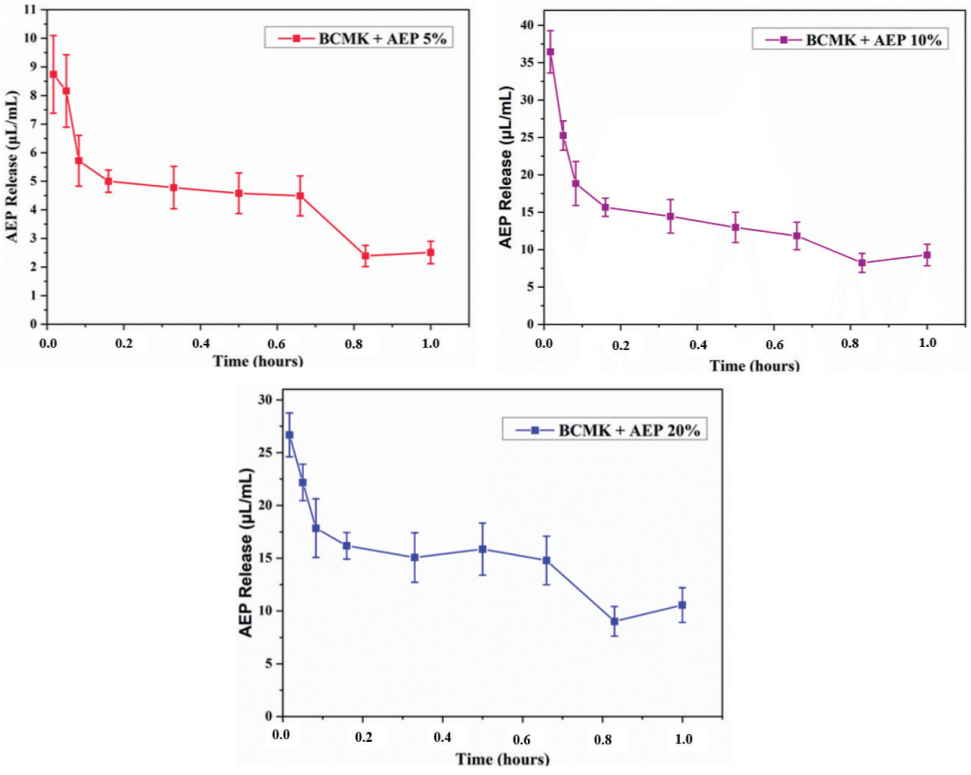
The BCMK incorporated with different concentrations of propolis extracts had their release kinetics determined. Thus, Figures 5, 6, and 7 show the spectra obtained for them with varying concentrations of dry, aqueous, and alcoholic propolis extracts, respectively.

Figure 5 - Propolis extract release test - PDE with 5, 10 and 20%.



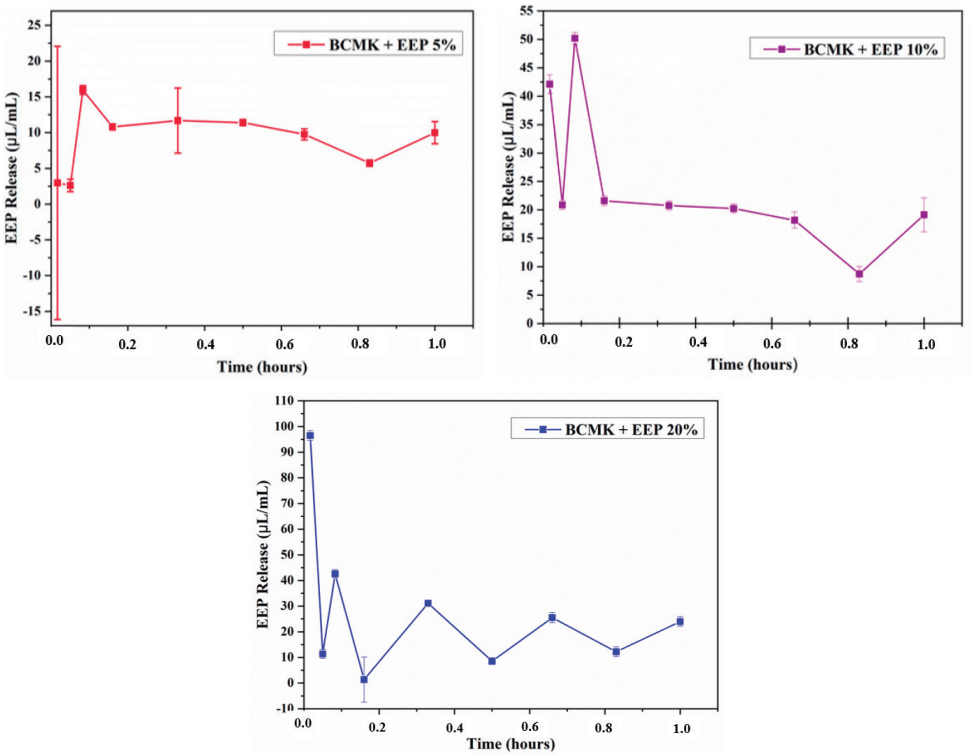
Source: Own elaboration.

Figure 6 - Propolis extract release test - AEP with 5, 10 and 20%.



Source: Own elaboration.

Figure 7 - Propolis extract release test - EEP with 5,10 and 20%.



Source: Own elaboration.

Upon analyzing the results obtained in the initial hours of the assay, it was observed that drug release on the bacterial cellulose membrane of kombucha occurred between 1 and 2 hours, as illustrated in Figures 5 and 6. The membrane incorporated with 5% alcoholic propolis, compared to other samples, shows stability in its release kinetics due to the alcoholic medium. Additionally, the high release peaks observed in membranes with different concentrations of propolis can be valuable in a delivery system, as they provide rapid release.

In the literature, it is reported that the bacterial cellulose membrane has a complex three-dimensional structure, which likely makes the diffusion path of the drug tortuous, thereby justifying the reduction in release rate observed in the graphs (ZANOTI, 2017).

CONCLUSION

It was possible to obtain bacterial cellulose membranes from kombucha through a simple technique using a natural and low-cost culture medium such as green tea. The obtained membranes are pure and do not contain lignocellulose, lignin, or hemicellulose in their composition. Propolis, on the other hand, is a natural product with numerous properties ranging from anti-inflammatory to antifungal, making it suitable for the proposed treatment. These characteristics confer potential and promising applicability for the membranes produced in this study.

Through FTIR analysis, it was concluded that the bacterial cellulose membranes of kombucha with different concentrations of propolis showed good physical interaction. Additionally, the release assay indicated that the membrane likely has a three-dimensional structure, causing the path of propolis release to be tortuous. This observation may explain the reduced propolis release rate in the medium.

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