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Antimicrobial and antibiofilm activities of *Cichorium intybus*: a review

Atividade antimicrobiana e antibiofilme da *Cichorium intybus*: uma revisão

Actividad antimicrobiana y antibiopelícula de *Cichorium intybus*: una revisión

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Abstract
The plant *Cichorium intybus L.*, also known as Chicory, is found in different parts of the world and has a rich phytochemical composition. Within its spectrum of action, the plant has been studied about its performance against pathogenic microorganisms and biofilm. Therefore, the objective of the present study is to realize a literature review on the antimicrobial and antibiofilm actions of the species *Cichorium intybus.* For this, searches were carried out in the databases PubMed / MEDLINE, EMBASE, Gale - Academic OneFile and Science Direct for articles published until August 2020, using the MeSH descriptors “Anti-infective agents“, “Dentistry” and “Periodontal disease” and its derivatives together with the keyword “*Cichorium intybus*” and its variants. A total of 998 results were found. After a critical reading of titles and abstracts, 18 articles were selected for the preparation of the study. The review includes articles published without time restriction and that approach the species *Cichorium intybus* with antimicrobial and antibiofilm action. Case reports and literature reviews were excluded. Chicory has a rich variety of chemical compounds that ensure it a wide range of uses, presenting action against bacteria, fungi and viruses, especially the Hepatitis B virus. Therefore, Almeirão has a good antimicrobial and antibiofilm performance in vitro, however, more studies are needed to standardize the study methodology, in addition to elucidating the clinical practice of the plant.
Keywords: Anti-infective agents; Antibiofilm; Antimicrobial; *Cichorium intybus*.

Resumo
A planta *Cichorium intybus L.*, também conhecida como Chicória, é encontrada em diferentes partes do mundo e possui uma rica composição fitoquímica. Dentro de seu espectro de ação, a planta vem sendo estudada quanto ao seu desempenho contra microrganismos patogênicos e biofilme. Portanto, o objetivo do presente estudo é realizar uma revisão da literatura sobre as ações antimicrobiana e antibiofilme da espécie *Cichorium intybus*. Para isso, foram realizadas buscas nas bases de dados PubMed / MEDLINE, EMBASE, Gale - Academic OneFile e Science Direct para artigos publicados até agosto de 2020, utilizando os descritores MeSH “Anti-infective agentes”, “Dentistry” and “Periodontal disease” e seus derivados juntamente com a palavra-chave “*Cichorium intybus*” e suas variantes. Um total de 998 resultados foram encontrados. Após a leitura crítica dos títulos e resumos, 18 artigos foram selecionados para a elaboração do estudo. A revisão inclui artigos publicados sem restrição de tempo e que abordam a espécie

Cichorium intybus com ação antimicrobiana e antibiofilme. Relatos de caso e revisões de literatura foram excluídos. A chicória possui uma rica variedade de compostos químicos que lhe garantem uma ampla gama de utilizações, apresentando ação contra bactérias, fungos e vírus, principalmente o vírus da Hepatite B. Portanto, o Almeirão apresenta um bom desempenho antimicrobiano e antibiofilme in vitro, porém, mais estudos são necessários para padronizar a metodologia do estudo, além de elucidar a prática clínica da planta.
Palavras-chave: Agentes anti-infecciosos; Antibiofilme; Antimicrobianos; *Cichorium intybus*.

Resumen
La planta *Cichorium intybus* L., también conocida como a chicoria, se encuentra en diferentes partes del mundo y tiene una rica composición fitoquímica. Dentro de su espectro de acción, se ha estudiado la planta en cuanto a su comportamiento frente a microorganismos patógenos y biofilm. Por tanto, el objetivo de este estudio es realizar una revisión de la literatura sobre las acciones antimicrobianas y antibiofilm de la especie *Cichorium intybus*. Para ello, se realizaron búsquedas en las bases de datos PubMed / MEDLINE, EMBASE, Gale - Academic OneFile y Science Direct de artículos publicados hasta agosto de 2020, utilizando los descriptores MeSH "Agentes antiinfecciosos", "Odontología" y "Enfermedad periodontal" y sus derivados junto con la palabra clave "*Cichorium intybus*" y sus variantes. Se encontraron un total de 998 resultados. Luego de la lectura crítica de los títulos y resúmenes, se seleccionaron 18 artículos para la elaboración del estudio. La revisión incluye artículos publicados sin restricción de tiempo y que abordan la especie *Cichorium intybus* con acción antimicrobiana y antibiofilm. Se excluyeron los informes de casos y las revisiones de la literatura. La achicoria tiene una rica variedad de compuestos químicos que garantizan una amplia gama de usos, actuando contra bacterias, hongos y virus, especialmente el virus de la Hepatitis B. Por lo tanto, Almeirão tiene un buen desempeño antimicrobiano y antibiofilm in vitro, sin embargo, se necesitan más estudios para estandarizar la metodología de estudio, además de dilucidar la práctica clínica de la planta.
Palabras clave: Agentes anti-infecciosos; Antibiopelícula; Antimicrobianos; *Cichorium intybus*.

1. Introduction

In the last years, the search for natural alternatives to conventional treatments has grown vertiginously. Since antiquity, records of the use of compounds from natural agents, such as plants, were found for different medicinal purposes (Eldin & Dunford, 2011). The phenomenon of phytotherapy has invited an increasing number of people and studies, because it has natural compounds that have, among other advantages, greater bioavailability, greater accessibility for acquisition by the population, less toxic effects due to biocompatibility and, finally, pharmacological results equivalent or better than conventional ones (Francisco, 2010).

Among the studies in the field of phytotherapy, there is the species *Cichorium intybus* L., popularly known for "Chicory" (Shaikh *et al.*, 2016; Khatami *et al.*, 2018) or "Purple Swallow" (Mazzaglia *et al*., 2020) or "Almeirão" (Bezerra *et al., 2017*). The genus *Cichorium*, to which the species belongs, is found in various places in the world, is more common in the region of Europe and Asia. Its use is reported in Greece, China and India due to its broad medicinal spectrum (Brieudes *et al.*, 2016; Aisa *et al.*, 2020). Of these uses in traditional medicine, the use of plant roots in the treatment of wounds, stings of venomous animals, such as snakes and scorpions, skin diseases, in addition to anti-inflammatory, antiangiogenic and antinociceptive, antiprotozoal actions, potentially anticancer and, according to studies in rats, has a protective effect against the immunotoxicity of alcohol (Kim *et al*., 2002; Lee *et al.*, 2015; Kandil *et al*, 2019; Woolsey *et al.*, 2019; Aisa *et al.*, 2020).

Its composition rich in phenylpropenoids, flavonoids, polysaccharides (such as inulin), sesquiterpenoids, triterpenoids, steroids, proteins, lipids, nitrogenous components (such as caffeine) and organic acids may be the reason for the variety of actions to which the plant is attributed (Daglia *et al.*, 2011; Bezerra *et al.*, 2017; Aisa *et al.*, 2020). Among the organic acids of the species, chicoric acid demonstrated antiviral action against the Hepatitis B virus and Human Immunodeficiency Virus (HIV). Caftáric acid is found in higher concentrations than in other plant species researched in the literature (Brieudes *et al.*, 2016).

In addition, evidence of the use of the species within the dental field is also found, such as in the increase of salivary secretion in cases of xerostomia (Chamami *et al.*, 2011), in the fight against caries disease by inhibiting the adhesion of the bacterial species *Streptococcus mutans* (Gazzani *et al.*, 2012; Signoretto *et al*., 2013), in the control of the species

Pseudomonas aeruginosa, related to patients affected with nosocomial pneumonia (Petrovic *et al*., 2004; Souto *et al.*, 2014), adjuvant to the treatment of periodontal disease, aiming to control this condition (Babaei *et al.,* 2018) and in the antibacterial activity against *Prevotella intermedia* and *Actinomyces naeslundii*, species related to gingivitis (Canesi *et al*., 2012).

Given the above, the objective of the present study was to evaluate the antimicrobial and antibiofilm action of bitter chicory from the existing literature, focusing on activities of interest in dentistry.

2. Methodology

The literature review followed the precepts of the exploratory study, through a bibliographic search in books and scientific articles on the subject. The qualitative method was used by the researchers because it allows the interpretation and issue of their opinions about what is studied (Pereira et al., 2018). Different searches were carried out, including articles that addressed the plant's antibiofilm or antimicrobial properties, without time restrictions but the articles should be published until 2020, august. The searches were carried out by a single researcher in the period of September 2020.

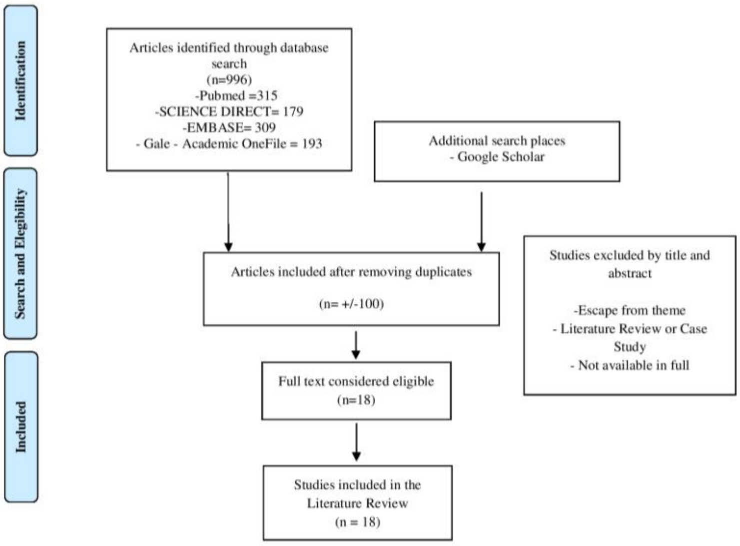
Literature reviews and books relevant to the topic were used in the body of the text, contributing to the discussion of the results. Articles were excluded by the exclusion criteria (escape from the theme, duplicates, not available in full) until reaching the articles included in the literature review. Electronic searches were performed in the PubMed / MEDLINE, EMBASE, Gale - Academic OneFile and Science Direct databases for articles published until August 2020, in addition to the complementary use of Google Scholar.

In the PUBMED database, the first research was carried out by combining the MeSH descriptors *"Anti-infective agents" "Dentistry" and "Periodontal disease"* and its derivatives, together with the keyword "*Cichorium intybus*" and synonyms joined with Boolean operator “AND”. In total, 315 articles were found for further analysis of the title and abstract.

In the EMBASE library with terms cataloged in Emtree, 309 studies were found. Finally, the latest searches were carried out in the Science Direct and Gale - Academic OneFile databases using a combination of keywords resulting in 179 and 193 articles, respectively.

The flowchart (Figure 1) presented describes the number of articles found, how many excluded by the exclusion criteria (escape from the theme, duplicates, not available in full) until reaching the articles included in the literature review. Selection according to criteria was fundamental for the best reliability and power of generalization of the conclusions of this study.

Figure 1: Study flowchart



Source: Own Authorship, 2022

3. Results and Discussion

After the vast literature search, the articles were selected by title and abstract, subsequently eliminating duplicates and performing a critical reading of the studies considered eligible (998 articles). Articles were excluded by the exclusion criteria (escape from the theme, duplicates, not available in full) until reaching the articles included in the literature review. From the total of studies found, 18 scientific articles were selected that contemplated the plant's antimicrobial and antibiofilm action for discussion of experimental studies, in addition to ten articles (five *in vitro* studies and five literature reviews) and two books to complement the results. The selection following criteria was fundamental for the better reliability and generalizability of the conclusions of this study.

Phytochemical characteristics of the species Cichorium intybus L.

The plant *Cichorium intybus* L. belongs to the family Asteraceae. It is a small biennial or perennial fragrant herb, which is very common in regions in Europe, North America, Australia and Iraq. Elsewhere, such as in South Africa and Chile, this species is widely used to produce coffee substitutes from the dried, roasted and ground roots of Chicory, which results in a healthier and more affordable drink as a final result. Its leaves are also used in cooking, being consumed as cooked or raw vegetables. In general, fresh chicory contains inulin (68%), sucrose (14%), protein (6%), cellulose (5%), ash (4%) and other compounds (3%) in contrast to dry chicory, which contains inulin (98%) and other compounds (2%) (Nwafor *et al*., 2017; Janda *et al*, 2021). It is rich in phenylpropenoids, flavonoids, such as myricetin, naringenin, apigenin, catechin and luteolin, polysaccharides, sesquiterpenoids, triterpenoids, steroids, nitrogen components and organic acids (Bezerra *et al*., 2017; Gur *et al*., 2017; Aisa *et al.*,2020, Suleman *et al*., 2020). In addition, it has high levels of chicory acid (antiviral action), caffeic acid (Brieudes *et al.*,2016) quinolinic acid, succinic acid, oxalic acid and chiquimic acid (Papetti *et al.*, 2013).

Bitter chicory leaves are used in several studies (Rani *et al*., 2004, Quave *et al*., 2008; Zhang *et al*., 2014; Eslami *et al*., 2017; Abdullah *et al*. 2019). In relation to the composition, total phenolic content (higher in leaves) was 865.91 mg gallic acid equivalent/100 g (d.w.), being catechein (96.41 mg/100 g d.w.), catechol (5.13 mg/100 g d.w.), epicatachin (13.12 mg/100 g d.w.) and coumarin (11.10 mg/100 g d.w.); flavonoid contente was 112.38 mg quercetin equivalent (QE)/100 g d.w. (Khafaf *et al*., 2018). Caffeic acid (1.27 mg/100 g d.w.), gallic acid (1.52 mg/100 g d.w.), 4-amino-benzoic (8.61 mg/100 g d.w.), p-

OH-benzoic (11.93 mg/100 g d.w.), caffene (68.76 mg/100 g d.w.), ferulic acid (5.85 mg/100 g d.w.), iso-ferulic acid (49.10 mg/100 g d.w.), e-vanilic acid (131.02 mg/100 g d.w.), benzoic acid (77.50 mg/100 g d.w.), ellagic acid (91.19 mg/100 g d.w.), alpha-cumaric (7.58 mg/100 g d.w.), 3,4,5-methoxycinnamic (6.37 mg/100 g d.w.), salycilic acid (15.76 mg/100 g d.w.) and cinnamic acid (0.70 mg/100 g d.w.) was identificate (Khalaf *et al*., 2018). Moreover, the plant is rich in chicory acid with a content of 370 mg / kg fw reported by Bahri et al. (2012). Ferioli and D'Antuono (2012) detected various sesquiterpene lactones in leaves of two different cultivars of chicory. They quantified the presence of free and bounded forms of sesquiterpene lactones, 25 and their content was: 11(S), 13-dihydrolactucin (437.4 mg/kg d.w.), lactucin (350.3 mg/kg d.w.), 8-deoxylactucin (598.8 mg/kg d.w.), 11(S),13-dihydro-8-deoxylactucin (613.9 mg/kg d.w.), 11(S),13- dihydrolactucopicrin (69.5 mg/kg d.w.) and lactucopicrin (315.7 mg/kg d.w.) (Perovic *et al*l., 2021).

Its roots is rich in inulin, consider major natural source, it is a fructose polymer with β-(2-1)-glycosidic-linkage which is a long-chain carbohydrate. That content varies from 11-20 g inulin/100 g in the fresh root (Figueira *et al*, 2004) to 44.69% inulin on dry root weight basis (Nwagor *et al*, 2017). Chicory root contains higher amount of camphor, gamaterpinene and cymene (20.74%, 13.24% and 15.06%, respectivement). Other volatile compounds found in chicory root are octane (34.3-69.8%), nonadecane (0.3-3.9%), aliphatic compounds and their derivates (64.1-81.3%) and tentatively identified compounds (4.8-22.7%) (Judzentiene & Budiene, 2008). There are three sesquiterpene hydrocarbons, two oxygenated sesquiterpenes and nine aliphatic compounds with share of 17.1%, 4.8% and 78.1 %, respectively. According Spina et al. (2008), total phenolic contents were significantly different for wild and cultivated chicory root (22.4 and 35.1 mg gallic acid equivalent /100 g, respectively). Juśkiewicz, Zduńczyk, Żary-Sikorska, Król, Milala e Jurgoński (2011) found the content of caffeoylquinic acids (0.50 g / 100 g), monocaffeoylquinic acids (0.30 g / 100 g) and Dicafeoilquinic acids (0.20 g / 100 g) in lyophilized chicory root. Caffeic acid 1.27 mg/100 g d.w. is present in chicory root with content of 35.22%, protocatechuic (7.98 mg/100 g d.w.), p-hydroxybenzoic (11.04%), iso vanillic (1.97%, 30.66 mg/100 g d.w.) and p-coumaric acids (9.65%, 22.84 mg/100 g d.w.) were also present in chicory root (Nwafor *et al*., 2017). The most abundant sesquiterpene lactones isolated from the root of *Cichorium intybus* L. are lactucin, 8- deoxylactucin, 11(S),13-dihydro-8-deoxylactucin, lactucopicrin, 11(S),13-dihydrolactucopicrin, jacquinelin, crepidiaside B, lactuside A (Willeman *et al*., 2014). Poli et al. (2002) mentioned that sequiterpene lactone content depends on the harvest date. This composites are target of studies with the purpose of evaluating the plant's antimicrobial activity (Quave *et al*., 2008).

The seeds of the species *C. intybus* were the most prevalent among the selected studies, mainly due to their rich composition demonstrated in the phytochemical analysis by other authors (Mehmood *et al*., 2012; Aisa *et al*, 2020). Tannins and flavonoids are present in *Cichorium intybus L.* seeds in percent of 14.53±0.02, 14.13% respectively (Abbas *et al*., 2012). Jurgoński, Juśbkiewicz, Zdunczyk and Bogusław (2012) determined 9.6 g phenolic compounds/100 g fresh mass including mono- and dicaffeoylquinic acids (caffeoylquinic acids (CQA), 2.8 g/100 g f.w. and 6.8 g/100 g f.w. respectively) and contain the smallest amount of total fructans (1.9% d.w.) (PEROVIC et al., 2020).

The plant's stem and flowers are used on a smaller scale (Abdullah *et al*, 2019; Moghaddam *et al*., 2019). Shad et al. (2013) determined the most important compound is phenolic acids content of 2.09±0.21g/100g d.w.

Thus, it is observed that there is a wide range of phytochemical compounds presented by *C. intybus* L., which are distributed in all parts of the plant. While reading the selected articles that aimed to evaluate the antimicrobial and antibiofilm activity of the species under study and other plants, it was observed that many researchers chose to use different extracting solvents, due to the different polarities of the chemical compounds, among which they ethanolics (Ahmad *et al*, 1998; Quave *et al*., 2008; Shaikh *et al*, 2016; Gur *et al* 2017), aqueous (Ahmad *et al*, 1998; Rani *et al*, 2004; Quave *et al*., 2008; Sharma *et al*, 2014; Rahman *et al*., 2016; Shaikh *et al*, 2016; Khatami *et al*., 2018), hexanolic (Ahamad *et al*, 1998; Rahman *et al*., 2016), methanolics (Rani *et al*, 2004; Mehmood *et al*., 2012; Abdullah *et al*, 2019; Moghaddam *et al*, 2019) ethyl acetate (Shaikh *et* *al*, 2016), chloroform (Rahman *et al*, 2016), hydroethanolic (Eslami *et al*., 2017) hidroethanolic (Eslami *et al*., 2017) and hydromethanolic (Suleman *et al*., 2020).

In addition, other authors extracted fractions of the prefabricated extracts, and obtained aqueous solutions (Rehman *et al*., 2014), ethanolic (Rehman *et al*, 2014), in ethyl acetate (Mehmood *et al*., 2012; Rahman *et al*., 2014), n-hexane (Mehmood *et al*, 2012; Rahman *et al*, 2014), chloroform (Mehmood *et al*., 2012; Rahaman *et al*., 2014), and n-butanol (Mehmood *et al*., 2012). Two studies also used low and high molecular weight fractions, which are being increasingly searched for their promising results (Spratt *et al*., 2012; Papetti *et al*., 2013).

Experimental studies of the species Cichorium intybus L.

Experimental studies that addressed the theme of *C. intybus* antimicrobial or antibiofilm actions are shown in Table 1.

Table 1: Characteristics Experimental Studies.

AUTHOR	OBJECTS, DESIGN	MICROOGANISM	EXTRACT/ FRACTION	PART	*RESULTS*
AHMAD; MEHMOOD; MOHAMMAD, 1998	82 Indian plant species, among them the *Cichorium intybus, in vitro*	*Bacillus subtilis; Escherichia coli; Proteus vulgaris; Salmonella typhimurium; Pseudomonas aeruginosa; Staphylococcus aureus*	Extracts: Aqueous; Ethanolic; Hexanolic (20g:100ml)	Whole plant	*Ethanol extract: Action against the growth of B. subtilis and S. aureus bacteria. Aqueous extract: No results. Hexanolic extract: No results*
RANI; KHULLAR, 2004	54 plants, including *Cichorium intybus*	*Salmonella typhi (*B330) Antibiotic resistent *Salmonella typhi* (MTCC 531)	Extracts: Aqueous; Methanolic (50mg/mL)	Leaf	*Methanolic extract: Moderate inhibiting activity against S. typhi (B330). Aqueous extract: Without inhibition.*
QUAVE ET AL., 2008	168 plants	*Staphylococcus aureus methicillin resistant*	Extract: Ethanol (1g: 10mL) Aqueous (1g: 50mL)	Basal leaves Roots	*Ethanolic extract: Limited in relation to S. aureus, and has shown no results in inhibiting the formation of its biofilm. Aqueous extract: No results.*
MEHMOOD ET AL., 2012	*Cichorium intybus*	*Pasteurella multocida, Escherichia coli; Bacillus subtilis; Staphylococcus aureus; Aspergillus flavus; Aspergillus niger; Rhizoctonia solani*	Extract: Methanolic Fractions: Ethyl acetate; Chloroform; N-butanol; N-hexane (Does not report concentration used)	Seed	*Methanolic extract: It showed good activity against E. coli and P. multocida, but less activity was shown against A. niger and B. subtilis. Fraction of ethyl acetate: Strong activity against E. coli. and S. aureus, but bad against A. flavus and A. niger Chloroform fraction: Good against S. aureus and E. coli, but bad against B. subtilis and P. multocida. N-butanol fraction: Good against P. multocida and S. aureus, but bad against A. flavus and A. niger. N-hexane fraction: Good against S. aureus and E. coli, but bad against A. flavus and B. subtilis.*
SPRATT ET AL., 2012	Green and black tea *(Camellia sinensis)* Cranberry juice *(Vaccinium macrocarpo)* Rasberry *(Rubus idaeus)* Shiitake mushrooms *(Lentinula edodes)* Red chicory *(Cichorium intybus)* Beer (Guinness)	*Streptococcus sanguinis; Actinomyces naeslundii; Fusobacterium nucleatum; Prevotella intermedia; Streptococcus mutans; Lactobacillus casei; Veillonella dispar; Neisseria subflava*	Fractions: Low molecular mass High molecular mass (Does not report concentration or solvent used)	-	*Satisfactory action of Low Molecular Mass: Preventing the formation of biofilm of species related to gingivitis, disrupting pre-existing biofilms of dental caries bacteria and inhibiting the adhesion and invasion of the bacterium A. naeslundii to gingival epithelial cells.*

PAPETTI ET AL., 2013	Quinolinic acid Succinic acid Oxalic acid Shikimic acid (*C. intybus compounds*)	*Actinomyces naeslundii; Prevotella intermedia; Streptococcus mutans; Fusobacterium nucleatum; Veilonella dispar; Neisseria subflava; Streptococcus sanguinis; Lactobacillus casei*	Fraction: Low molecular mass (Does not report concentration or solvent used)	-	*Succinic acid: inhibited biofilm formation of all bacteria* *Quinolinic acid: Inhibited the biofilm formation of microorganisms, especially S. mutans and P. intermedia.* *Shikimic acid: It broke the biofilm of S. mutans and A. naeslundii.*
SHARMA ET AL., 2014	*Cichorium intybus* Coffe	*Streptococcus mutans*	Extract: Aqueous (20g:250mL)	-	*C. intybus pure:It showed a smaller number of bacterial colonies than the other groups.*
ZHANG ET AL., 2014	Chicory acid (one of the main compounds in *C. intybus*)	Hepatitis B vírus	(Does not report the solvent used)	Sheets	*Chicory acid: Effective against the virus.*
REHMAN ET AL., 2014	Cichorium intybus	*Escherichia coli; Klebsiella pneumoniae; Pseudomonas aeruginosa; Staphylococcus epidermidis; Staphylococcus aureus* (resistente à meticilina); *Bacillus subtilis; Aspergillus flavus; Aspergillus niger; Aspergillus fumigatus; Fusarium solani*	Extract: Ethanol (3mg / mL) Fractions: N-hexane; Chloroform; Watery; Ethyl acetate (4 mg / mL)	Whole plant	*Ethanol extract: Activity against P. aeruginosa, A. niger, A.flavus and S. aureus.* *Fractions of n-hexane and chloroform: Activity in P. aeruginosa, K. pneumoniae, B. subtilis, S. epidermidis and S. aureus.* *Aqueous fraction: Activity against P. aeruginosa, A. niger, A. fumigatus, A. flavus and S. aureus.* *Fraction of ethyl acetate: Activity against F. solani, B. subtilis and S. aureus.*
RAHMAN ET AL., 2016	*Cichorium intybus*	*Pseudomonas aeruginosa; Staphylococcus aureus; Escherichia coli; Acinetobacter baumannii*	Extracts: Aqueous; Chloroform; Ethanolic; Hexanolic (25g / L in DMSO)	Seed	*Aqueous extract: Very satisfactory results on P. aeruginosa and A. baumannii.* *Chloroform, ethanolic and hexanolic extracts: Good results in inhibiting the bacteria S. aureus.*
SHAIKH; RUB; SASIKUMAR, 2016	*Cichorium intybus*	*Staphylococcus aureus; Pseudomonas aeruginosa; Candida albicans; Escherichia coli*	Extracts: Ethyl acetate; Aqueous; Ethanol (1mg / mL)	Seed	*Ethyl acetate extract: Inhibited the growth of P. aeruginosa and S. aureus.* *Ethanolic extract: affected the fungus C. albicans and the bacterium E. coli.* *Aqueous extract: Maximum activity on S. aureus.*
GUR ET AL., 2017	*Cannabis sativa* *Cichorium intybus* *Lavandula stoechas* *Valeriana officinalis* *Glycyrrhiza glabra*	*Bacillus subtilis; Candida albicans; Enterobacter aerogenes; Enterococcus faecalis; Enterococcus faecium; Escherichia coli; Klebsiella pneumoniae; Pseudomonas aeruginosa; Pseudomonas fluorescens; Salmonella enteritidis; Salmonella infantis; Salmonella kentucky; Salmonella typhimurium; Staphylococcus aureus; Staphylococcus epidermidis*	Extract: Ethanol (10-30g / 250mL)	Whole plant	*Ethanol extract: Action against C. albicans and E. faecalis.* *No results: E. aerogenes, E. faecium, E. coli, K. pneumonia, P. aeruginosa, P. fluorescence, S. infantil, S. kentucky, S. aureus, S. epidermidis*
ESLAMI ET AL., 2017	*Cichorium intybus*	*Candida glabrata; Candida krusei*	Extract: Hydroethanolic (1g: 100mL)	Leaf	*Extract: Greater sensitivity of the C. krusei fungus, however a low Minimum Inhibitory Concentration was observed for the two fungi.*
ZHU ET AL., 2018	Chicory acid	*Lactobacillus plantarum; rhamnosus; crispatus; Bifidobacterium longum; Salmonella enteritidis; Shigella typhimurium; Escherichia coli; Listeria monocytogenes*	(Does not report concentration or solvent used)	-	*Chicory acid: did not affect the growth of L. plantarum, L. rhamnosus, L. crispatus and B. longum.* *The concentrations of 120 and 160 mM of the acid inhibited the growth of the pathogens S. enteritidis, S. typhimurium, E. coli and L. monocytogenes.*
KHATAMI ET AL., 2018	*Cichorium intybus* (Silver nanospheres biosynthesized with the plant)	*Pseudomonas aeruginosa; Klebsiella pneumoniae; Acinetobacter baumannii; Fusarium solani*	Extract: Aqueous (7g: 100mL)	Seed	*Nanospheres: Excellent antibacterial activity against selected bacteria, with low values of MIC, MBI, highlighting the results against the fungus F. solani.*
ABDULLAH; AL-SAEDI; SALMAN, 2019	*Cichorium intybus*	*Staphylococcus aureus; Pseudomonas aeruginosa; Escherichia coli; Klebsiella spp.; Proteus vulgaris; Enterobacter spp; Lactobacillus spp; Streptococcus faecalis*	Extract: Methanolic (30g: 300mL)	Leaf Stalk Seed	*Best results: Concentration of 1000 mg / mL of methanolic extract from the leaves against S. aureus, P. aeruginosa, Klebsiella spp., P. vulgaris, Lactobacillus spp. and S. faecalis. Extracts produced from the stem and seeds did not produce satisfactory results.*
MOGHADDAM ET AL., 2019	Fifteen species of medicinal herbs, including *Cichorium intybus*	*Bacillus subtilis; Staphylococcus aureus; Pseudomonas aeruginosa; Escherichia coli; Candida albicans*	Extract: Methanolic (2g: 20mL)	Flowers	*C. intybus: Antibacterial activity against B. subtilis, E. coli and S. aureus, but there was no apparent action against P. aeruginosa and C. albicans*
SULEIMAN, 2020	*Cichorium intybus* *Cinnamomum camphora* *Commiphora myrrha* *Foeniculum vulgare*	*Candida albicans; lipolytica; Enterococcus faecalis; Streptococcus mutans; Micrococcus sp.; Enterobacter cloaca;*	Extract: Hydromethanolic (10g: 100mL)	Seed	*C. intybus: Higher results in Candida lipolytica.*

Source: Own authorship (2021).

In vitro studies were carried out in order to evaluate the effectiveness of *Cichorium intybus* extracts on the bacterium *Staphylococcus aureus*. As noted, this microorganism is predisposed to offer resistance to antibiotics such as methicillin (MRSA), in addition to being a major cause of nosocomial pneumonia and bacterial endocarditis. Many studies have found that the plant acts with the extracts of ethyl acetate, chloroform, n-butanol and n-hexane (Mehmood *et al*., 2012; Rahman *et al*., 2014, Rehmen *et al*., 2016), ethanolic and hexanolic (Ahman *et al*., 1998; Rehman *et al*., 2014), aqueous (Rahman *et al*., 2016), and methanolic (Abdullah *et al*., 2019; Moghaddam *et al*, 2019). Quave et al. (2008), when using ethanolic extracts from basal leaves and roots, concluded that the bacteriostatic activity of bitter chicory was limited in relation to MRSA, and did not show results in inhibiting the formation of its biofilm.

Ahmad et al. (1998) found inhibition of the growth of *Bacillus subtilis* from the ethanolic extract, a bacterium found in dental biofilm. The results of this study differ from Rehman et al. (2014) and Gur et al. (2017) who did not observe the plant's effect on the microorganism in this extract. However, Rehman et al. (2014) observed activity in the fractions of n-hexane, chloroform and ethyl acetate on *B. subtilis*. In methanolic extract, Mehmood et al. (2012) did not observe antibacterial activity on *B. subtilis*, a result different from that found by Moghaddam et al. (2019). The findings can be explained by the different parts of the plant that were used in each study, as well as the concentrations of the extract that were used in the *in vitro* studies.

In the case of the genus *Salmonella spp*., Which is related to intestinal infections, Rani et al. (2004) found action in the methanolic extract, made from the leaves of *C. intybus*, on the serovariety *Salmonella typhi.* Zhu et al. (2018), studying the action of chicoric acid, one of the most abundant organic acids in bitter chicory, also found promising results on a bacterium of the genus, *S. enteritidis*, in concentrations of 120 and 160 mM of the acid. Such antimicrobial action was not observed in the study by Ahmad et al. (1998). Gur et al. (2017) did not identify in the aqueous extracts, ethyl acetate and ethanolic, produced from the seeds of the plant, action on the microorganisms *S. enteritidis, S. infantil, S. kentucky and S. typhimurium*. Suleiman (2020), using the hydromethanolic extract of seeds from the plant on *S. typhimurium* also did not find this effect. This can be explained by the different parts of *C. intybus* used in the study, concentration of extracts and serotypes researched.

The microorganism *Escherichia coli*, involved in infections of sterile tissues (such as the urinary tract) was used to evaluate the antimicrobial activity of *Cichorium intybus.* Mehmood and collaborators (2012), in their study with the seed of the plant, obtained promising results on the bacterium in fractions of ethyl acetate, chloroform and methanolic extract, as well as Moghaddam et al. (2019), who observed in the same extract inhibitory effect of the bacteria. Shaikh et al. (2016) found the action of ethanolic extract on *E. coli*. Other authors have not identified such an action (Ahamam *et al*., 1998; Rehman *et al*., 2014; Rahman *et al*., 2016; Gur *et al*., 2017; Abdallah *et al*, 2019), which can be justified by the use of different parts of the plant, concentrations and solvents.

With regard to the microorganism *Pseudomonas aeruginosa*, frequently associated with pneumonia in people with mechanical ventilation, most of the selected studies found the action of at least one extract or fraction on the bacterium, the most relevant being the fractions of n-hexane and chloroform (Rehman *et al*., 2014), aqueous extracts (Rahman *et al*., 2016), ethyl acetate (Shaikh *et al*., 2016) and methanolic (Abdullah *et al*.,2019). Khatami et al. (2018) demonstrated the effectiveness of nanospheres synthesized from the seeds of bitter chicory on the bacteria in their in vitro study. Ahmad et al. (1998), Gur et al. (2017) and Moghaddam et al. (2019) did not find the same results, and explain that further studies on the use of the ethanolic and methanolic extracts *of Cichorium intybus on P. aeruginosa* are still needed.

The main bacterium involved in the development of caries disease, *Streptococcus mutans*, was investigated in an in vitro study by Spratt et al. (2012), who sought to elucidate the antibacterial activity of bitter chicory on the microorganism in question. Its results with low molecular weight fractions were satisfactory, with the disruption of pre-existing biofilms from the bacteria *S. mutans and L. casei* (also involved in tooth decay). Papeti et al. (2013) also found action in the low molecular weight fraction of succinic, quinolinic and chiquimic inhibition of the *S. mutans biofilm*, while Sharma et al. (2014), when comparing the effects of bitter chicory with coffee, found the same results in inhibiting the bacteria. Suleiman (2020), in his study using the hydromethanolic extract of the plant's seeds, did not observe this same action on *S. mutans*. It is observed that the action of low molecular weight fractions demonstrated promising effects on *S. mutans.*

Still related to oral diseases, two studies aimed to elucidate the action of low molecular weight fractions of *Cichorium intybus* on the microorganisms *Streptococcus sanguinis, Actinomyces naeslundii, Fusobacterium nucleatum and Prevotella intermedia*, involved with gingivitis. Spratt et al. (2012) observed that the fractions prevented the formation of the biofilm of the species, in addition to inhibiting the adhesion and invasion of the bacterium *A. naeslundii* to the gingival epithelial cells. The results of Papeti et al. (2013) with the organic acids present in the plant (quinolinic, succinic, oxalic and chiquimic acids) entered into consensus with Spratt et al. (2012), as they pointed to the effectiveness of succinic and quinolinic acids in inhibiting all bacteria, with emphasis on *P. intermedia* in quinolinic acid. In addition, the shikimic acid presented a rupture of the biofilm of *A. naeslundii*, thus showing the effectiveness of the plant on the growth and biofilm of the microorganisms present in gingivitis.

When understanding that biofilm constitutes a complex microbial community and dysbiosis causes oral problems as well as in face of the unviability of the use of antimicrobials in a continuous way, due to the side effects caused as the dental staining due to the use of chlorhexidine continuously; the search for alternatives becomes inevitable (Marsh & Martin, 2018).
In terms of the plant's antiviral activity, Zhang et al. (2014) studied one of the main compounds of the *C. intybus* plant, chicory acid, seeking to evaluate its effects on the Hepatitis B virus. For the preparation of the extract, its leaves were used. After the analysis, it was observed that the acid was effective against the virus, so it could be improved and later used as an antiviral agent. Brieudes et al. (2016) also highlighted the antiviral action of this organic acid due to its action against the HIV virus.

Regarding the antifungal activity *of C. intybus*, most of the results observed in the studies demonstrate a good action of the aqueous, ethanolic and ethyl acetate fractions against *Aspergillus flavus, Aspergillus niger, Aspergillus fumigatus and Fusarium solani,* (Rehman et al., 2014; Khatami et al., 2018). Ethil acetate fraction inhibiting the total growth of the first three species presented and aqueous to *F.solani* (Rehman et al., 2014), the mechanism of action of these fractions has not yet been explored by the studies but it is essential to find alternatives since the antifungal resistance rises remarkably, requiring alternatives (Buzina et al., 2013).

Mehmood and collaborators (2012), however, found no action of methanolic extract or fractions of ethyl acetate, chloroform, n-butanol and n-hexane on the fungi *Aspergillus flavus, Aspergillus niger and Rhizoctonia solani.* Regarding the fungi *Candida albicans, C. krusei and C. lipolytica*, the ethanolic, hydroethanolic, methanolic and hydromethanolic extracts were effective (Shaikh *et al*., 2016; Gur *et al*., 2017; Eslami *et al*., 2017; Moghaddam *et al*., 2019; Suleman *et al*., 2020).

On the toxicity of the plant, Spratt et al. (2012) found no cytotoxic activity of bitter chicory tested by the trypan blue exclusion test, in agreement with Eslami et al. (2017), who cited the low toxicity reported in laboratory studies performed on rats. Furthermore, Zhang et al. (2014) did not observe cytotoxic activity of chicory acid, one of the main compounds of the plant, on hepatocytes, agreeing with previous authors.

In view of the observed results, it is possible to notice a wide antimicrobial and antibiofilm action of *C. intybus* in the most polar solvents, such as ethanol and methanol, intermediate polarity, such as ethyl acetate and chloroform, and low molecular weight fractions. The microorganisms that were most sensitive to the action of the plant and its chemical components were the bacteria *S. aureus, S. mutans, P. aeruginosa, B. subtilis, S. sanguinis, A. naeslundii, F. nucleatum and P. intermedia.*

The fungi most affected were *C. albicans, C. lipolytica, C. krusei and F. solan*i. In addition, an antibiofilm action was observed, mainly in low molecular weight fractions, in bacteria *S. mutans, L. casei, S. nguinis, A. naeslundii, F. nucleatum and P. intermedia*. Finally, a study also revealed a good action of chicory acid on the Hepatitis B virus.

However, there is no consensus in the literature on the concentration of extracts, the part of the plant and the solvents to be used. Thus, it is necessary to standardize the methodology of the studies to better compare the results, in addition to the selection of microorganisms more sensitive to the bioactive compounds of the species so that promising results are found that prove the antimicrobial and antibiofilm action of *Cichorium intybus*.

4. Conclusion

In view of the observed results, it is possible to notice a wide antimicrobial and antibiofilm action of *C. intybus* in the most polar solvents, such as ethanol and methanol, intermediate polarity, such as ethyl acetate and chloroform, and low molecular weight fractions. The microorganisms that were most sensitive to the action of the plant and its chemical components were the bacteria *S. aureus, S. mutans, P. aeruginosa, B. subtilis, S. sanguinis, A. naeslundii, F. nucleatum and P. intermedia.* The fungi most affected were *C. albicans, C. lipolytica, C. krusei and F. solan*i. In addition, an antibiofilm action was observed, mainly in low molecular weight fractions, in bacteria *S. mutans, L. casei, S. sanguinis, A. naeslundii, F. nucleatum and P. intermedia*. Finally, a study also revealed a good action of chicory acid on the Hepatitis B virus.

However, there is no consensus in the literature on the concentration of extracts, the part of the plant and the solvents to be used. Thus, it is necessary to standardize the methodology of the studies to better compare the results, in addition to the selection of microorganisms more sensitive to the bioactive compounds of the species so that promising results are found that prove the antimicrobial and antibiofilm action of *Cichorium intybus* L.

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