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ANTI-BACTERIAL AND TOXICOLOGICAL ACTIVITY *IN SILICO* OF *CINNAMOMUM CASSIA* ESSENTIAL OIL

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ABSTRACT: The search for natural anti-microbials present in plants has been the target of intense scientific studies over the last years. The objective of this study was to assess the *in-vitro* antibacterial potential and *in silico* toxicology of the essential oil of *Cinnamomum cassia* (Chinese cinnamon) against *E. coli* and *S. aureus* strains. The essential oil was initially solubilized in tween 80 and dimethyl sulphoxide acid (DMSO). The antibacterial action was assessed by means of the minimum inhibitory concentration (MIC) determined from the microdilution in double-concentrated brain heart infusion broth (BHI) and the minimum bactericidal concentration (MBC) which was determined by the depletion in nutrient agar (NA) technique with aliquots of 10µL of the MIC, MIC × 2 and MIC × 4. The MIC and the MBC presented satisfactory and varied results; the *E. coli* LPM 4459, LPM 1243, LPM 4010 and LPM 4896 strains, had a MIC of 256 µg/mL and MBC of 512 µg/mL respectively. As for the *E. coli* LPM 2810 and *S. aureus* LPM 55 strains, they showed a MIC of 128 µg/mL and MBC of 256 µg/mL. In the *in silico* toxicological analysis, a toxic potential was observed only in the p-Cymene and 3-Carene fractions. However, in the p-Mentha-1,4(8)-dien fraction there was no evidence of toxicity. Therefore, the essential oil of *Cinnamomum cassia* has satisfactory anti-bacterial activity, in addition to having a low theoretical oral toxicity when compared to other compounds commonly used in the therapeutics of bacterial infections.

INTRODUCTION: The infectious diseases have become a global concern as the clinical efficiency of many existing antibiotics is being threatened by the rapid growth of multiresistant pathogens [1].

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There is a continuous need to discover new antimicrobial compounds with adequate chemical structures and a new mode of action against pathogenic agents [2].

The natural products present many properties and versatilities for the development of new drugs, especially the anti-microbials, which may have a therapeutic potential for the treatment of infectious diseases [3]. The essential oils (EOs) are suitable to be antimicrobials, both individually, and individually in their isolated compounds, including terpenes,

terpenoids and aromatic compounds, in which have been shown antimicrobial activity against a wide range of pathogens with various spectrum of activities [4]. The phytotherapeutic agents are the main sources of new medicines and may constitute an alternative to usual medicines [5].

The Chinese cinnamon is popularly used to treat inflammatory processes, pain, menstrual disorders, disorders of the blood circulation and fever [6 - 8]. Ethereal extracts of *Cinnamomum cassia* exhibit antioxidant activities and in traditional medicine are used for anti-ulcer effects [9]. The anti-*Candida* and anti-dermatophytic effects of the EO of various species of Cinnamomum have been evidenced over the years [10, 11].

Cinnamon is a dietary phytochemical which demonstrates anti-microbial properties and is particularly significant, in which the dietary chemical products are considered to be reliable and used routinely [12]. Thus, this work aimed to analyze the *in-vitro* antibacterial activity and *in silico* toxicology of the essential oil of *Cinnamomum cassia* against *E. coli* and *S. aureus* strains.

MATERIALS AND METHODS:

Phytoconstituent and Substances: The following substances used in this work were obtained commercially: essential oil (EO) of *Cinnamomum cassia* (purity > 95%), dimethyl sulfoxide acid (DMSO) and tween 80 (0.02%) (all from Sigma-Aldrich, São Paulo, SP, Brazil). The tween 80 and the DMSO were solubilized in a proportion which did not exceed 0.5 % in the tests, subsequently was diluted in sterile distilled water with the EO of the cinnamon in order to obtain a doubly concentrated emulsion of 2048 µg/mL [13, 14].

Bacterial Strains: The tests were carried out with bacterial strains: *E. coli* LPM 2810, LPM 4459, LPM 1243, LPM 4040, LPM 4896 (clinical isolates), *E. coli* ATCC 8859 and ATCC 2536 (standard strains), *S. aureus* (LPM 45 and 55) (clinical isolates) and two standard strains of *S. aureus* ATCC 6538 and ATCC 25213. All the samples belong to the collection of the Research in Microbiology Laboratory (LPM) of the Integrated Faculties of Patos (FIP). All the strains were maintained in NA at 4 °C. Cultures of 24 hrs incubated at 35 ± 2 °C were used in the test.

Inoculum: The suspensions were prepared from recent bacterial cultures streaked in NA and incubated at 35 ± 2 °C during 24hrs. After the incubation, approximately 4-5 colonies were transferred (with a sterile loop) to test tubes containing 5.0 mL of sterile saline solution (NaCl at 0.85%). The resulting suspensions were agitated during 15 seconds with the aid of a vortex mixer (Fanem Ltd., Guarulhos, SP, Brazil). The turbidity of the final inoculum was normalized using a barium sulfate suspension (tube of 0.5 in McFarland's scale). The final concentration obtained was of 1-5 × 10^8 colony forming units per milliliters (CFU/mL) [15, 16].

Determination of the Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC): The determination of the MIC of the product on the strains used in the biological tests was determined by the broth microdilution method as proposed by the National Committee for Clinical Laboratory Standards (NCCLS) [17] and Santurio *et al*., [18] A hundred microliters (100 µL) of the double concentrated BHI liquid medium were transferred to the cavities of a microdilution plate with 96 u-shaped wells (Alamar, Diadema, SP, Brazil). Subsequently, 100 µL of the emulsion of the double concentrated product were inoculated in the first horizontal row of the dish wells. Two-fold serial dilutions were carried out, and an aliquot of 100 µL was removed from the most concentrated well to the following one, producing concentrations of 1024-16 µg/mL.

Finally, 10µL of the bacterial suspensions were added to each well of the plate, in which each column represented a strain. In parallel, the controls were made for the bacterial viability and for the susceptibility to the standard antibiotic chloramphenicol (100 UI/mL). The plates were sealed and incubated at 35 ± 2 °C during 24hrs. After the appropriate incubation time, the presence (or absence) of microbial growth was visually observed. The formation of bunches of cells or "buttons" in the dish wells was considered. The MIC of the EO was defined as the lowest concentration of the product which produced a visible inhibition of growth of the bacteria.

The antimicrobial activity of the product was interpreted (considered active or not) according to

the values of the MIC against the studied pathogens, where the proposed classification criteria are: strong/good activity (MIC < 100 µg/ mL), moderate activity (MIC 100-500 µg/mL), weak activity (MIC 500-1000 µg/mL) and inactive product/no anti-microbial effect (MIC > 1000 µg/mL) [19, 20].

In order to determine the MBC, aliquots of 10µL of the MIC, MIC × 2 and MIC × 4 of the test product were subcultivated. The chloramphenicol (100UI/mL) was the bacterial growth control in Petri dishes containing NA. After 24 hrs of incubation at 35 ± 2 °C a reading was carried out to evaluate the MBC based on the controls. The MBC was defined as the lowest concentration of the product capable of inhibiting bacterial growth or allowing a growth inferior to three CFU, thus resulting in bactericide activity of 99.9 % [15, 21].

The biological activity tests were carried out in duplicate and the results were expressed as the arithmetic average of the MIC and the MBC.

***In silico* Analysis (Osiris):** The prediction process of the biological effects executed by the Osiris software is based on a pre-computerized set of molecular fragments which give origin to the toxicity alerts, in the case of being found in the currently designed molecular structure. The toxicity predictions of the Osiris result in molecular groups capable of producing effects of mutagenicity, tumorigenicity, irritability, possible damages to the reproductive system, cLogP, druglikeness and drug-score of the molecules [22].

Lipinski's rule of five [23] evaluates the similarity of drugs. It determines if a chemical compound with validated pharmacological or biological activity has properties which make it a probable active drug orally in human beings. This rule describes the molecular properties which are important for the pharmacokinetics of a chemical compound in the human body including its absorption, distribution, metabolism and excretion (ADME).

The established rule for the majority of "drug-like" molecules has cLogP ≤ 5, molecular weight ≤ 500 Da, number of hydrogen acceptors ≤10 (nALH ≤ 10) and the number of hydrogen donors ≤ 5 (nDLH ≤ 5). Molecules which violate one of these parameters may have serious problems with bioavailability [23, 24].

RESULTS: The results of the antibacterial activity of the EO of *Cinnamomum cassia* were found from the MIC and the MBC determined by broth microdilution. The values of the MIC for *S. aureus* LPM 45 was 32 µg/mL and the MBC 128 µg/mL. The strains of *E. coli* LPM 4459, LPM 1243, LPM 4040 and LPM 4896, had MIC of 256 µg/mL and MBC 512 µg/mL. The strains *S. aureus* LPM 55 and *S. aureus* ATCC 25213 had MIC 128 and 256 µg/mL, MBC 256 and 1024 µg/mL respectively. The strains *E. coli* ATCC 2536, ATCC 8859 and LPM 2810 had MIC of 256, 256 and 128 µg/mL, as well as a MBC of 1024, 1024 and 256 µg/mL respectively (**Table 1** and **2**).

Besides the values of the MIC and the MBC, *in silico* toxicological analysis of the components of the EO of cinnamon was also carried out, as well as its pharmacological properties enabling an evaluation of the parameters mutagenicity, tumorigenicity, irritability and the possible damage to the reproductive system caused by these compounds in comparison with standard antibiotics **Table 3**.

TABLE 1: MIC VALUES (µg/mL) OF CINNAMON ESSENTIAL OIL AGAINST BACTERIAL STRAINS

Bacterial strains /Treatment	*E. coli* LPM 2810	*E. coli* LPM 4459	*E. coli* LPM 1243	*E. coli* LPM 4040	*E. coli* LPM 4896	*E. coli* ATCC 8859	*E. coli* ATCC 2536	*S. aureus* LPM 45	*S. aureus* LPM 55	*S. aureus* ATCC 25213
1024 µg/mL	+	+	+	+	+	+	+	+	+	+
512 µg/mL	+	+	+	+	+	+	+	+	+	+
256 µg/mL	+	+	+	+	+	+	+	+	+	+
128 µg/mL	+	-	-	-	-	-	-	+	+	-
64 µg/mL	-	-	-	-	-	-	-	+	-	-
32 µg/mL	-	-	-	-	-	-	-	+	-	-
Negative control	-	-	-	-	-	-	-	-	-	-
Positive control	+	+	+	+	+	+	+	+	+	+

(+) inhibition (-) no inhibition

TABLE 2: MBC VALUES (µg/mL) OF CINNAMON ESSENTIAL OIL AGAINST BACTERIAL STRAINS

Bacterial strains /Treatment	*E. coli* LPM 2810	*E. coli* LPM 4459	*E. coli* LPM 1243	*E. coli* LPM 4040	*E. coli* LPM 4896	*E. coli* ATCC 8859	*E. coli* ATCC 2536	*S. aureus* LPM 45	*S. aureus* LPM 55	*S. aureus* ATCC 25213
1024 µg/mL	+	+	+	+	+	+	+	+	+	+
512 µg/mL	+	+	+	+	+	-	-	+	+	-
256 µg/mL	+	-	-	-	-	-	-	+	+	-
128 µg/mL	-	-	-	-	-	-	-	+	-	-
64 µg/mL	-	-	-	-	-	-	-	-	-	-
Negative control	-	-	-	-	-	-	-	-	-	-
Positive control	+	+	+	+	+	+	+	+	+	+

(+) inhibition (-) no inhibition

TABLE 3: OSIRIS CALCULATIONS OF TOXICITY RISKS AND DRUG-SCORE OF COMPOUNDS p-CYMENE, P-MENTHA-1,4(8)-DIEN AND 3- CARENE MONOTERPENES COMPARED TO THE STANDARD ANTIBIOTICS DRUGS

Compounds	Toxicity risk[a]				Drug score[b]					
	MUT	TUMO	IRRI	REP	CLP	S	D-L	nALH	nDLH	Da
p-Cymene					3.19	-2.83	-2.50	0.00	0.00	134.22
p-Mentha-1,4(8)-dien					3.45	-2.33	-3.01	0.00	0.00	136.24
3-Carene					2.72	-2.51	-3.35	0.00	0.00	136.24
Vancomycin					-6.75	-9.42	1.82	33.0	19.0	1449.27
Chloramphenicol					-0.42	-2.36	-2.36	7.00	3.00	323.13

Nontoxic: , Slighlytoxic: , Highlytoxic: [a]MUT: Mutagenic; TUMO: Tumorigenic; IRRI: Irritant; REP: Repro ductive effective. [b]CLP: cLogP; S: Solubility; DL: Drug-likeness; DS: Drug-Score; nALH: number of acceptors hydrogen bonding; nDLH: number of hydrogen bond donor groups; Da: Molecular Weight.

DISCUSSION: The essential oils obtained have been showing bactericidal potential over the years. In which, *Cinnamomum* species have already had reported bactericidal potential from plant species [25]. Naveed *et al*., [2] showed in researches related to antibacterial activity of EOs that the *Cinnamomun verum* obtained excellent activity against the bacterial strains in study, including *Salmonella typhi* G7 and *Pseudomonas fluorescens*.

The antimicrobial activity of the EO of *Cinnamomun cassia* was investigated against 10 bacterial strains, in which showed activity against all the tested strains, which include seven strains of *E. coli* and three of *S. aureus*. The low MIC and MBC values especially against strains of *S. aureus* LPM 45, LPM 55 and *E. coli* LPM 2810 (**Table 1** and **2**), confirm the excellent bactericidal potential of the *Ciannamomum cassia*. These results are quite similar to the findings of Unlu *et al*., [26] in which the *Cinnamomum zeylanicum* inhibited the growth of gram-positive and gram-negative bacteria thereby demonstrating to be an excellent antimicrobial agent.

The *S. aureus* bacteria is one of the main causes of human infections worldwide, the severity of these infections vary a lot from minor skin infections up to fatal necrotizing pneumonia [27]. In addition, these bacteria have an excellent capacity of acquiring resistance to antibiotics [28]. The *S. aureus* is one of the most prevalent clinical pathogens isolated from hospital settings, and recently has become generalized in community settings [29].

The bacteria *E. coli* occurs naturally in the human intestine, however, certain strains which can cause infections, are becoming resistant to antibiotics. These bacteria are responsible for urinary tract infections (UTIs) and are also associated to blood stream infections [30]. The identification of the dissemination of nosocomial infections and to interrupt the development of outbreaks caused by *E. coli* is becoming a demanding challenge due to the rapid global growth and constant and increasing influx of these bacteria from the community to the hospital environment [31].

The variation of the susceptibility of the tested microorganisms may be attributed to their intrinsic properties which are related to the cell surface permeability the molecules which constitute the EO in study [32]. In the present study, these variations are well established; the EO and its fractions demonstrated variable activities in strains of a same species. Notoriety well represented between the standard strain *S. aureus* ATCC 25213 (MIC 256 µg/mL) and clinical strains *S. aureus* LPM 55 (128 µg/mL) and *S. aureus* LPM 45 (MIC 32 µg/mL), bearing in mind that the later has proved to be more susceptible to the compound.

In contrast, the MBC of the compound followed the methodology of Hafidh *et al*., [33] considering that a phytoconstituent presents bactericidal property when the coefficient between the MBC/MIC is between 1 and 2, and effect which is capable of causing the eventual death of the microorganism. Thus, the *Cinnamomun cassia* presents bactericidal effect, proving to be effective against the majority of the strain present in this study.

The term "*in silico* toxicity" refers to computational experiments, mathematical calculations or scientific analysis of data of chemical substances by means of computational tools which analyze them and make the prediction of a possible toxicological activity [34]. The software Osiris generates alerts about the mutagenicity, tumorigenicity, irritability and damage to the reproductive system. The predictions are registered by means of a color code which indicates the degree of the effects. With the color red indicating risks of undesirable effects, yellow, moderate risk and green, absence of risk [35].

With respect to the *in silico* analysis, the toxicological effects produced by constituents of the *Cinnamomun cassia* were based on the principles of Morales *et al*., [20] and Ursu [36]. However, the determination of the pharmacokinetic profile of the phytoconstituent follows the methodology proposed by Lipinski *et al*., [24] so that the compound has to have at least three of the four proposed requirements (nDLH ≤ 5, nALH ≤10, DA ≤ 500 Da and cLogP ≤ 5).

The major fractions of the EO, which consist of p-Cymene, p-Mentha-1,4(8)-dien and 3-Carene, were analyzed. The results obtained demonstrate that the phytoconstituents present low levels of toxicity when compared to other phytochemicals and to conventional antibiotics, presenting Drug-likeness values (-2.50, -3.01 and -3.35) respectively and Drug-Score (0.22, 0.44, 0.16) respectively. Of the monoterpenes which constitute the essential oil, the only one which demonstrated to have an evident toxic potential was the p-Cymene, revealing itself as a tumorigenic and irritating agent. The 3-Carene showed to have a slight tumorigenic and irritating potential and the p-Mentha-1,4(8)-dien, however, did not reveal any toxic potential. By contrast, the chloramphenicol, broad-spectrum antibiotic frequently used to treat severe bacterial infections, proved to be strongly toxic with irritating, tumorigenic characteristics and possible damages to the reproductive system, as well as mutagenic effects.

CONCLUSION: In conclusion, the EO of *Cinnamomum cassia* has satisfactory antibacterial activity. Once again confirming the phytoconstituents as an efficient alternative in medicinal therapeutics. In this study, the *Cinnamomum cassia* proved to be effective against *E. coli* and *S. aureus* strains. The *in silico* analysis also proved to be interesting, seen as all the fractions of the EO respected the criteria proposed by Linpinski *et al*., [24] in relation to the pharmacokinetics, with exceptions only for the toxic potential of two of the molecules. Therefore, this essential oil and its major components are promising bactericides. However, subsequent studies are necessary for a more detailed investigation of the *in-vitro* and *in-vivo* pharmacological and toxicological properties of these molecules.

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CONFLICT OF INTEREST: The authors declare that there is no conflict of interests regarding the publication of this paper.

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