Int.J.Curr.Microbiol.App.Sci (2019) *8*(5): 434-445

International Journal of Current Microbiology and Applied Sciences
***ISSN: 2319-7706* Volume 8 Number 05 (2019)**
Journal homepage: http://www.ijcmas.com

Original Research Article https://doi.org/10.20546/ijcmas.2019.805.051

Evaluation of Antimicrobial Activity of Cinnamaldehyde against Carbapenem-Resistant *Acinetobacter baumannii* Nosocomial Isolates

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Keywords

Acinetobacter baumannii, Cinnamaldehyde, Multidrug-resistance, Nosocomial infection, Teaching hospital

Article Info

Accepted:
07 April 2019
Available Online:
10 May 2019

A B S T R A C T

The emergent and rapid spread of carbapenem-resistant *A. baumannii* isolates poses a severe threat to public health. Thus, the growing interest in new therapies based on natural products is the basic and primary source for the emergence of new antimicrobials. The aim of this study was to evaluate the antimicrobial activity of cinnamaldehyde against carbapenem-resistant *A. baumannii* nosocomial strains (n=47) isolated from patients in four teaching hospitals at Ceará, Brasil. Phenotypic identification and susceptibility to different antimicrobials were determined by VITEK®2, additionally gene blaOXA-51 was amplified by PCR on all presumptively identified as *A. baumannii* and the clinical characteristics were analyzed. The MIC of the cinnamaldehyde was performed according to microdilution methodology in standard 96-well polystyrene plates, according to the CLSI recommendations and MBC was determined. The MIC ranged from 125 to 500 µg/mL (Mean = 210.93 ± 58.55) and the MBC for most isolates was 250 µg/mL (Mean = 510.41 ± 230.39). Bloodstream was the most frequent isolation site, and most of the strains were isolated from Intensive Care Units. These data demonstrated a potent inhibitory and bactericidal effect of cinnamaldehyde against carbapenem-resistant *A.baumannii* nosocomial strains, suggesting the prospection of this compound for the development of a new antibacterial substance.

Introduction

The multidrug-resistant *Acinetobacter baumannii* (MDRB) have emerged worldwide as an important cause of hospital infections, exhibiting high rates of resistance (Lee *et al.*, 2017; Raro *et al.*, 2017). *A. baumannii* infections occur in Intensive Care Units (ICUs), where they are commonly found to be a cause of pneumonia associated with mechanical ventilation, urinary tract infections, secondary meningitis, and

bacteremia (Clark *et al.,* 2016; Maragakis and Perl, 2008). These microorganisms have great ability to increase their regulation of antimicrobial resistance or to acquire resistance determinants (Hu *et al.,* 2016). Furthermore, *A. baumannii* is prone to develop biofilms on solid surfaces, including medical devices (Gayoso *et al.,* 2014). Thus, the combination of the vast resistance mechanisms of *A. baumannii* species and their survival capacity in the hospital environment make them potential nosocomial pathogens (Montagu *et al.,* 2016).

These microorganisms are considered opportunistic pathogens because they are isolated from immunosuppressed patients who have undergone major surgeries, antibiotic therapies, burns, use of devices and mainly mechanical ventilation, and can cause severe infections (Doi *et al.,* 2015).

A. baumannii has been shown to develop resistance to several classes of antibiotics, including aminoglycosides, cephalosporins, carbapenems, tigecycline, and colistin (Bonnin *et al.,* 2013). One an important mechanism of resistance is the presence of β-lactamases, including oxacillinases, which are enzymes capable of hydrolyzing carbapenems, imipenem, and meropenem, important antimicrobials as a therapeutic resource against resistant multidrug bacteria (Nordmann *et al.,* 2012). Carbapenems are important antibiotics to treat *A. baumannii* because they are highly efficacious and have low toxicity (Evans *et al.,* 2013). However, the increasing prevalence of carbapenem-resistant *A. baumannii,* particularly in the last two decades, has been of immense concern such that carbapenem-resistant *A. baumannii* is now listed as the top priority pathogen in urgent need of new antimicrobials by the World Health Organization in February 2017 (World Health Organization, 2017).

In this context, it is necessary to search for new therapeutic approaches, among which the prospection of compounds is that have activity against multiresistant bacteria, such as compounds and molecules isolated from plants.

Essential oils and their secondary metabolites, since the Middle Ages, are used as bactericides, insecticides, antiseptics, and fungicides. Due to its multiple properties, these compounds are currently widely used in the pharmaceutical and food industries, cosmetics, medical equipment, among others (Bakkali *et al.,* 2008; Perricone *et al.,* 2015).

Studies have shown that cinnamaldehyde is the major compound (83.6%) among components of cinnamon oils (Yeh *et al.,* 2013). In the literature, there are reports of the antibacterial activity of cinnamaldehyde against gram-positive and gram-negative bacteria, however, studies of the activity of this substance against multidrug-resistant microorganisms are scarce. Therefore, the aim of this study was to evaluate the antimicrobial activity of cinnamaldehyde against *A. baumannii* nosocomial strains resistant to carbapenems isolated from patients in different teaching hospitals in the State of Ceará, Brazil.

Materials and Methods

The present study was conducted according to the Declaration of Helsinki, and the protocol was approved by the Institutional Ethics Committee of the State University of Vale de Acaraú, Sobral, Ceará, Brazil (Protocol nº1,843,504).

Bacterial strains

Carbapenem-resistant *A. baumannii* strains analyzed in this study were part of the database of the Microbiology and Parasitology Laboratory of the FAMED

(UFC/ Sobral), which were collected during the period from November 2016 to April 2017, from Santa Casa de Misericórdia de Sobral (SCMS), Hospital Geral Cesar Cals (HGCC), Hospital Geral de Fortaleza (HGF), and from Hospital Universitário Walter Cantídio (HUWC). Phenotypic identification and susceptibility to antimicrobials were determined by the VITEK®2 automated system (BioMérieux, Marcy-l'Etoile, France) in the microbiology laboratories of these hospitals.

Phenotypic confirmation of the strains by detection of *bla*$_{OXA-51}$ gene

A. baumannii presents the natural occurrence of intrinsic carbapenemases genes such as the *bla*$_{OXA-51}$ gene (Turton *et al.*, 2006). Therefore, the nosocomial species of *A. baumannii* resistant to carbapenems were analyzed for the detection of *bla*$_{OXA-51}$ gene by Polymerase Chain Reaction (PCR). The primers and protocols previously described by Ma *et al.*, (2015) were used to amplify the *bla*$_{OXA-51}$ gene. The sequence of the fragments that were amplified, the size of the amplicons and the annealing temperature is described in Table 1.

Preparation of cinnamaldehyde solution

The cinnamaldehyde was purchased from Sigma (purity ≥ 95%; BCD: 1345; CAS: 104-55-2). Solubilized in 5% DMSO and diluted in Brain Heart Infusion (BHI) medium (KASVI, Curitiba, Brazil) to obtain a concentration of 2,000 µg/mL. Starting from this concentration, a serial dilution was performed in 96-well plate with an initial concentration of 1,000 µg/mL.

Preparation of bacterial suspension

Bacteria were reactivated from the inoculation of 50 µL of a culture stocked in a test tube containing 5 mL of BHI broth (KASVI, Curitiba, Brazil), then incubated at 37° C for 18 h in aerobic conditions.

After this period, the bacterial suspensions were inserted into a 96-well plate and the absorbance reading was performed, where the concentration was adjusted by spectrophotometer (Abs = 620 nm) at 10^8 CFU/mL. These bacterial suspensions with 10^8 CFU/mL were used to determinate the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC).

Minimum Inhibitory Concentration (MIC)

The determination of the minimum inhibitory concentration (MIC) of cinnamaldehyde was performed according to microdilution methodology in standard 96-well polystyrene plates according to the M7-A 10th edition, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, according to Clinical and Laboratory Standards Institute (CLSI, 2018). Subsequently, the plates were analyzed by the Elisa reader (BIO Trak II - Plate Reader®).

The test was performed on eight replicates for the same microorganism and the concentrations from 1,000 µg/mL to 1.95 µg/mL were analyzed. In the last column of the 96-well plate were the controls: negative (bacterial suspension + medium), turbidity (medium + test substance) and control of contamination of the medium.

After completing the plate assembly, an initial reading (zero time) was performed by an ELISA reader (BIO Trak II - Plate Reader®) with a wavelength of 620 nm.

Then the microplate was incubated at 37° C for 24 hours and after that period a new reading was performed to evaluate bacterial growth through turbidity with the aid of the ELISA.

Minimum bactericidal concentration (MBC)

The determination of the minimum bactericidal concentration (MBC) was performed using the method proposed by Courvalin *et al.*, (1995). After determination of the MIC, 10 µL of the wells where there was no visible microbial growth were transferred for Petri dishes containing Muller Hinton Agar medium (KASVI, Curitiba, Brazil), then incubated at 37° C for 24 hours in the aerobic growth greenhouse. MBC was considered the lowest concentration of cinnamaldehyde where there was no cell growth on the surface of the inoculated agar (99.9% of microbial death).

Statistical analysis

Statistical analyzes were performed using GraphPad® Prism software version 5.04 for Windows (GraphPad Software, San Diego California USA). The level of significance was 0.01 ($p \leq 0.01$). The difference between replicate means was verified using the One-way ANOVA with Bonferroni post-test.

Results and Discussion

Table 2 shows the distribution of 47 nosocomial strains of *A. baumannii* isolated from patients in the four teaching hospitals surveyed per hospital unit, isolation site, and hospitalization sector.

It was observed that bloodstream was the most frequent isolation site, followed by tracheal aspirate and secretion from the surgical wound. Furthermore, most of the strains were isolated from Intensive Care Units, followed by clinical and surgical wards (Table 2).

Table 3 shows the results of the *in vitro* antimicrobial susceptibility profile of 47 nosocomial *A. baumannii* MDR against 16 antimicrobials of various classes, including β-lactams, glycylcyclines, quinolones, aminoglycosides, and polymyxins. Isolates showed different sensitivity profiles to clinically available antibiotics, but all presented resistance to carbapenems and sensitivity to colistin. Furthermore, 8 (17.0%) isolates were resistant or intermediately susceptible to tigecycline. So, the minimum inhibitory concentrations were determined by a broth microdilution technique for isolates resistant to tigecycline following the recommendations of the Clinical and Laboratory Standards Institute (CLSI, 2018).

The minimum inhibitory concentration (MIC) of cinnamaldehyde to the tested isolates ranged from 125 to 500 µg/mL (Mean = 210.93 ± 58.55) and the minimum bactericidal concentration for most isolates was 250 µg/mL (Mean = 510.41 ± 230.39) (Table 4).

The alarming increase in antibiotic-resistant bacteria has led to many undesirable phenomena such as the failure of antimicrobial therapy and the frequency of infections by multiresistant microorganisms (Aelenei *et al.*, 2016; Perez *et al.*, 2017; Turton *et al.*, 2006). In this regard, the identification of new natural substances with antimicrobial activity may be effective alternatives against these pathogens. Currently, the use of natural substances, especially essential oils (EOs) and their isolated substances are studied for the prevention and treatment of infections caused by MDR bacteria (Burt, 2004; Chouhan *et al.*, 2017).

A. baumannii presents the natural occurrence of carbapenemases genes intrinsic to this species (Turton *et al.*, 2006). The first report of this genetic event presented the $bla_{\text{OXA-51}}$ gene. Subsequently, the presence of variants

similar to this gene has been reported, these being named *bla*$_{\text{OXA-51-LIKE}}$ genes (Turton *et al.,* 2006). Usual phenotypic examinations in the laboratory routine are often ineffective in identifying *Acinetobacter* sp. when not associated with molecular tests, such as PCR (Kooti *et al.,* 2015). Thus, it is necessary to use another test as confirmation criterion showing reliable results for the therapeutic choice. In this search, the confirmation of the phenotypic identification obtained by the automated system the VITEK® 2 was obtained by the detection of the *bla*$_{\text{OXA-51}}$ gene, validating all the results provided by the equipment.

In this study, *A. baumanni* was more isolated from the bloodstream and tracheal aspirate, often associated with patients admitted to intensive care units (ICUs). These data corroborate findings in the literature that this microorganism is responsible for increasingly severe outbreaks of infections and the incidence of nosocomial infections in the bloodstream caused by this pathogen is becoming more frequent (Bianco *et al.,* 2016). Infections by *A. baumannii* are more frequent in ICUs, where they are commonly found to be a cause of ventilator-associated pneumonia, urinary tract infections, meningitis, and bacteremia (Dahdouh *et al.,* 2017; Li *et al.,* 2013).

Regarding the sensitivity profile, the isolates analyzed presented different sensitivity patterns. Colistin and tigecycline have been shown to be the most effective antimicrobials; these results are relevant with other studies demonstrating that these drugs may be the best therapeutic option for the treatment of patients with carbapenem-resistant *A.baumannii* infections (Castilho *et al.,* 2017; Dahdouh *et al.,* 2017; El-shazly *et al.,* 2015). However, in this study almost 20% of the isolates analyzed were resistant or intermediate susceptible to tigecycline. The resistance rate of this microorganism to imipenem and meropenem, increased from 31% in 2005 to 62.4% in 2014 and from 39% in 2005 to 66.7% in 2014, respectively (Hu *et al.,* 2016).

It should be noted that the worldwide emergence of multidrug-resistant *A. baumannii* reduced the number of antibiotics available against this pathogen, including resistance to β-lactams, fluoroquinolones, tetracyclines, and aminoglycosides (Cai *et al.,* 2012). Thus, bacterial resistance to the available antibiotics induced the search for new therapies and strategies aimed at decreasing the development of MDR bacteria (Ferro *et al.,* 2016). Importantly, in this study cinnamaldehyde showed significant antimicrobial activity against clinical isolates of *A. baumannii* that presented a phenotype of resistance to carbapenems, which are the most effective antibiotics for the treatment of infections caused by this pathogen.

In the literature there are reports of the toxicity of this substance, providing data from *in vivo* studies suggesting that cinnamaldehyde is safe when administered orally in a single dose (2,220 mg/kg) or for up to 2 years (550 mg/kg/day). It is worth noting that the rate of excretion of cinnamaldehyde after 24 h of administration varies from 70 to 98% in rodents, depending on the route of administration, and reaches 100% within 8 h when administered orally to healthy human volunteers (Cocchiara *et al.,* 2015). Cinnamaldehyde has been identified and utilized as a non-toxic, food-grade antimicrobial agent. It is generally regarded as safe by the US Food and Drug Administration (USFDA, 2017). Only high concentrations for prolonged exposures have been shown to cause detrimental physiological changes in mammals (Hooth *et al.,* 2004). In this study, cinnamaldehyde presented a MIC of 250 µg/mL for 70.2% and an MBC of the same

value for 23.5% of the analyzed strains, these data were statistically significant and presenting lower inhibitory concentrations than those observed by Guerra *et al.*, 2012) that evaluated the antimicrobial activity of cinnamon oil against *Acinetobacter* sp. MDR. However, they analyzed the MIC of the volatile oil, obtaining a MIC of 625 µg/mL for 71% of the strains analyzed and an MBC that ranged from 2,500 µg/mL to 1,250 µg/mL.

Table.1 Primers for amplification of the blaOXA-51 gene

Primer	Sequence (5'-3')	Amplicon (pb)	Anellament temperature (^{0}C)
	Amplification of *bla*$_{OXA-51}$	353	53ºC
***bla*$_{OXA-51}$ F**	TAA TGC TTT GAT CGG CCT TG		
***bla*$_{OXA-51}$ R**	TGG ATT GCA CTT CAT CTT GG		

Table.2 Distribution of *A. baumannii* nosocomial strains per hospital unit, isolation site, and hospitalization sector*

	n	%
Microorganism		
Acinetobacter baumannii	47	100.0
Hospital unit		
SCMS	12	25.5
HGCC	12	25.5
HGF	12	25.5
HUWC	11	23.4
Isolation site		
Blood	15	32.0
Tracheal aspirate	11	23.4
Secretion	8	17.0
Urine	5	10.6
Catheter tip	2	4.2
Tissue fragmente	2	4.2
Alveolar bronchial lavage	2	4.2
Nasal swab	1	2.1
Ulcer tissue	1	2.1
Hospitalization sector		
UTI	31	65.9
Clinical and surgical wards	12	25.5
Neurology	2	4.2
Traumato orthopedics	2	4.2

*Reports generated by automated identification system Gram-negative bacillus GN, VITEK® 2; *BioMérieux*, France.

Table.3 The antimicrobial resistance profiles of *A. baumannii* nosocomial strains from the four teaching hospitals analyzed

Antimicrobial	Resistant		Sensitive		Intermediate		No tested	
	n	%	n	%	n	%	n	%
Amikacin	23	48.9	10	21.2	3	6.3	11	23.4
Ampicillin	46	97.8	0	0.0	1	2.1	0	0.0
Ampicillin sulbactan	23	48.9	2	4.2	21	44.6	1	2.1
Cefepime	42	89.3	1	2.1	4	8.5	0	0.0
Cefoxitin	43	91.4	1	2.1	2	4.2	1	2.1
Ceftazidime	45	95.7	0	0.0	1	2.1	1	2.1
Ceftriaxone	41	87.2	0	0.0	6	12.7	0	0.0
Cefuroxime	47	100	0	0.0	0	0.0	0	0.0
Cefuroxime axetil	47	100	0	0.0	0	0.0	0	0.0
Ciprofloxacin	44	93.6	3	6.3	0	0.0	0	0.0
Colistin	0	0.0	47	100	0	0.0	0	0.0
Gentamicin	24	51	18	38.2	5	10.6	0	0.0
Imipenem	47	100	0	0.0	0	0.0	0	0.0
Meropenem	47	100	0	0.0	0	0.0	0	0.0
Piperacillin/tazobactam	47	100	0	0.0	0	0.0	0	0.0
Tigecycline	3	6.3	38	80.8	5	10.6	1	2.1

Data expressed as absolute frequency and percentage.

Table.4 Minimal inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of cinnamaldehyde against 47 *A. baumannii* nosocomial isolates

Nosocomial strains	MIC	MBC	Hospital Unit
AB1LAMP	250 µg/mL	500 µg/mL	SCMS
AB2LAMP	250 µg/mL	250 µg/mL	SCMS
AB5LAMPR	250 µg/mL	500 µg/mL	SCMS
AB10LAMPR	125 µg/mL	500 µg/mL	SCMS
AB12LAMPR	125 µg/mL	250 µg/mL	SCMS
AB16LAMPR	125 µg/mL	250 µg/mL	SCMS
AB18.1LAMP	250 µg/mL	1000 µg/mL	SCMS
AB18.2LAMP	125 µg/mL	250 µg/mL	SCMS
AB20LAMPR	250 µg/mL	500 µg/mL	SCMS
AB23LAMPR	250 µg/mL	500 µg/mL	SCMS
AB25LAMPR	250 µg/mL	1000 µg/mL	SCMS
AB35LAMPR	250 µg/mL	500 µg/mL	SCMS
AB52LAMP	125 µg/mL	250 µg/mL	HGF
AB57LAMP	125 µg/mL	500 µg/mL	HGF
AB60LAMPR	250 µg/mL	500 µg/mL	HGF
AB62LAMPR	125 µg/mL	500 µg/mL	HGF
AB66LAMPR	125 µg/mL	500 µg/mL	HGF
AB68LAMPR	250 µg/mL	250 µg/mL	HGF

AB75LAMP	125 µg/mL	250 µg/mL	HGF
AB78LAMP	125 µg/mL	500 µg/mL	HGF
AB79LAMPR	125 µg/mL	500 µg/mL	HGF
AB80LAMPR	250 µg/mL	250 µg/mL	HGF
AB81LAMPR	125 µg/mL	1000 µg/mL	HGF
AB125LAMPR	250 µg/mL	1000 µg/mL	HGF
AB48LAMP	125 µg/mL	250 µg/mL	HGCC
AB83LAMP	250 µg/mL	500 µg/mL	HGCC
AB84LAMPR	250 µg/mL	500 µg/mL	HGCC
AB87LAMPR	250 µg/mL	500 µg/mL	HGCC
AB88LAMPR	250 µg/mL	500 µg/mL	HGCC
AB90LAMPR	250 µg/mL	500 µg/mL	HGCC
AB93LAMP	250 µg/mL	500 µg/mL	HGCC
AB100LAMP	250 µg/mL	500 µg/mL	HGCC
AB102LAMPR	250 µg/mL	1000 µg/mL	HGCC
AB105LAMPR	250 µg/mL	500 µg/mL	HGCC
AB108LAMPR	250 µg/mL	500 µg/mL	HGCC
AB110LAMPR	250 µg/mL	1000 µg/mL	HGCC
AB140LAMP	125 µg/mL	250 µg/mL	HUWC
AB141LAMP	250 µg/mL	500 µg/mL	HUWC
AB142LAMPR	250 µg/mL	500 µg/mL	HUWC
AB143LAMPR	250 µg/mL	500 µg/mL	HUWC
AB145LAMPR	250 µg/mL	500 µg/mL	HUWC
AB146LAMPR	250 µg/mL	250 µg/mL	HUWC
AB147LAMP	250 µg/mL	500 µg/mL	HUWC
AB148LAMP	250 µg/mL	500 µg/mL	HUWC
AB149LAMPR	250 µg/mL	1000 µg/mL	HUWC
AB150LAMPR	250 µg/mL	500 µg/mL	HUWC
AB151LAMPR	250 µg/mL	500 µg/mL	HUWC
AB216 reference strain	125 µg/Ml	250 µg/mL	-

Regarding the antimicrobial activity of cinnamaldehyde, these results reinforce the data of literature Li *et al.*, (2013) that demonstrate that the antimicrobial activity of cinnamon oil is due to cinnamaldehyde (Ooi *et al.*, 2006). Studies that evaluated the *in vitro* antimicrobial activity of cinnamon oil using the fusion disc method against *A. baumannii* and *Pseudomonas aeruginosa* resistant to carbapenems demonstrated effective qualitative results and confirmed that the antibacterial action was due to its major component, cinnamaldehyde (Kaskatepe *et al.*, 2016). However, no quantitative methods were used to measure MIC and MBC, as well as, the majority component was not tested against these pathogens alone. The antimicrobial effect of cinnamon oil was also demonstrated against *Escherichia coli*, *Klebsiella pneumoniae, P. aeruginosa*, *Proteus vulgaris*, *Bacillus subtilis* and *Staphylococcus aureus* species with MIC values ranging from 800 to 3,200 µg/mL (Prabuseenivasan *et al.*, 2006). The antimicrobial potential of different essential oils was analyzed, among them the cinnamon oil, and the researchers demonstrated that cinnamon oil demonstrated greater efficacy than the others, and its antimicrobial action was attributed to the presence of cinnamaldehyde, revealing that it was the main constituent of cinnamon oil Prabuseenivasan *et al.*, (2006), confirming the data of Baratta *et al.*, (1998), Sleha *et al.*,

(2014) and Utchariyakiat *et al.*, (2016) that also reported that cinnamaldehyde was the predominant active compound found in cinnamon oil.

Data in the literature report the antimicrobial activity of cinnamaldehyde against *Staphylococcus aureus* and *Enterococcus faecalis* with MDR phenotypes with MIC values ranging from 250 µg/mL to 500 µg/mL and MBC of 1,000 µg/mL (Chang *et al.*, 2001; Shen *et al.*, 2015; Utchariyakiat *et al.*, 2016). Therefore, these results demonstrated a potent inhibitory and bactericidal effect of cinnamaldehyde against carbapenem-resistant *A.baumannii* nosocomial isolates. Thus, these data suggest the prospection of this compound for the development of a new antibacterial substance, either as a medicament or in new products destined to the final disinfection of hospital environments, being able to reduce hospitalization costs and be safe in its use.

Funding information

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001 (granting the scholarship**)** and by Santa Casa de Misericórdia de Sobral (Edital DEPE 02/2017).

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How to cite this article:

Ana Jessyca Alves Morais, Izabelly Linhares Ponte Brito, Xhaulla Maria Quariguasi Cunha Fonseca, Vicente de Paulo Teixeira Pinto and Francisco Cesar Barroso Barbosa. 2019. Evaluation of Antimicrobial Activity of Cinnamaldehyde against Carbapenem-Resistant *Acinetobacter baumannii* Nosocomial Isolates. *Int.J.Curr.Microbiol.App.Sci.* 8(05): 434-445. doi: https://doi.org/10.20546/ijcmas.2019.805.051