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Original Article

Momordica Charantia L. Variety from Northeastern Brazil: Analysis of Antimicrobial Activity and Phytochemical Components

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ABSTRACT

Introduction: *Momordica charanthia* L., Curcubitaceae, is a pantropical food and medicinal plant. The plant is included in the Official List of Brazilian Medicinal Plants of interest to the Brazilian Unified Health System. The study aimed to perfom microbiological studies with extracts of *Momordica charanthia* L. including chemical characterization of the active extracts. **Methods:** The antimicrobial activity was evaluated with the hydroalcoholic and acetone extracts of *M. charantia* leaves, fruits and seeds from northeastern Brazil using microdilution broth technique on the selected clinical bacterial and fungal strains. Extracts that presented antimicrobial were subjected to ultra performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-QToF-ESI-MS). **Results:** The *in vitro* antimicrobial assays demonstrated that the leaves extracts presented good antibacterial effect against four *Staphylococcus aureus* strains, and a weak antifungal activity agaist *Candida albicans*. Fourteen compounds were identified in the hydroalcoholic extract, while 12 were found in the acetone extract. The most important compounds were kaempferol, quercertin and triterpenoids like cucurbitacins. **Conclusion:** The present study demonstrated the potential antibacterial activity of *M. charantia* L. from northeastern part of Brazil, in addition to important phytochemical metabolites known to possess antibacterial activities, particularly against microrganisms of clinical importance. The UPLC phytochemical profile of the Brazilian variety is reported here for the first time. The phytochemical profile of the LHE and FAE demonstrated the presence of biologically and pharmacologically active compounds. There is lack of biological and pharmacological studies to support the medicinal uses of this important plant. The Brazilian variety of *M. Charantia* could be a potential therapeutic agent in the treatment of infections.

Key words: Ethnopharmacology, *in vitro* activity, Antibacterial, Antifungal.

INTRODUCTION

Momordica charantia L. belongs to the cucurbitaceae family is a climbing plant found frequently covering fences and shrubs along the paths from north to south regions of Brazil, especially during the rainy season. It is a species native to Africa that was introduced to South America in the colonial period by black slaves from the African continent.[1,2]

Momordica charantia is found in nature in various forms distinguishable by the size of the fruits. Two of which are more frequent the northeastern Brazil, where it is popularly reffered to as the *Melão-de-Caetano*, *erva-de-lavadeira* "laundry-plant", because the whole plant is used in the washing of clothes in the rural areas. A variety of large fruits that can measure up to 30 cm in length and about 5 cm in diameter is the most common variety in the Asian countries, used both in food and in medicinal preparations. This variety was introduced to Brazil in this century, and its fruits can readily be found in the open markets like in the state of São Paulo (Figures 1 and 2).[3]

In the state of Ceará, northeastern Brazil, one of the earliest records of *M. charantia* is found in the *Coleção Descritiva das Plantas da Capitania do Ceará do Naturalista Feijó* "Descriptive collection of Plants of Cearáregion" by João da Silva Feijó, who was a Ceará naturalist in 1818.[4] As at that time, Brazil was still under Portuguese colonization. However, other works on northeastern Brazillian Flora by the naturalist Freire Allemão, who also recorded the species, were based on this collection.[5] In the twentieth century, the ethnobotanical descriptions of *M. charantia*, including its use in the popular medicine of the northeast, can be encountered in important works like the *Formulário Fitoterápico* (Phytotherapeutic Formulary) *of Professor Dias da Rocha*,[6] *Plantas do Nordeste, especialmente do Ceará* (Plants of the Northeast, especially of Ceará).[7] and *Plantas da Medicina Popular do Nordeste* (Plants of the Northeastern People's Medicine).[8]

In the Brazilian state of Ceará, the plant is used topically in compresses, plasters, washes for the treatment of ulcers and various skin disorders

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Figures 1 and 2: Photos of F. J. A. Matos: *Momordica charantia* L. variety.

(abscesses, boils, pediculosis, pruritus and burns). And recently, its ethnomedicinal uses from the same region was detailed in the Ethnopharmacopoeia of Professor Francisco José de Abreu Matos[9] which included wound healing, as antiseptic, treatments of gonorrhea, skin diseases, colitis, gynecological inflammation, external tumor, vaginal discharge, infected wounds and for weight loss. The plant parts used are theleaves (its juice, natural form or as poultice, decoction and maceration in water, fruit (natural form or as poultice, its branch and the whole plant). It is also prepared in form of tintures/alcohol extract and is employed externally to treat skin infections or parasite infestations.[10,11]

This plant has received a lot of attention due to its many ethnomedicinal and culinary uses. Biological and pharmacological studies of *M. charantia* have shown interesting therapeutic potentials, particularly its antidiabetic[12-17], antileishmania[18], anti-HIV[19], analgesics and anti-inflammatory activities.[20] In addition, pharmacological and biological action of its various metabolites have been cited.[21,22]

Due to the ethnomedicinal importance of the local Brazilian variety, this species has been included in the National List of Medicinal Plants of Interest to Brazilian Public Health System[23] and is also part of the Official List of Medicinal Plants of Ceará, a northeastern state of Brazil (REPLAME-CE).[24] The plant also featured in the Brazilian Pharmacopoeia Phytotherapeutics Formulary.[25]Although, the antimicrobial properties of varieties other than that from Brazil have been cited in many studies using varying biological and pharmacological models, extracts from varying solvents[26-28], few studies have been done on *M. charantia* antimicrobial activities collected in the northeastern region of Brazil.[29,30] To the best of our knowledge, there is no detailed phytochemical studies of this important medicinal and food plant of thislocal variety from northeastern region of Brazil, despites being part of the Official Plant Lists. It is on this basis that we conducted the present study to establish scientific proof for its popular use in treating infections, to standardize extract with promising antibacterial activity and relate its metabolites content based on literature sources to it ethnomedicinal uses by people inhabiting northeastern region (Caatinga Biome) of Brazil.

In this study, we reported the antimicrobial activity of six extracts (hydroethanolic and acetone extracts of *M. charantia* leaves, fruits and seeds) obtained from the northeastern region of Brazil in order to justify its popular use, in addition to conducting phytochemical profile of the most promising extracts.

MATERIALS AND METHODS

Chemicals and reagents

Brain heart infusion media and Agar Sabouraud Dextrose (Kasvi), Müller-Hinton agar, methanol, trichloroacetic acid, ascorbic acid, potassium phosphate buffer, acetonitrile, ethanol, and methanol, used were hypergrade for LC-MS LiChrosolv® and are products of MerkKGaA, Germany. Others such as formic acid 98-100% and n-Hexane were also purchased from MerkKGaA, Germany. Dimethylsulfoxide (Biology applications grade, Sigma-Aldrich, Inc), Oxacilin and fluconazol (Sigma Chemical Company, St. Louis, MO, USA.

Botanical material

The plant was collected from the Medicinal Plants Garden of Prof. Francisco José de Abreu Matos, Universidade Federal do Ceará, in the flowering and fruiting period, precisely in June 2018. The herbarium specimens' were deposited in the Herbarium Prisco Bezerra the Universidade Federal do Ceará with specimen voucher number EAC31609 and identified as *Momordica charantia* L. For the preparation of the extracts, the leaves, fruits and seeds were submitted to drying in an air circulating oven at 45ºC until constant weight, then milled with the aid of a knife mill.

Preparation of leaf, fruit pulp and seeds extracts for microbiological tests

Two extractions were performed for each part of the plant, with ethanol/H_2O (7: 3) and with acetone. 0.80 g of the leaf powder, fruit pulp and seed were weighed separately, and placed in a test tube with 4 mL hexane for degreasing. Subsequently, 4 mL of ethanol/H_2O solution (7: 3) was added, homogenized and the polar compounds extracted in an ultrasonic bath for another 20 min with fixed power (135 W). The samples were then centrifuged (3000 rpm/10 minutes). Thehexanic phase was discarded. The hydroethanolic phase (ethanol/H_2O) was filtered on a 0.22 µm PTFE (polytetrafluoroethylene) filter, and thereafter the filtrate was collected in small vials, with subsequent drying and weighing.

For the extraction with acetone, the same procedure was performed, except that before adding acetone the hexanic phase was removed.

Thus, six extracts were obtained and coded as follows: Leaves - hydroethanolic extract/ethanol/H_2O (LHE) and acetone extract (LAE); Fruits - ethanol/H_2O extract (FHE) and acetone extract (FAE); Seeds- ethanol/H_2O extract (SHE) and acetone extract (SAE). All these samples were dried and weighed to calculate their yields.

To evaluate the antimicrobial action, the extracts were dissolved in 1% dimethyl sulfoxide solution (DMSO, Merck).

Microorganisms

All bacterial and fungal strains used in *in vitro* experimental models were obtained from the collection of the reference microorganisms used in Sanitary Surveillance (CMRVS, FIOCRUZ-INCQS, Rio de Janeiro) and were maintaned in the Applied Microbiology Research Laboratory of Universidade Federal do Ceará. These are *Staphylococcus aureus*

ATCC 14458 (oxacillin sensitive), *S. aureus* CCBH 5330 (oxacillin resistant and methicillin resistant strain MRSA), *Staphylococcus epidermidis* ATCC 35984, *Pseudomona aeruginosa* ATCC 9027 and *Candida albicans* ATCC 10231.

To prepare the microbial inoculum, the strains were cultured in Brain Heart Infusion (BHI) broth for bacteria or Sabouraud broth for yeasts. Subcultures were incubated for 24 hours at 37 °C. For standardization of the inocula, aliquots taken from the subcultured tube were transferred to 0.85% sterile saline to otained turbidity equivalent to the McFarland 0.5 scale (about 10^8 CFU/mL or 10^6 CFU/mL for bacteria and yeast, respectively). This suspension was diluted to obtain the final microbial colony forming units (CFU) of 10^6 CFU/mL for bacteria or 10^4 CFU/mL for yeasts, and which were used in all the microbiological assays.

The determination of the Minimum Inhibitory Concentration (MIC) was performed according to the methodology recommended by the Clinical and Laboratory Standard Institute.[31,32] In the 96-well, sterile microplates, 100 µL of culture medium (BHI broth for bacteria or Sabouraud for yeast), 20 µL of the sample (extract), were added in serial concentrations ranging from 2000.0 to 31.2 µg/mL and 80 µL of the microbial suspensions (10^6 and 10^4 CFU/mL, for bacteria and yeast, respectively). Controls of turbidity, medium sterility, microbial growth, diluent sterility and inhibition by the diluent were performed. As positive controls, oxacillin and fluconazole were used for bacteria and yeasts, respectively, at concentrations ranging from 0.0488 to 100 µg/mL.

The microplates were incubated for 24 hours at 37 °C and after this period, the visual reading of bacterial growth was carried out. MIC was determined as the lowest concentration of test substance capable of inhibiting microbial growth to the naked eye, as evidenced by the absence of turbidity.[31,32]

For extracts with intense turbidity, 10 µL of resazurin (0.01%) was added and incubated at 37 °C for 2 hours. The maintenance of the blue color in the wells was interpreted as absence of bacterial growth, and the development of pink color, as occurrence of bacterial growth. The MIC was defined as the lowest concentration of the test substance in which there was no change in coloration.[33] The experiments were performed in triplicate and at two different times.

For determination of Minimum Bactericidal Concentration (MBC), 5 µL aliquots of microplate wells used to determine MIC that did not show bacterial growth were seeded in Petri dishes containing plate count agar and incubated for 24 hours at 37 °C. After this period, colonies were counted. MBC was considered as the lowest concentration capable of inhibiting bacterial growth by at least 99.9% of the initial inoculum.[34,35]

Analysis by ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-QTOF-ESI-MS)

Phytochemical analysis was performed only on extracts that presented significant antimicrobial activity. The extracts were prepared as described in Section 2.2 for UPLC analysis. After filtration in 0.22 µm PTFE filters, each extract was withdrawn and 100 µL of the standard internal solution (anthracene-9-carboxylic acid) was added at a concentration of 10 µg/mL (10 ppm). Only LHE and LAE extracts were subjected to UHPLC analysis.

The analysis was performed in Acquity UPLC system (Waters), coupled to a Quadrupole / Flight Time (QToF, Waters) system. Chromatographic runs were performed on a Waters Acquity UPLC BEH column (150 x 2.1 mm, 1.7 um), fixed temperature of 40 °C, mobile water phases with 0.1% formic acid (A) and acetonitrile with 0.1% formic acid (B), gradient ranging from 2% to 95% (15 min), flow rate of 0.4 mL/min and injection volume of 5 µL. High-resolution mass conditions - XEVO-QToF. The ESI-mode was acquired in the range of 110-1180 Da, fixed source temperature at 120 °C, desolvation temperature 350 RegularC, withdrawal gas flow of 500 L/h, extraction cone of 0.5 V, capillary voltage of 2.6 kV. ESI + mode was acquired in the range of 110-1180 Da, source temperature 120 fixed RegularC, desolvation temperature 350 °C, desolvation gas flow 500 L/h and the capillary voltage of 3.2 kV. Leucine encephalin was used as a lock mass. The acquisition mode was MSE. The instrument was controlled by Masslynx 4.1 software (Waters Corporation).

The software used for data processing was the Masslynx (Waters Corporation) where the molecular formulas were calculated with their respective masses. The identification of the compounds was made based on comparison of spectral patterns already discussed in the literature regarding the species of *M. charantia*. In addition, online databases containing information on characterized metabolites such as Scifinder, Knapsack, PubChem and Chemspider were also consulted.

RESULTS AND DISCUSSION

Extracts yields

The yields of the six extracts, previously encoded, were as follows: LHE 9.8%, LAE 4.2%, FHE 17%, FAE 5.2%, SHE 13% and SAE 5.4%.

Microbiological assays

The only extracts that presented significant antimicrobial activity were those of the leaves, which are LHE and LAE, and therefore data for extracts without activity were not shown in the Table 1.

In the present study, antimicrobial activity of LHE and LAE was detected against four of the five clinically important bacterial and fungal isolates. The highest effect was observed for the acetone extract (LAE) (Table 1).

According to Aligiannis *et al.*[36], MIC values <0.5 mg/mL are considered potent inhibitors; MICs between 0.6 and 1.5 mg/mL are moderate inhibitors; and MIC> 1.6 mg/mL are weak inhibitors. Thus, the LAE extract is a potent inhibitor on strains of *S. aureus*, moderate on *S. epidermidis* and weak on yeasts (*C. albicans*). The antibacterial activities of extracts and fractions prepared from different parts of *M. charantia* have been reported from various parts of the world.[28-30,37,38] The parts with reports of antimicrobial activities include the fruits, seeds, leaves and the stems. However, it is interesting to note that comparison based on literature reports is difficult based on many reasons. Sometimes, the minimal concentrations employed are in excess of up to 10 times the maximum concentration that we employed or even difficult to deduce[37,38], in some others the concentrations were not stated, but rather the activity stated[38,39] and there seems not to be any clear criteria for reporting plants' extracts antimicrobial activities in many cases.[37,39] in addition, the solvents or the methods employed are completely different.[37,39,40]

On this basis, true comparison of the activities reported on *M. charantia* from different parts of the world seem to be a daunting and a very difficult task. In the case of divergent in the activities reported for the plants with similar methods used, the differences in the activities reported can be due to one of or combination of the following reasons: variations in the seasons of collections, temperature, water availability, ultraviolet radiation, nutrients availability, atmospheric pollution, mechanical damage, and pathogen attacks.[41]These external differences invariably influence the composition and levels of important secondary metabolites of the plant materials employed in these different studies, in addition to the variations related to methodological approaches in the antimicrobial assays.[42]

LHE extract, on the other hand, is a potent inhibitor of *S. aureus* strains, but moderate on *S. epidermidis*. The differences observed in the

antimicrobial potential between LAE and LHE extracts on strains of *Staphylococcus* may be due to the differences in metabolites composition of both extracts. Some cucurbitacins have been shown to have *in vitro* antibacterial activities.[43-46] An excellent review on cucurbitacins and its derivatives was made by Jian *et al.*[47] Interested reader would find the review interesting.

Identification of chemical constituents of the hydroethanolic and acetone extracts (LHE and LAE)

The major chemical constituents of *M. charantia* leaves are the tetracyclic triterpenoids and their glycosides, most of which are referred to as cucurbitans, and are known for their bitterness and biological effects, in addition to quercetins and kaempferols.

The cucurbitacins belong to a class of plant triterpenic, tetracyclic compounds and highly oxygenated derivatives cucurbitane skeleton. Cucurbitane-like molecules have several polarities due to the variation of substitutions in the side chain or portions of glucose or rhamnose[47-56]. Several compounds were isolated from extracts of *M. charantia* by separations involving chromatographic processes, which served as reference in the identification of the chemical constituents of the present study.

The chromatograms of the hydroethanolic (LHE) and acetone (LAE) extracts obtained in the positive ionization mode are shown in Figures 3A and B, respectively. The characterized compounds are summarized in Table 2 with the relevant data, including retention time, experimental mass and calculated *m/z*, molecular formula, error in ppm provided by the software and the MS/MS fragments. Chemical profile of the extracts afforded the tentatively identification of 14 compounds. These are one amino acid, four flavonoids and nine triterpenoids derivatives.

A brief comparison between the hydroethanolic extract and acetone extract of the leaves of *M. charantia* revealed some striking differences. Tryptophan, quercetin and kaempferol hexoside were found only in the LHE extract, while LAE extract presented two unknown compounds, Table 2.

Tryptophan was identified by the precursor ion at *m/z* 205 ($C_{11}H_{13}N_2O_2$) and the characteristic fragment at *m/z* 130 (indol nucleus).[57] Quercetin-*O*-hexoside isomers showed a precursor ion at *m/z* 465 ($C_{21}H_{21}O_{12}$) and a product ions at *m/z* 303, key fragment of quercetin aglycone, resulted from the loss of glucose unit. Additionally, quercetin-O-rhamnoside shows a typical precursor ion *m/z* 449 ($C_{21}H_{21}O_{11}$) and the characteristic fragment at *m/z* 303, loss of rhamnose.[64] Kaempferol-*O*-hexoside showed an *m/z* at 449 ($C_{21}H_{21}O_{11}$), with a key fragment of the kaempferol nucleus at *m/z* 287 indicated by the loss of a hexose. Prior studies have identified these compounds in *M. charantia*.[58,65,66]

Curburbitane-type triterpenes were identified due the losses of H_2O (18 Da), CO (28 Da) as well as because of a diagnostic fragment ion at *m/z* 109 resulting from the break of C17-20 linkage. Thus, hydroxycucurbitatetraenal isomers were identified by the precursor ion at *m/z* 437 ($C_{30}H_{45}O_2$) and its product ions at *m/z* 419, 409, 391, 109. An example of this fragmentation pattern occurs with the 3*β*-hydroxycucurbita-5 (10), 6,22 (E), 24-tetraen-19-al, Figure 4, as previously reported in *M. charantia*.[59-63,67] Epoxy isomers showed an additional oxygen (16 Da) and same fragmentation pattern. The Figure 5 depicts the MS fragmentation to 5*β*,19-epoxycucurbita-6,22(E),24-triene-3*β*,19-diol[59,61], and 3-[(5-formyl-7β,25-dihydroxymethoxycucurbita-5,23-dien-3-yl)oxy]-3-oxopropanoic acid[62], Figure 6.

Table 1: Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC), in mg/mL, of EtOH/H_2O and acetone extracts of *M. charantia*.

Microorganism	Leaves extracts		
	LHE	LAE	
	MIC	MIC	MBC
***S. aureus* ATCC 14458**	0.5	0.25	-
***S. aureus* CCBH 5330**	-	0.125	2.0
***S. epidermidis* ATCC 35984**	2.0	1.0	-
***P. aeruginosa* ATCC 9027**	-	-	-
***C. albicans* ATCC 10231**	-	2.0	2.0

LHE: leaves hydroethanolic extract (ethanol/H_2O, 7:3); LAE: acetone extract.

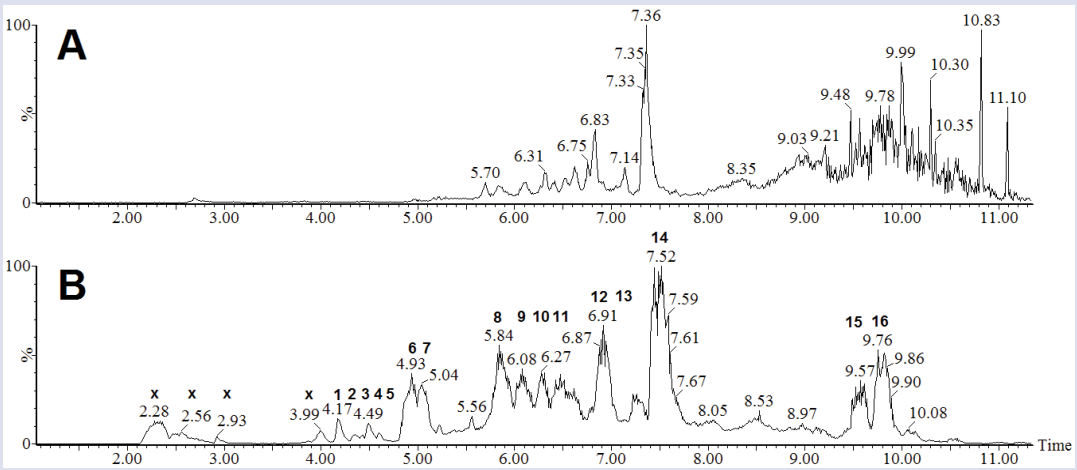

Figure 3: Chromatograms of the UPLC-ESI-QTof MS extracts, LHE (A) and LAE (B), of *M. charantia* obtained in positive ionization mode. Peaks with "X" are impurities.

Table 2: Chemical identification of compounds of the hydroalcholic (FEC) and acetone (FAC) extracts from the leaves of *Momordica charantia* L. "Melão-de-são-caetano".

Peak	Rt min	$[M+H]^+$/ $[M+Na]^+$ Observed	$[M+H]^+$/ $[M+Na]^+$ Calculated	Product Ions (MS/MS)	Empirical Formula	Ppm (error)	Putative Name	LHE	LAE	Ref
1	4.17	205.0974	205.0977	146.0581, 130.0630	$C_{11}H_{13}N_2O_2$	-1.5	Tryptophan	x	-	57
2	4.35	465.1047	465.1033	303.0482	$C_{21}H_{21}O_{12}$	3.0	Quercetin-*O*-hexoside	x	-	58
3	4.49	465.1031	465.1033	303.0475	$C_{21}H_{21}O_{12}$	-0.4	Quercetin-*O*-hexoside	x	x	58
4	4.52	449.1071	449.1084	303.0463	$C_{21}H_{21}O_{11}$	-2.9	Quercetin-*O*-rhamnoside	x	x	58
5	4.60	449.1101	449.1084	287.0553	$C_{21}H_{21}O_{11}$	3.8	Kaempferol-*O*-hexoside	x	x	58
6	4.93	805.5035	805.5043	787.4910, 614.4079, 175.1103	$C_{52}H_{69}O_7$	-1.0	Unknown	x	-	-
7	5.03	769.4990	769.4985	333.1419, 175.1169	$C_{56}H_{65}O_2$	0.6	Unknown	x	-	-
8	5.84	437.3416	437.3420	419.3302, 409.3449, 391.3350, 109.0965	$C_{30}H_{45}O_2$	0.9	Hydroxycucurbitatetraenal isomer	x	x	59
9	6.08	437.3431	437.3420	419.3287, 409.3463, 391.3387, 109.1014	$C_{30}H_{45}O_2$	2.5	Hydroxycucurbitatetraenal isomer	x	x	59
10	6.27	437.3434	437.3420	419.3312, 409.3437, 391.3375, 109.1018	$C_{30}H_{45}O_2$	3.2	Hydroxycucurbitatetraenal isomer	x	x	59
11	6.47	629.3694	629.3690	437.3415, 419.3294, 409.3463, 391.3355, 109.1007	$C_{36}H_{53}O_9$	0.6	Oleanane- triterpenoid saponin	x	x	60
12	6.91	455.3530	455.3525	437.3390, 419.3274, 409.3472, 391.3347, 109.1015	$C_{30}H_{47}O_3$	1.1	Epoxycurcubitatrienediol isomer	x	x	22,61
13	7.26	581.3455	581.3454	541.3593, 523.3412, 495.3454, 437.3396, 409.3545, 391.3342, 109.0979	$C_{33}H_{50}O_7Na$	0.3	3-[(5-formyl-7β,25-dihydroxymethoxycucurbita-5,-23-dien-3-yl)oxy]-3-oxopropanoic acid isomer	x	x	62
14	7.52	455.3527	455.3525	437.3463, 419.3361, 409.3446, 391.3396, 109.1000	$C_{30}H_{47}O_3$	0.4	Epoxycurcubitatrienediol isomer	x	x	59,63
15	9.57	477.3376	477.3376	437.3398, 419.3287, 391.3346, 109.0984	$C_{32}H_{45}O_3$	1.5	Unknown	x	x	-
16	9.76	525.3571	525.3580	493.3336, 437.3434, 419.3293, 391.3380, 109.1009	$C_{33}H_{49}O_5$	-1.7	Unknown	x	x	-

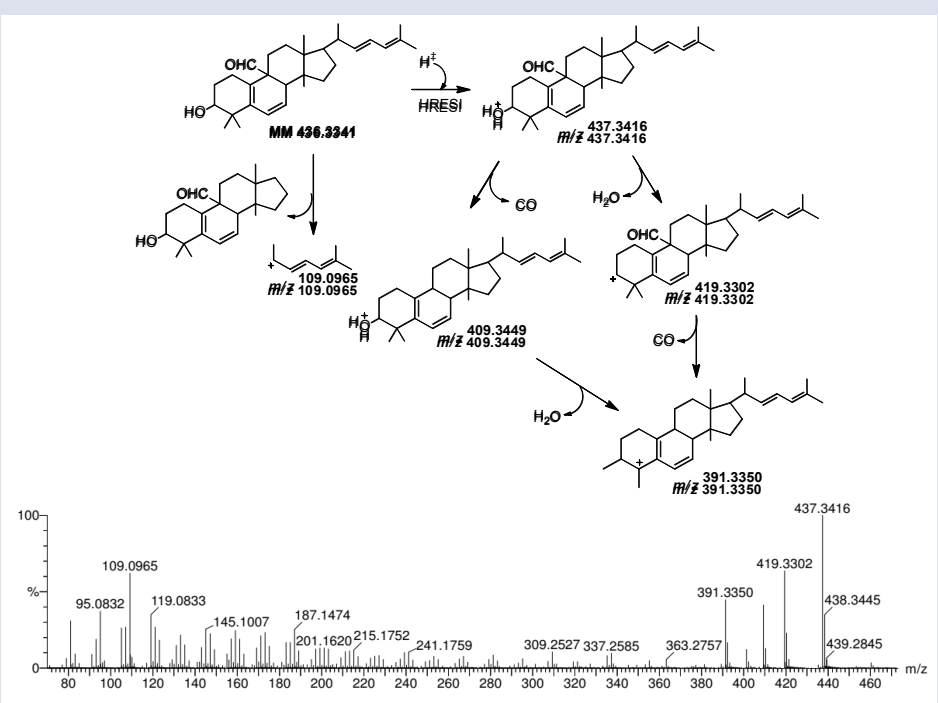

Figure 4: Fragmentation patterns of the 3β-hydroxycucurbita-5 (10), 6, 22 (E), 24-tetraen-19-al.

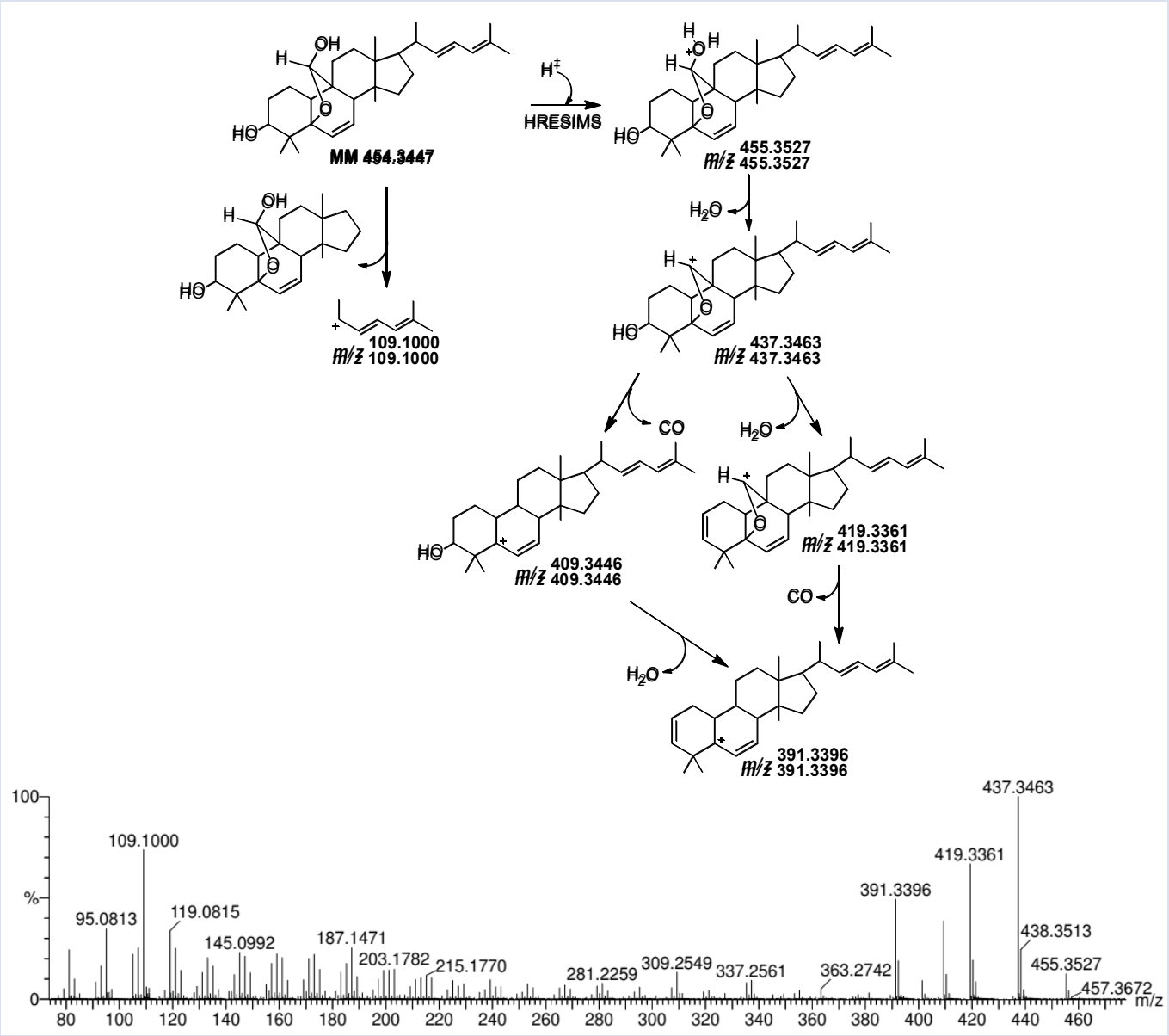

Figure 5: Fragmentation patterns of the 5β, 19-epoxycurcubita-6, 22(E), 24-triene-3β, 19-diol..

Literature survey of ethnomedicinal uses and biological or pharmacological compounds identified or isolated from M. charantia.

We present the ethnomedicinal uses reported from the northeastern region of Brazil (Table 3) and then made a summary of phytochemicals reportedly identified or isolated from *M. charantia* and verified in this present local variety, with the view of presenting plausible role for these metabolites in the potential therapeutic effects of this plant.

Literature survey of the ethnomedicinal uses in the northeast region of Brazil of *M. charantia* and its identified metabolites revealed some interesting findings. In spite of the widespread uses of this important food and medicinal plants, there are still lack of rigorous preclinical and clinical studies, particularly for many of its ethnomedicinal claims. In fact, there is no clinically supported medicinal uses.[68] It is also surprising that some of the biological activities reported are anecdotal due to poor experimental designs, among others. For example, some studies related its biological activities using solutions made from the plants parts without stating the concentrations or dose used, the use of solvents other than those used reported in the ethnomedicinal uses, the parts used in the studies and sometimes the route of administration of the extracts. The most pre-clinically substantiated activities of *M. charantia* are its anti-diabetic and anti-neoplastic activities[16,20,26,27,69,70].

In the present study, we demonstrated the antibacterial and antifungal activities of the leaves extracts of *M. charantia* against clinically important bacterial and fungal strains. Similar reports have been observed in the literature[28-30,37,106]. In order to be able to give plausible explanation as to the activity observed as well as to standardized the extracts, we performed phytochemical studies on the two extracts studied in the present work. Among the structures identified by UPLC in LHE and LAE extracts of *M. charantia*, a number of compounds derived from flavonoids and many of which have been shown to possess antimicrobial activities were identified in LHE. However, some of these

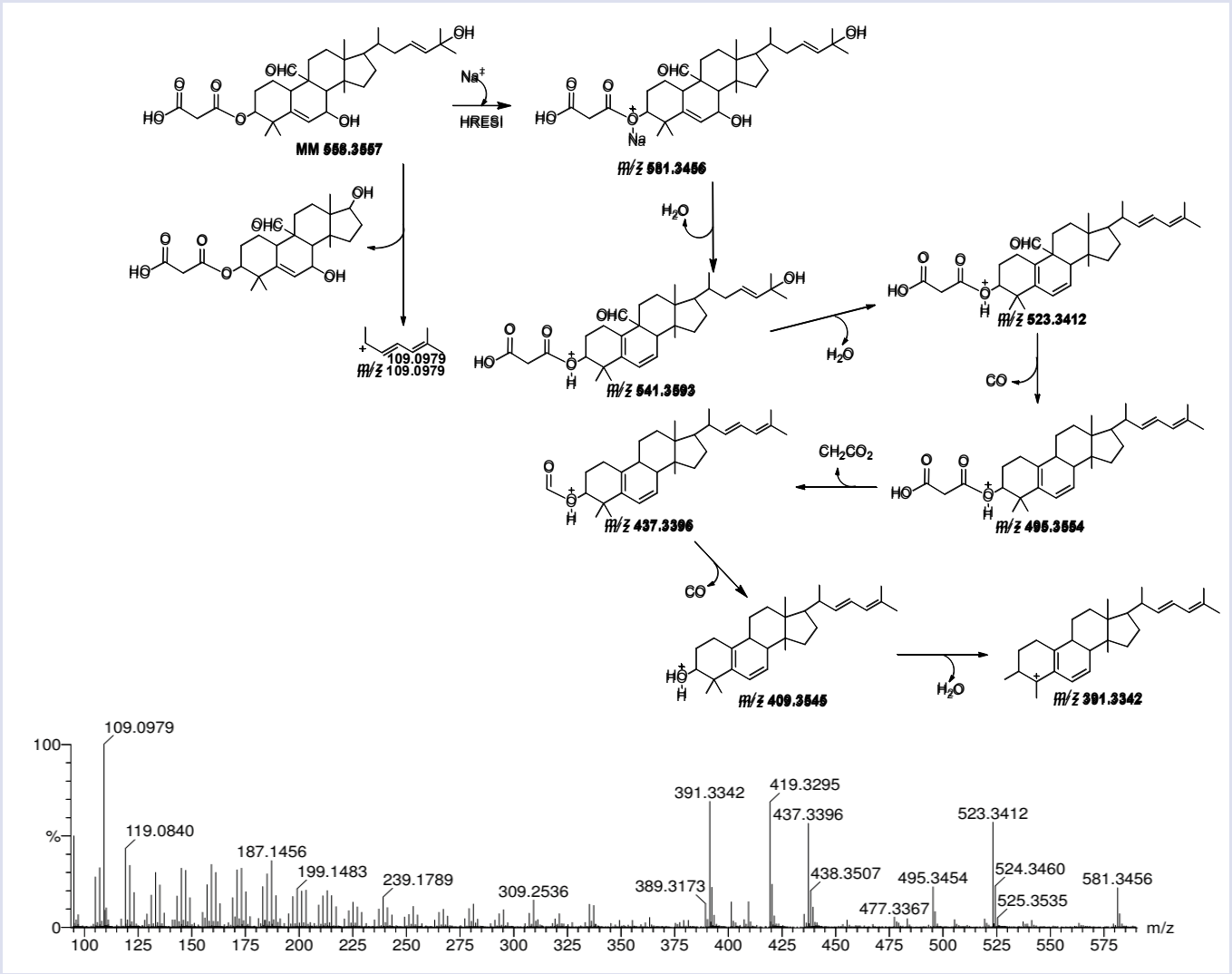

Figure 6: Fragmentation patterns of the 3-[(5-formyl-7β, 25-dihydroxymethoxycucurbita-5, 23-dien-3-yl) oxy]-3-oxopropanoic acid.

constituents do not appear in LAE extract, which presented better antimicrobial and antifungal activity, suggesting that there are other metabolites, that were not identified in the present work and, which may contribute, at least in part, to the antibacterial and antifungal activities observed.

To the best of our knowledge, there are no sufficient chemical and biological studies to indicate the substances responsible for antibacterial or antifungal activity of *M. charantia.*

These results further demonstrate therapeutic potential of *M. charantia* extracts and calls for further biological and pharmacological prospecting of this important plant. There is need for *in vivo* antimicrobial assays to confirm the potential antimicrobial activity of the plant and its phytochemical constituents that are yet to be subjected to biological/pharmacological studies. In fact, most of its important phytochemical compounds are without biological or pharmacological studies. Majority of studies on its isolates are focused on antidiabetic and anti-cancer activities. In addition, there is lack of studies on many of its ethnomedicinal uses. Furthermore, there is need to carry out mechanistic studies to determine how *M. charantia* and or its constituents afford the antimicrobial action observed here as in many studies.

CONCLUSION

The hydroethanolic extract (LHE) and acetone (LAE) from *M. charantia* L. showed different patterns of antimicrobial action against Gram-positive bacteria (*S. aureus* and *S. epidermidis*) and on yeast (*C. albicans*), which are believed to be due to the differences in the composition of extracts as shown by the UPLC analysis of constituents. The study is a pioneer in the association between antimicrobial activity of different Brazilian bitter gourd extracts and its chemical constituents. Nevertheless, studies that will evaluate the compounds alone and in association, as well as those investigating their mechanisms of action are needed to elucidate this pharmacological effect.

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Table 3: Summary of ethnomedicinal uses, chemical compounds identified, and activities reported in the literature that corresponds to *M. charantia* ethnomedicinal uses in the northeastern region of Brazil.

Ethnomedicinal uses	Confirmed biological/ pharmacological activities	Chemical compounds or extracts with activity	References
Indication in skin treatments wound healing.	Wound healing: various model	Fruit powder, extracts	26,71–77
Antiseptic (skin infections, mycoses) and antimicrobial	Antibacterial and antifungal activities	Quercetin-*O*-hexoside isomers, kaempferol, tannins, flavonoids and alkaloids, various crude extracts	29,78–90
Antiviral	antiviral activity (inhibit HRV2 replication)	Quercetin-7-Glucoside	91,92
Scabies, vermifuge, anthelminthic	Anti-helminthic activity	Crude extracts	93
Tumor and benign breast neoplasm	Antineoplastic and anti-tumor, anti-hepatocellular carcinoma; renal carcinoma cells in-vitro anticancer, malignant melanoma, cytotoxicity against chondrosarcoma SW 1353 cell line; modulates the progression of androgen-independent human prostate cancer cell line.	MAP30, Cucurbitacins (Cucurbitacin E glucoside, and Cucurbitacin I glucoside, cucurbitacines A, B, D, E), Kuguacin J and Cucurbitane-type triterpenoids (charantosides, momordicosides, karavilosides, karavilagenin D) and quercetin	19,20,26,27,45,47,49–54,56,70,94–105
Anti-diabetic	Antidiabetic activity, stimulatory effect on insulin secretion and various others, including clinical trials(too numerous to mention all)	Different extracts of M. charantia, Kuguacin (The Kuguacin R and Kuguacin II, 3β,7β,25-trihydroxycucurbita-5,23(E)-diene-19-al, momordicine I, Momordicosides L, charantoside VII	15,17,26,27,61,69,106–108
Internal and external inflammation	Pre-clinical anti-inflammatory activities, and in patients with primary knee osteoarthritis	Cucurbitacins, quercetin, kaempferol, and plant crude extracts	17,20,71,105,109–119
Contraceptive	Antiestrogen activity	Triterpenoid, Kaempferol Cucurbita-6, 22 (E), 24-trien-3β-ol-19,5β-olide, crude extract	59,120
Immunostimulanting	Immunomodulatory activity	Polysaccharides from *M. charantia*	121
Antimalarial	In vitro (positive) and in vivo (no effect) anti-plasmodium activity	Crude extracts	122,123
Anti-diarrheal	In vivo anti-diarrheal activity	Crude aqueous extract	124
Indication in skin treatments: eczema, acne, scabies, hemorrhoid, and furuncles, carbuncle	No report	No report	
Gastroenteritis	No reports	No reports	
Colitis	No reports	No reports	
Gynecological inflammation	No report	No report	
Vaginal discharge	No report	No report	
Hemostatic	No reports	No reports	
Nasal congestion	No reports	No reports	

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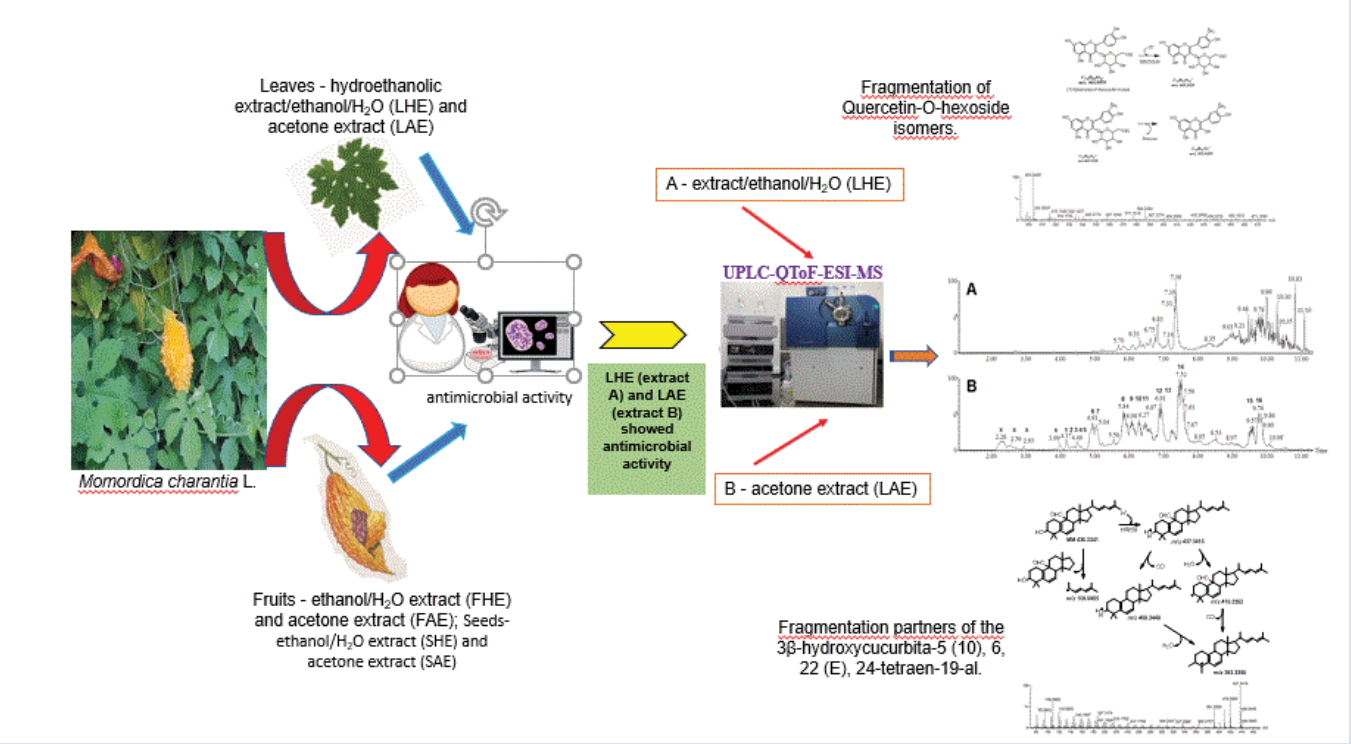
GRAPHICAL ABSTRACT



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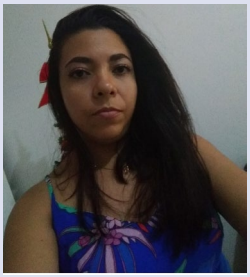

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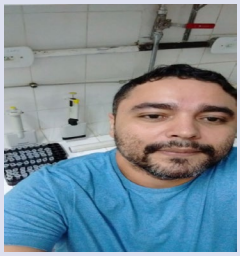

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