

Virulence Inhibitors from Brazilian Peppertree Block Quorum Sensing and Abate Dermonecrosis in Skin Infection Models

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Supplementary Table 1: English translation of *Historia Naturalis Brasiliæ* section “*De Aroeira eiusque qualitatibus*”. Note the reference to medicinal uses of the plant, including the fruit oils and resin as plasters (topical applications) and aqueous leaf extractions to “drive out disease”, most likely taken as an internal medicament. Latin excerpt from: Piso, W. *Historia Naturalis Brasiliæ* (Joannes de Laet, 1648).

Original Latin	English Translation
<p style="text-align: center;">Cap. XI</p> <p style="text-align: center;">De Aroeira eiusque qualitatibus</p> <p>Arbor arenosis, littore imprimis & promontorio Olindae frequens, <i>Aroeira</i> nuncupatur. Myro silvestri nostrati qualitate non valde absimilis, ad Lentiscos tamen referri debet. Praeter eximias facultatues, quas cum <i>Araca</i>, & <i>Myrto</i>, arboribus habet communes, hisce peculiaribus pollet, quod resinam fundat fragrantissimam instar Lentisci, ex qua emplastrum adversus frigidos affectus componitur.</p> <p>Foliis convenit cum <i>Guabirabae</i> foliis, nisi quod hujus sint Paulo minora: Sunt autem in ramulis bina sibi invicem opposite, & quinque aut septem in extremitate. Ad cujuslibet ramuli exortum, ramulus est brevior, plenus, flosculis minimis, qui constant quinque foliolis ex albo subluteis.</p> <p>Fructum fert (sert) exiguum sanguinei coloris, racematum congestum ac pendulum, cuius acrimonia & siccitate carnes recentes à putredine conservatur.</p> <p>Oleum quoque ex succulentis illius baccis exprimitur, eidem usui cum resina inserviens.</p> <p>Folia insignem & nobilissimum odorem emitunt, si conterantur, quae subamara, cum quadam vi adstringendi, aromaticas calidasque partes habent conjunctas, quemadmodum è balneis & lavacris, quae ex illis siunt, videre est.</p> <p>Has vero virtutes tum profunde exserit, ut per destillationem foliorum, imprimis recentium, odorifera & adstringens aqua inde eliciatur, quae tum ad pellendos corporis affectus, tum ad delicias servatur.</p> <p>Tempore paroxysmi febricitanti, Empyricorum more, exhibent cum successu, oculos seu gemmas arboris ex aqua nocturne rori expositos.</p> <p>Caeterum sciendum est in ramis <i>Aroeira</i>, luxuriante saepe polypodium, illo quod è terra prosilit longe probatius.</p>	<p style="text-align: center;">Cap. XI</p> <p style="text-align: center;">On Aroeira and its qualities</p> <p>The tree from sandy places, particularly frequent in shores and promonotories of Olinda [historic city in the state of Pernambuco], is called Aroeira. In its quality not very different from the native wild Myrtle, it must remind one of the Lentisks. Besides certain uncommon properties, which it shares with the Araca & Myrto trees, it flourishes in these in particular, because it pours extremely fragrant resin like that of the Lentisk, out of which one can make a plaster against cold affections.</p> <p>The leaves approximate those of the Guabirabae, except hers are smaller than those of the Paulo: they also are in the branch in pairs opposite each other, & with five or seven ends. They spring up from any branch; the branch is shorter, stout, with minimal flowerettes, which consist of five leaflets of a white-saffron yellow [NT: sub- prefix probably points to a white out of the yellow].</p> <p>It bears fruit of an exiguous blood-color, with clusters of berries dense and hanging down, whose fresh flesh is preserved from rotting by pungency and dryness.</p> <p>Also, the oil of her succulent berries is pressed out, same use as the useful resin.</p> <p>The leaves emit a notable & extremely noble odor when ground, slightly bitter, with binding force in a certain place, they have the aromatic and hot parts together, as it can be seen, for example, outside restrooms and baths, which is done out of these.</p> <p>It reveals these true excellent properties so profoundly that for the distillation of the leaves, especially when fresh, a fragrant & binding water may be thence extracted, which at times can drive out disease from the body, at other times can be saved for pleasure.</p> <p>In times of feverish paroxysms, they appear with success in the custom of Empyrics, eyes or buds of the tree exposed out of the nocturnal water of the dew.</p> <p>Another thing that is to be known, the <i>Aroeira</i>, often a luxurious polypodium, in its branches that which is out of the ground bursts forth quite far.</p>

Supplementary Table 2: Summary of select previous reports of antimicrobial bioactivity from different tissues of *Schinus terebinthifolia*.

Plant Tissue	Extraction method	Antimicrobial Bioactivity [†]	Attributed Chemistry*	Ref.
Stem bark	Crude hydroethanolic extract	<u>Anti-viral</u> : Herpes Simplex Virus-1 (EC ₅₀ : 14 µg mL ⁻¹ ; SI: 22.5)	flavan-3-ols	¹
	Aqueous extract	<u>Antifungal</u> : <i>Trichophyton rubrum</i> (MIC/MFC: 1 mg mL ⁻¹); <i>Trichophyton. mentagrophytes</i> (MIC/MFC: 1 mg mL ⁻¹)	-	²
	Ethanol:water extract	<u>Antifungal</u> : <i>Trichophyton rubrum</i> (MIC/MFC: 62.5 µg mL ⁻¹); <i>Trichophyton. mentagrophytes</i> (MIC/MFC: 62.5 µg mL ⁻¹)	-	²
	50% Hydroalcoholic extract of	<u>Antibacterial</u> : <i>Staphylococcus aureus</i> (MIC: 250 µg mL ⁻¹), <i>Pseudomonas aeruginosa</i> . (MIC: 1000 µg mL ⁻¹), <i>Bacillus subtilis</i> (MIC: 1000 µg mL ⁻¹) <u>Antifungal</u> : <i>Candida albicans</i> . (MIC: 0.49 µg mL ⁻¹), <i>C. parapsilosis</i> (MIC: 62.5 µg mL ⁻¹), <i>C. tropicalis</i> . (MIC: 62.5 µg mL ⁻¹)	-	³
Stems	Dichloromethane fraction of hydroalcoholic extract	<u>Antifungal</u> : <i>Paracoccidioides brasiliensis</i> (MFC: 30 µg mL ⁻¹)	biphenyl 4'-ethyl-4-methyl-2,2',6,6'-tetrahydroxy[1,1'biphenyl]-4,4'-dicarboxylate	⁴
Fruits	Essential oil extraction by hydrodistillation	<u>Antibacterial</u> : <i>Corynebacterium</i> sp. (MIC: 3.55 µg mL ⁻¹), <i>Bacillus</i> sp. (MIC: 7.11 µg mL ⁻¹), <i>Nocardia</i> sp. (MIC: 7.11 µg mL ⁻¹), <i>Enterobacter</i> sp. (MIC: 56.86 µg mL ⁻¹), <i>Enterobacter agglomerans</i> (MIC: 28.43 µg mL ⁻¹), <i>Escherichia coli</i> (MIC: 28.43 µg mL ⁻¹), <i>Klebsiella oxytoca</i> (MIC: 28.43 µg mL ⁻¹)	monoterpenes (δ-3-carene, limonene, α-phellandrene, α-pinene) and Sesquiterpenes (trans-caryophellene)	⁵
Leaves	Dichloromethane extract	<u>Antibacterial</u> : <i>Staphylococcus aureus</i> (MIC: 600 µg mL ⁻¹), <i>Pseudomonas aeruginosa</i> (MIC: 550 µg mL ⁻¹), <i>Escherichia coli</i> (MIC: 850 µg mL ⁻¹) <u>Antifungal</u> : <i>Aspergillus niger</i> (MIC: 750 µg mL ⁻¹), <i>A. parasiticus</i> (MIC: 800 µg mL ⁻¹), <i>Candida albicans</i> (MIC: 700 µg mL ⁻¹),	monoterpenes and sesquiterpenes	⁶
	Methanol extract; hydroalcoholic solution	<u>Antibacterial</u> : <i>Streptococcus mutans</i> (MICA: 7 µg mL ⁻¹) <u>Antifungal</u> : <i>Candida albicans</i> (MICA: 7 µg mL ⁻¹)	-	⁷
	Hexane fraction of hydroalcoholic extract	<u>Antifungal</u> : <i>Paracoccidioides brasiliensis</i> (MFC: 15-125 µg mL ⁻¹)	schinol	⁴

* SI: Selectivity Index; EC₅₀: 50% inhibitory concentration; MIC: minimum inhibitory concentration; MFC: minimum fungicidal concentration; MICA: Minimal inhibitory concentration of adherence (biofilm)

* “-”: no information on the bioactive chemistry provided

Supplementary Table 3: 430D-F5 inhibits *agr* fluorescent reporter signaling with minimal growth (OD600nm) effects at concentrations < 64 µg mL⁻¹. Data are reported as percent vehicle control.

Conc. 430D-F5 (µg mL ⁻¹)	OD600 % Vehicle Control (± Standard Deviation)			
	<i>agr I</i> (AH1677)	<i>agr II</i> (AH430)	<i>agr III</i> (AH1747)	<i>agr IV</i> (AH1872)
2	110.4 ± 2.3	114.9 ± 2.4	104.7 ± 1.9	102.6 ± 0.7
4	114.5 ± 2.3	118.9 ± 4.0	111.5 ± 1.4	101.4 ± 1.9
8	120.5 ± 3.1	125.4 ± 6.1	115.6 ± 3.0	108.3 ± 1.4
16	120.0 ± 9.8	126.9 ± 5.4	111.8 ± 1.4	104.8 ± 3.8
32	121.6 ± 3.8	122.7 ± 1.4	100.2 ± 2.9	96.3 ± 7.6
64	92.5 ± 4.2	108.5 ± 1.7	69.5 ± 1.4	85.9 ± 3.6
128	65.8 ± 1.5	76.9 ± 4.9	56.5 ± 0.6	65.2 ± 1.6

Conc. 430D-F5 (µg mL ⁻¹)	Fluorescence % Vehicle Control (± Standard Deviation)			
	<i>agr I</i> (AH1677)	<i>agr II</i> (AH430)	<i>agr III</i> (AH1747)	<i>agr IV</i> (AH1872)
2	47.8 ± 4.2	51.5 ± 3.1	56.2 ± 1.7	83.5 ± 2.3
4	36.7 ± 2.3	33.3 ± 0.5	40.8 ± 0.8	64.7 ± 3.0
8	30.0 ± 1.1	25.1 ± 1.8	32.1 ± 0.5	54.9 ± 1.8
16	26.0 ± 4.6	18.6 ± 0.9	27.8 ± 0.3	51.4 ± 5.2
32	18.2 ± 2.2	14.6 ± 0.4	18.1 ± 0.3	41.3 ± 2.2
64	16.9 ± 0.8	14.3 ± 0.2	11.2 ± 0.3	27.0 ± 3.3
128	11.7 ± 0.3	13.3 ± 2.0	6.7 ± 0.2	21.0 ± 0.2

Supplementary Table 4: Negative and positive ESI Mass spectrometry (*m/z*) analysis of 430D-F5. The corresponding HPLC-DAD chromatogram is reported in Fig. 9a and putative structures in Fig. 9b.

Peak #	RT (min)	(%) Relative Abundance		Formula (Δ - ppm) ^a	Putative Compounds	ESI Mode	<i>m/z</i> ^b	MS ²
		Neg. Mode	Pos. Mode					
1	39.78	0.00	0.55	C ₅₄ H ₅₉ O ₆ (1.3)	no matches	+	391.2296, 413.2114, 803.4316	ND
2	45.70	11.65	3.59	C ₃₀ H ₁₇ O ₁₀ (0.2)	amentoflavone; agathisflavone; robustaflavone	-	537.0828	375.1374, 443.1003
3	46.28	8.39	2.14	C ₃₀ H ₁₇ O ₁₀ (0.2)	see peak 1	-	537.0826	375.1590, 443.1464
4	47.25	22.13	3.37	C ₃₀ H ₂₁ O ₁₀ (1.4)	chamaejasmin; tetrahydroamentoflavone; tetrahydrorobustaflavone	-	541.1147 , 1083.2380	389.1906, 415.1563
5	47.79	3.03	0.62	C ₃₀ H ₂₁ O ₁₀ (-0.2)	see peak 3	-	541.1138	389.1694, 415.1370
6	48.19	4.66	0.73	C ₅₃ H ₉₅ O ₁₅ (-1.3)	no matches	-	485.3277, 531.3344, 971.6664	941.8088, 951.2601, 971.7518
7	49.49	1.14	0	C ₃₁ H ₄₅ O ₇ (-0.6)	no matches	-	529.3167	485.5292
8	51.12	0.53	0.93	C ₄₅ H ₆₆ O ₁₅ (-0.3)	no matches	+	415.2112, 432.2376, 493.2250, 846.4404	ND
9	51.43	0.27	0.54	C ₂₉ H ₃₇ O ₃ (3.7)	no matches	-	433.2764 , 455.2583	400.9561, 415.3339
10	52.01	3.5	0.43	C ₃₀ H ₄₅ O ₆ (0.5)	no matches	-	501.3224	439.3959
11	53.10	0	0.31	C ₄₈ H ₇₀ O ₃ (-9.6)	no matches	+	356.2793, 694.5253	542.3829, 676.2984
12	53.53	0.98	1.31	C ₄₀ H ₆₉ O ₈ (0.9)	no matches	+	356.2795, 377.2299, 677.4993 , 699.4816	557.3066, 647.4799
13	54.48	0	2.11	C ₄₀ H ₆₉ O ₈ (2.5)	no matches	+	677.5004 , 699.4831	525.4104, 5557.4151, 647.5023
14	55.01	5.33	2.33	C ₃₀ H ₄₅ O ₄ (0.9)	albsapogenin; (3 α ,13 α ,14 β ,17 α ,20S,24Z)-3-hydroxy-21-oxo-lanosta-8,24-dien-26-oic acid; (13 α ,14 β ,17 α ,20R,24Z)-3 α -hydroxy-21-oxolanosta-8,24-dien-26-oic acid; (3 α ,13 α ,14 β ,17 α ,24Z)-3-hydroxy-7-oxo-lanosta-8,24-dien-26-oic acid; mollinoic acid	-	469.3327 , 515.3390, 939.6748	351.3897, 451.4088
15	55.44	2.14	2.33	C ₃₀ H ₄₅ O ₄ (2.9)	see peak 13	-	469.3336 , 515.3379	ND
16	56.12	0.63	1.78	C ₄₀ H ₆₁ O ₆ (0.9)	no matches	-	533.3491, 637.4479 , 683.4534	607.5950
17	56.58	7.99	8.52	C ₃₀ H ₄₅ O ₄ (1.0)	see peak 13	-	469.3328 , 515.3391,	407.4528

Peak #	RT (min)	(%) Relative Abundance		Formula (Δ - ppm) ^a	Putative Compounds	ESI Mode	<i>m/z</i> ^b	MS ²
		Neg. Mode	Pos. Mode					
							939.6760	
18	57.76	1.52	2.86	C ₃₀ H ₄₇ O ₄ (3.1)	see peak 13	+	471.3483	453.4008
19	58.06	1.05	2.09	C ₃₀ H ₄₅ O ₄ (3.4)	isomasticadienonalic acid	+	469.3328	260.1903, 332.2413, 452.3980
20	58.32	1.09	2.77	C ₅₃ H ₉₇ O ₁₃ (2.1)	no matches	+	471.3485, 621.4551, 941.6944	941.6543
21	58.48	2.07	0	C ₃₀ H ₄₅ O ₆ (0.1)	no matches	-	501.322	439.3777
22	58.74	3.49	10.4	C ₃₀ H ₄₅ O ₄ (2.2)	see peak 13	-	469.3333 , 515.3384, 939.6736	439.4702
23	59.35	2.39	3.43	C ₃₀ H ₄₇ O ₄ (1.9)	see peak 13	+	471.3488	217.1912, 435.3044, 453.3376
24	59.73	5.37	4.12	C ₃₀ H ₄₅ O ₅ (2.1)	no matches	-	485.3282 , 531.3338, 971.6649	453.3968, 467.3944
25	60.44	2.06	2.55	C ₃₀ H ₄₅ O ₄ (0.1)	see peak 13	-	469.3323 , 515.3383, 939.6758	451.3724
26	60.75	1.23	1.48	C ₃₀ H ₄₅ O ₄ (0.8)	see peak 13	-	469.3327 , 515.3375	451.3639
27	61.72	1.56	2.29	C ₃₀ H ₄₇ O ₅ (1.5)	no matches	-	487.3436 , 533.3478, 975.6950	455.4224, 469.4080

^aThe empirical formula corresponds to the [M+H]⁺ or [M-H]⁻ ion as determined by the ionization mode.

^bThe reported ions correspond to the [M+H]⁺ or [M-H]⁻ ion as determined by the ionization mode. When multiple ions were formed, the number in **bold font** indicates the [M+H]⁺ or [M-H]⁻ and underwent MS² analysis.

Supplementary Table 5: Description of bacterial strains used in the study.

Species	Strain ID	Characteristics [†]	Source	Ref.
<i>Corynebacterium amycolatum</i>	SK46; HM-109	Isolated from the right arm normal skin of a 57-year-old male; a reference genome for the species. Genbank sequence: ABZU00000000	BEI; HMP	
<i>Corynebacterium striatum</i>	FS-1	Clinical isolate from Italy (2005-2007)	BEI	
<i>Micrococcus luteus</i>	SK58; HM-114	Isolated from normal skin of the left arm of a 57-year-old male; a reference genome for the species. Genbank sequence: ADCD00000000	BEI; HMP	
<i>Propionibacterium acnes</i>	HL005PA2; HM-493	Isolated from human skin; a reference genome for the species. Genbank sequence: ADZN00000000	BEI; HMP	
<i>Staphylococcus aureus</i>	LAC; AH1263	USA300		⁸
	UAMS-1; ATCC49230	Clinical isolate from osteomyelitis; USA200	MS	⁹
	UAMS-929	ΔsarA mutant of UAMS-1	MS	¹⁰
	AH1677	AH845 + pDB59 cm ^R ; agr type I YFP reporter; USA300	AH	¹¹
	AH430	SA502a + pDB59 cm ^R ; agr type II YFP reporter;	AH	¹¹
	AH1747	MW2 + pDB59 cm ^R ; agr type III YFP reporter	AH	¹¹
	AH1872	MN EV (AH407) + pDB59 cm ^R ; agr type IV YFP reporter	AH	¹¹
	AH2759	LAC + pAmiAgrP3 cm ^R ; agr P3-lux reporter	AH	¹²
	AH3052	Δspa mutant of LAC	AH	¹³
	AH1589	Δhla mutant of LAC	AH	¹⁴
	NRS225	Clinical isolate from UK (1976). mecA+; pen ^R . CC121, ST121	NARSA	
	NRS230	Clinical isolate from 2 year old male in France (2002), associated with elbow arthritis with scarlet fever. agr type IV; egc+, (lukE-lukD)+, hlgv+, mecA-. erm ^R , pen ^R , ST121-SLV, CC121	NARSA	
	NRS232	Clinical isolate (blood) from 4 year old male in France (2002), associated with necrotizing pneumonia. agr type I; egc+, (lukS-lukF PVL)+, hlg+, mecA-; erm ^I , gent ^R , pen ^R ; 2 colony variants. ST22, CC22	NARSA	
	NRS242	Clinical isolate from 1 year old female in France (2002), associated with impetigo. agr type IV; egc+, (lukS-lukF)+ PVL+, (lukE-lukD+), hlgv+, mecA-. erm ^I , pen ^R . CC121, ST121	NARSA	
	NRS249	Clinical isolate (blood) from 5 year old male in France (2002), associated with native valve endocarditis. agr type I; sea+, hlgv+, mecA+. cipx ^R , cli ^R , erm ^R , gen ^R , oxa ^R , pen ^R . SCCmec type IV. ST247, CC8(247)	NARSA	
	NRS385; NR-46071	Clinical isolate from USA. USA500, agr type I, sea+, seb+, SCCmecIV, mecA+. cipx ^R , cli ^R , erm ^R , gen ^R , oxa ^R , pen ^R , tet ^R , tmp/sm ^R .	NARSA	¹⁵
<i>Staphylococcus epidermidis</i>	NIHLM001; HM896	Isolated in 2008 from an alar crease of a healthy 27-year-old white male volunteer in the United States; a reference genome for the species. Genbank sequence: AKHC01000000	BEI; HMP	

Species	Strain ID	Characteristics ^T	Source	Ref.
	NRS101; RP62A; ATCC 35984	Clinical isolate from USA, catheter sepsis. Prototype biofilm producer, produces polysaccharide adhesin. <i>mecA+</i> ; <i>clin^R</i> , <i>erm^R</i> , <i>gen^R</i> , <i>oxa^R</i> , <i>pen^R</i>	NARSA	
<i>Staphylococcus haemolyticus</i>	NRS116	Clinical isolate from 45 year old male in USA (2002); variant small colony type of NRS115; <i>mecA+</i> ; <i>van^I</i> ; <i>tec^I</i>	NARSA	
<i>Staphylococcus warneri</i>	SK66	Isolated from normal skin of right arm of healthy 57 year old male; a reference genome for the species. Genbank sequence: ACPZ00000000	BEI; HMP	
<i>Streptococcus mitis</i>	F0392	Isolated from human oral cavity; a reference genome for the species	BEI; HMP	
<i>Streptococcus pyogenes</i>	MGAS15252	Clinical isolate from thigh of patient with an invasive soft tissue infection in Canada (2008); serotypeM59, Group A <i>Streptococcus</i> . Genbank sequence: CP003116	BEI	

^T**Characteristics:** CC: clonal complex; ST: Sequence Type; I: Intermediate; R: Resistant; cm: chloramphenicol; cipx: ciprofloxacin; cli: clindamycin; erm: erythromycin; gen: gentamicin; oxa: oxacillin; pen: penicillin; tec: teicoplanin; tmp/smx: trimethoprim/sulfamethoxazole.van: vancomycin.

***Source:** AH: A. Horswill, U. Iowa; BEI: Biodefense and Emerging Infections Research Resources Repository; HMP: Human Microbiome Project; NARSA: Network on Antimicrobial Resistance in *Staphylococcus aureus*; MS: M. Smeltzer, UAMS.

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