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Chemical constituents and antimicrobial activities of some isolated compounds from the Cameroonian species of *Senna alata* (*Cassia alata* L. Roxb synonym, The plant list 2013). (Leguminosae)

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ABSTRACT

One fatty acid (**1**), one monoglycol ester (**2**), three diterpenes (**3**-**5**), four steroids (**6**-**9**), four triterpenes (**10**-**13**), three flavonoids (**14**-**16**), three anthraquinones (**17**-**19**) and one benzoquinone (**20**), were isolated from the methanolic extract of the leaves and trunk of *Senna alata*. These compounds were obtained by extensive silica gel chromatography and their structures elucidated by 1D and 2D nuclear magnetic resonance (NMR) as well as comparison with literature data. Compounds (**2**-**4**) have been reported for the first time from this species. Some isolated compounds and methanolic crude extract of leaves and trunk were screened in vitro for their antimicrobial activities. Kaempferol (**16**) exhibited strong activity against all the tested strains, with MIC values varying from 15.5 to 31.2 µg/mL, emodin (**18**) was active with a strong activity (7.8 µg/mL) exhibited on Pseudomonas aeruginosa. The trunk crude extract showed a strong activity with MIC values varying from 15.6 to 62.5 µg/mL.

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1. Introduction

Medicinal plants of the Cameroonian rainforest, savannahs, and deserts, as in most other developing countries, have been known for millennia as a rich source of therapeutic agents for the treatment and prevention of various diseases caused by parasites such as malaria, typhoid fever, schistosomiasis, onchocerciasis, lymphatic filariasis, African trypanosomiasis, and dengue (Mohammadhosseini, 2017; Mohammadhosseini et al., 2017; Pavunraj et al., 2017). This knowledge was handed down from generation to generation either orally or mystically, and effective plants have been selected by trial and error. Today, a part of this traditional knowledge is still in use in Cameroon as in most other developing countries, especially in some villages of the West and North-West. The sacred forests from the central parts of the rainforest, in which no agriculture is allowed, still conserve knowledge on the bioeffectiveness of plants. These plants are used in various forms by local medicine practitioners as decoctions, infusions, ointment, powder and maceration, friction, and chewing. Several of these species, many of them are endemic to Cameroon or Western/Central (Wansi et al., 2018; 2019). Due to the unpleasant side effects and ineffectiveness of many conventional drugs, the search for new drugs from natural origin has gained momentum in recent years (Mohammadhosseini et al., 2019).

Among these, *Senna alata* (L.) Roxb is a shrub that can grow up to about 3 meters tall. Leaves are pinnate, 30 to 40 cm long. Flowers are roundish and golden-yellow. The juice from the fresh leaves of *Senna alata* has been credited for the treatment of hemorrhoids, constipation, inguinal hernia, intestinal parasitosis, blennorrhagia, syphilis, and diabetes (Adjanahoun et al., 1991; Ivan, 2003; Makinde et al., 2007; Shabina et al., 2015; Oluwole et al., 2020; Yingang et al., 2020).

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The powder made out of its leaves has been used against herpes in many tropical countries (Igoli et al., 2005) and also as antifungals in cosmetics (Adjanahoun et al., 1991). Previous chemical study of *Senna alata* led to the isolation of classes of compounds belonging to tannins, alkaloids, flavonoids, terpenes, anthraquinone, saponins, and phenolics, some of with interesting activities included hydroxyanthraquinones, chrysophanic acid, kampferin, and sannoxides A and B (Makinde et al., 2007; Yingang et al., 2020). Together with these, essential oil constituents such as 1, 8-cineole, caryophyllene, limonene, α-selinene, β-caryophyllene, germacrene D, cinnamic acid, and pyrazol-5-ol have also been reported from the plant (Wansi et al., 2018; Wansi et al., 2019; Oluwole et al., 2020).

To the best of our knowledge, no phytochemical study has been done on the Cameroonian species of *Senna alata*. Hence, the current work reports the isolation of twenty known compounds from the leaves and trunk of *Senna alata*. Glyceryl-1-hexacosanoate (**2**), copalic acid (**3**), and 3-β-acetoxycopalic acid (**4**) are reported for the first time from this species. In addition, the antimicrobial activities of the crude extracts and some isolated compounds are also being reported for the first time.

2. Experimental

2.1. General instrumentation

Ultraviolet spectra were recorded on a Hitachi UV 3200 spectrophotometer in MeOH. Infrared spectra were recorded on a JASCO 302-A spectrophotometer. EI-MS (Electronic Impact-Mass Spectra) were recorded on a Finnigan MAT 95 spectrometer (70 eV) with perfluoro-kerosene as reference substance for HR-EI-MS (High Resolution-Electrospray Ionization-Mass Spectra) were measured on Agilent Techn. 6220 TOF LCMS mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). The ^{1}H- and ^{13}C-NMR spectra were recorded at 500, 400, 125, and 100 MHz, respectively on Bruker AMX 600 NMR spectrometers. Homonuclear ^{1}H connectivity was determined using the COSY (Correlation Spectroscopy) experiment. ^{1}H-^{13}C one bond connectivity was determined using HSQC (Heteronuclear Single Quantum Correlation) gradient pulse factor selection. Two and three-bond connectivity were determined using HMBC (Heteronuclear Multiple Bond Connectivity) experiments. Chemical shifts are reported in δ (ppm) using TMS as internal standard and coupling constants (*J*) were measured in Hz. Column chromatography was carried out on silica gel (70-230 mesh, Merck). Thin Layer Chromatography (TLC) was performed on Merck pre-coated silica gel 60 F254 aluminum foil, and spots were detected using ceric sulfate spray reagent, UV lamp, iodine vapor, potassium permanganate, and vanillin. The purity of the compounds was investigated using TLC and LC-MS. The degree of purity of the positive control was ≥ 98%, while that of the isolated compounds was 95%. All other substances, if otherwise not specified, were purchased from Sigma-Aldrich (Germany). All reagents used were of analytical grade.

2.2. Plant material

The leaves and trunk of *Senna alata* were collected in Yabassi, more precisely at PK25 (Littoral region of Cameroon), in February 2018. With the geographical location 4°27′16″ North, 9°57′56″ East, at an altitude of 49 m. The plant was identified by Mr. Victor Nana of the National herbarium of Cameroon, where a voucher specimen (N°45226 HNC) has been deposited.

2.3. Extraction and isolation

The air-dried and powdered leaves and trunk of *Senna alata* ((3.5 kg) and (3.1 kg)), respectively were successively extracted with methanol at room temperature for 48 h and then concentrated under pressure to yield dark solid extract (221.31 g, 6.32%) for the leaves and brown extract (183.30 g, 10.15%) for the trunk. Approximatively 150.00 g of each crude extract was separately subjected to silica gel column chromatography (CC) over silica gel, the elution was carried out with a mixture of "*n*-hexane-EtOAc (2/5)", "*n*-hexane-EtOAc (3/5)", "*n*-hexane-EtOAc (4/5)", "*n*-hexane-EtOAc (1/1)" in increasing polarity resulting in 4 major fractions A-D for the leaves and 5 major fractions A′-E′ for the trunk.

2.3.1. Isolation of phytoconstituents from the leaves of *Senna alata*

Fraction A (11.56 g) was composed of sub-fractions 1-36 and eluted with an isocratic system of "*n*-hexane/EtOAc" (90/10, v/v), fractions of 50 mL were collected to yield a mixture of stigmasterol (**7**) and β-sitosterol (**6**) (47.50 mg), chrysophanol (**17**) (35.25 mg), and taraxerol (**13**) (10.30 mg). Fraction B (10.60 g) was composed of sub-fractions 37-89 and eluted with *n*-hexane-EtOAc (80/20, v/v), fractions of 50 mL were collected leading to betulin (**12**) (12.00 mg), 3-β-acetoxycopalic acid (**4**) (10.25 mg) and copalic acid (**3**) (12.32 mg). Fraction C (23.60 g) resulting from sub-fractions 90-137 was eluted with *n*-hexane-EtOAc (50/50), fractions of 50 mL were collected to give kaempferol (**16**) (58.10 mg). Finally, fraction D (15.25 g) was composed of sub-frac¬tions 138-220 followed by elution with *n*-hexane-EtOAc (20/80, v/v, up to 100% EtOAc) and fractions of 50 mL were collected to afford β-sitosterol-3-*O*-glucoside (**8**) (12.14 mg).

2.3.2. Isolation of phytoconstituents from the trunk of *Senna alata*

Fraction A′ (09.50 g) was composed of sub-fractions 1-42 and eluted with an isocratic system of "*n*-hexane-EtOAc" 90:10, v/v) and fraction of 50 mL were collected to yield a mixture of stigmasterol (**7**) and β-sitosterol (**6**) (35.14 mg), cerotic acid (**1**) (36.45 mg), lupeol (**10**) (11.25 mg) and campesterol (**9**) (30.05 mg), while fraction B′

(08.50 g) was composed of sub-fractions 43-87 and eluted with "*n*-hexane-EtOAc" 70/30, v/v), fractions of 50 mL were collected to give 2,6-dimethoxybenzoquinone (**20**) (12.40 mg), betulinic acid (**11**) (8.50 mg) and betulin (**12**) (14.00 mg). Fraction C' (11.50 g) resulting from sub-fractions 88- 112 and eluted with "*n*-hexane-EtOAc" 60/40, v/v), fractions of 50 mL were collected to afford glyceryl-1-hexacosanoate (**2**) (15.52 mg) and *ent*-15-oxo-kaur-16-en-19-oic acid (**5**). Fraction D' (12.50 g) was composed of sub-fractions 113-185 and eluted with "*n*-hexane-EtOAc" 30/70, v/v), fractions of 50 mL were collected to give emodin (**18**) (12.45 mg), apigenin (**14**) (28.15 mg) and alatinone (**19**) (15.75 mg). Finally, fraction E' (10.50 g) was composed of sub-fractions 186-232 followed by elution with "*n*-hexane-EtOAc" 10/90, v/v gradually up to 100% EtOAc) and fractions of 50 mL were collected to afford kaempferol (**16**) (27.07 mg) and luteolin (**15**) (17.47 mg).

2.3.2.1. Glyceryl-1-hexacosanoate (**2**)

(15.52 mg, mp 91-93 °C). White solid, (CH_2Cl_2/acetone), EI MS (rel. int): *m/z* 470 (32), M^+, 469 (21), 439 (2), 396 (7), 379 (5), 351 (3), 176 (3), 134 (47), 98 (91) and 57 (100); IR υ_{max} (KBr) cm^{-1}: 2918, 2850, 1732. ^{1}H-NMR (400 MHz, C_5D_5N, ppm) δ : 3.97 (1H, dd, *J* = 6.3 and 11.8 Hz, H-1a), 3.95 (1H, dd, *J* = 4.8 and 11.8 Hz, H-1b), 3.70 (1H, q, *J* = 5.8 Hz, H-2), 3.46 (1H, dd, *J* = 4.2 and 12.4 Hz, H-3a) 3.39 (1H, dd, *J* = 6.1, 12.4 Hz, H-3b), 2.19 (2H, t, *J* = 15.0 Hz, H-2'), 1.46 (2H, q, *J* = 14.0 Hz, H-3'), 1.13 (2H, br s, H-25'), 0.72 (3H, t, *J* = 13.0 Hz, H-26'). ^{13}C-NMR (100 MHz, C_5D_5N, ppm) δ 173.7 (C-1'), δ 66.7 (C-1), 70.9 (C-2) and 64.3 (C-3), δ 34.4 (C-2'), 25.3 (C-3') and 22.9 (C-25'), δ 14.2 (C-26') (Mbouangouere et al., 2007).

2.3.2.2. Chrysophanol (**17**)

(35.25mg, mp: 196 °C). Crystalline solid, golden yellow or brown crystal. ESI-MS (rel.int): *m/z* 252.9 of $[M-H]^-$ in negative ion scan mode while it is at 255 $[M]^+$ in positive mode. 254 (100), 226 (24.8), 152 (20.4), 115 (17.6), 197 (16.5), 198 (16.4), 76 (15.9), 255 (14.3), 63 (13.6), 141 (12.4): UV λ_{max} (MeOH), nm: 225, 257, 277, 287 and 428. The ^{1}H-NMR (400 MHz, C_3D_6O, ppm) δ: 11.96 (1H, s, C1-OH), 11.86 (1H, s, C8-OH), 7.80 (1H, dd, *J* = 8.4, 7.6 Hz, C6-H), 7.71 (1H, d, *J* = 7.6 Hz C5-H), 7.55 (1H, d, *J* = 0.8 Hz, C4-H), 7.38 (1H, d, *J* = 8.4 Hz, C7-H), 7.22 (1H, d, *J* = 0.8 Hz, C2-H), 2.44 (3H, s,-CH_3). ^{13}C-NMR (100 MHz, C_3D_6O, ppm) δ: 191.4 (C-9), 181.3 (C-10), 161.4 (C-8), 161.1 (C-1), 149.0 (C-3), 137.2 (C-6), 133.2 (C10a), 132.8 (C-4a), 124.2 (C-2), 123.9 (C-7), 120.4 (C-4), 119.2 (C-5), 115.7 (C-8a), 113.6 (C-9a) 21.6 (-CH_3) (Prateeksha et al., 2019).

2.3.2.3. Emodin (**18**)

(12.45 mg, mp: 258-260 °C). UV λ_{max} (MeOH), nm: 218, 250, 262, 287, 436. IR υ_{max} (KBr) cm^{-1}: 3450, 1660, 1630. ^{1}H NMR (500 MHz, C_3D_6O, ppm) δ: 12.80 (1H, s, OH-3), 12.30 (1H, s, OH-1), 12.12 (1H, s, OH-8), 7.63 (1H, d, *J* = 1.3 Hz, H-4), 7.29 (1H, d, *J* = 2.4 Hz, H-7), 7.10 (1H, d, *J* = 1.3 Hz, H-2), 6.68 (1H, d, *J* = 2.4 Hz, H-5), 2.46 (3H, s, CH_3). ^{13}C NMR (125 MHz, C_3D_6O, ppm) δ: 189.9 (C-9), 181.5 (C-10), 165.6 (C-8), 164.4 (C-1), 161.4 (C-6), 148.3 (C-3), 135.2 (C-10a), 132.9 (C-4a), 124.2 (C-4), 120.5 (C-2), 113.4 (C-9a), 108.9 (C-5), 108.8 (C-8a), 107.9 (C-7), 21.8 (-CH_3). HR-ESI-MS *m/z* 270.0607 of $[M+H]^+$ (calculated for $C_{15}H_{10}O_5$, 270.0628) (Refaz et al., 2017).

2.4. Antimicrobial assay

The minimum inhibitory concentration (MIC) of samples was evaluated using the broth microdilution method as described by Eloff, with slight modifications (Eloff, 1998). Extracts, compounds, and reference drugs were dissolved in DMSO-MHB. The suspension formed was adjusted to give a turbidity equivalent to that of a 0.5 McFarland standard to give an approximate 1.5 × 108 CFU/mL Ciprofloxacin was used as the positive control. 100 µL of Mueller Hinton Broth were added into all wells of the 96-well plate, and 100 µL of the compounds/extracts were introduced to the wells in the first row (A) and mixed thoroughly. The sample mixture (100 µL) was removed from wells of row A to perform a two-fold serial dilution down the rows (B-H). The last 100 µL was discarded. Then, 100 µL of the inoculum was introduced into the corresponding wells. The final volume in each well was 200 µL. Each extract concentration was assayed in duplicate and each test was realized twice. After the incubation period of 18 hours at 37 °C, 20 µL of alamarBlue was added to each well. The plates were then re-incubated for 30 Min at 37 °C. The blue color in the well was scored as ''no bacterial growth," and a pink color was scored as ''growth occurrence" MIC values were read as those concentrations where a pronounced change of color formation was noticed (from blue to pink).

3. Results and Discussion

3.1. Phytochemical study

The methanol extract of the air-dried leaves and trunk of *Senna alata* was chromatographed on a column of silica gel eluted with pure *n*-hexane, then using "*n*-hexane-EtOAc" mixture and finally EtOAc in increasing polarity to afford twenty known compounds (Fig. 1). By comparison with the reported data, the known compounds were identified as cerotic acid (**1**) (Qu et al., 2015), glyceryl-1-hexacosanoate (**2**) (Mbouangouere et al., 2007), copalic acid (**3**) (De S Vargas et al., 2015), 3-β-acetoxycopalic acid (**4**) (De S Vargas et al., 2015), ent-15-oxo-kaur-16-en-19-oic acid (**5**), (Yarima et al., 2007), a mixture of β-sitosterol (**6**) and stigmasterol (**7**) (Prakash et al., 2003), β-sitosterol-3-*O*-glucoside (**8**) (Maiyo et al., 2016), campesterol (**9**) (Moreno et al., 2017), lupeol (**10**) (Castilho et al., 2008), betulinic acid (**11**) (Esposito et al., 2013), betulin (**12**) (Patocka, 2003), taraxerol (**13**) (Arunava et al., 2010), apigenin (**14**) (Liu et al., 2013), luteolin (**15**) (Muhammad et al., 2000), kaempferol (**16**) (Nguyen et al., 2016),chrysophanol (**17**) (Prateeksha et al., 2019), emodin (**18**) (Refaz et al., 2017),

alatinone (**19**) (Hemlata et al., 1993), 2,6-dimethoxybenzoquinone (**20**) (Morris Kupchan et al., 2006) (Fig. 1). Among them, glyceryl-1-hexacosanoate (**2**), copalic acid (**3**), and 3-β-acetoxycopalic acid (**4**) are reported here from this species for the first time.

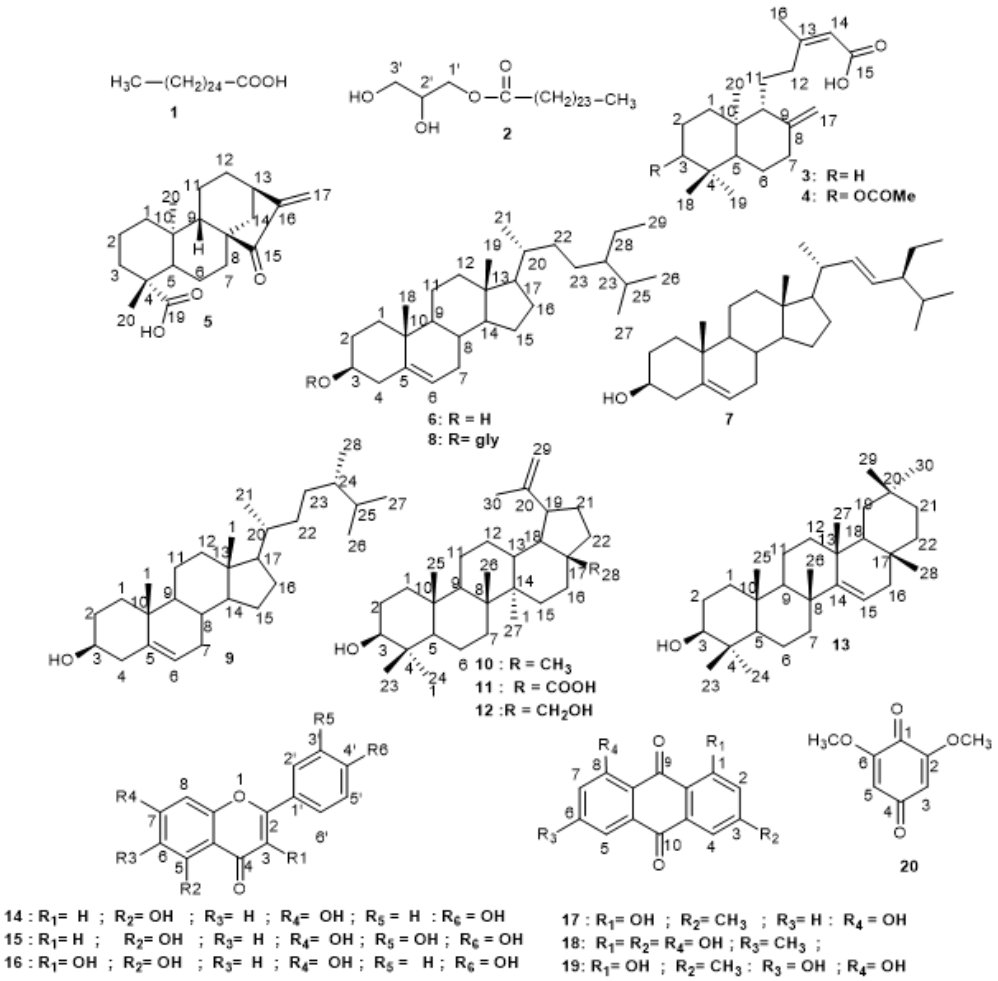

Fig. 1. Structures of isolated and identified compounds **1**-**20.**

3.2. Antibacterial assay

The methanolic extract obtained from the trunk and the leaves of the plant was tested for activity against *Staphylococcus aureus* ATCC43300, *Pseudomonas aeruginosa* (HM801), *Streptococcus pneumoniae* ATCC491619 and *Escherichia coli* ATCC25322, *Salmonella typhi*, and *Enterobacter cloacae*. The results (Table 1) showed that the methanolic trunk extract exhibited a strong activity on almost all the tested strains with MIC varying from 15.6 to 62.5 µg/mL, while the methanolic extract from the leaves showed no activity on all the tested strains. For pure compounds, strong activities on almost all the tested strains with MIC varying from 15.5 to 31.2 µg/mL for chrysophanol) (**17**) isolated from the leaves and also emodin (**18**) isolated from the trunk was active on all the tested strain, with a strong activity (7.8 µg/mL) exhibited on *Pseudomonas aeruginosa* while β-sitosterol-3-O-glucoside (**8**) isolated from the leaves of *Senna alata* showed a weak activity with MIC of 250 to 500 µg/mL, and glyceryl-1-hexacosanoate (**2**) isolated from the leaves was active on only three tested strain with strong activity (15.6 µg/mL) exhibited on *Staphylococcus aureus* ATCC43300 (Table 1). It is therefore clear that some isolated compounds have a bactericidal effect on some bacteria tested based on the different values of the MIC obtained. Notably, activities kept close to those measured for the crude extracts indicating synergic processes between compounds. Sub-Saharan populations depending on crude drugs for their primary health care may profit from these actions taking place between bark ingredients when treating bacterial infections.

4. Concluding remarks

This study shows that the trunk and leaves extract of *Senna alata* (are rich in phytochemicals such as triterpenes, steroids, flavonoids, and anthraquinones, which are of anti-infective importance. In the present work, we report the isolation of twenty previously described compounds: one fatty acid (**1**), one monoglycol ester (**2**), three diterpenes (**3**-**5**), four steroids (**6**-**9**), four triterpenes (**10**-**13**), three flavonoids (**14**-**16**), tree anthraquinones (**17**-**19**) and one benzoquinone (**20**). The antimicrobial effects of the methanolic extract

Table 1
In vitro antibacterial assay of leaves and trunk of *Senna alata* minimal inhibitory concentration (MIC) in µg/mL.

Strains / Samples	*Salmonella typhi* (Clinical isolate CPC)	*Staphylococcus aureus* ATCC43300	*Enterobacter cloacae* (Clinical isolate CHU)	*Pseudomonas aeruginosa* (HM801)	*Streptococcus pneumoniae* ATCC491619	*Escherichia coli* ATCC25322
Extract from the leaves	-[a]		-	-	-	-
Extract from the trunk	62.5	15.6	62.5	31.2	31.2	62.5
Chrysophanol (**17**)	31.2	31.2	15.6	31.2	31.2	31.2
β-Sitosterol-3-*O*-Glucoside (**8**)	500	500	500	250	500	500
Glyceryl-1-hexacosanoate (**2**)	-	15.6	-	125	250	-
3-β-Acetoxycopalic acid (**4**)	-	-	-	-	-	-
Emodin (**18**)	125	31.2	15.6	7.8	62.5	62.5
Ciprofloxcin[b]	0.015	0.15	0.015	0.07	0.031	0.015

[a] - : > 500 µg/mL; [b] Reference

of the trunk, and leaves, compounds (**2**) glyceryl-1-hexacosanoate, (**4**) 3-β-acetoxycopalic acid, (**18**) emodin, (**17**) chrysophanol, (**16**) kaempferol, and (**8**) β-sitosterol-3-*O*-glucoside were evaluated against six bacteria. They included four reference strains, namely *Staphylococcus aureus* ATCC43300, *Pseudomonas aeruginosa* (HM801), *Streptococcus pneumoniae* ATCC491619 and *Escherichia coli* ATCC25322. Then two clinical isolates of *Salmonella typhi* and *Enterobacter cloacae* from the Pasteur Center of Cameroon 'CPC' and CHU, respectively. According to the reference (Kuete, 2010), we can say that chrysophanol (**17**) exhibited strong activity on almost all the tested strains, with MIC varying from 15.5 to 31.2 µg/mL ,while β-sitosterol-3-*O*-glucoside (**8**) showed a weak activity with MIC of 250 to 500 µg/mL. On the other hand, the crude trunk extract of *Senna alata* exhibited a strong activity on almost all the tested strains with MIC varying from 15.6 to 62.5 µg/mL. Finally, emodin (**18**) isolated from the *Senna alata* trunk was active on all the tested strains, with a strong activity (7.8 µg/mL) exhibited on *Pseudomonas aeruginosa*.

Conflict of interest

The authors declare that there is no conflict of interest.

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