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Steroids from *Commiphora mukul* display antiproliferative effect against human prostate cancer PC3 cells via induction of apoptosis

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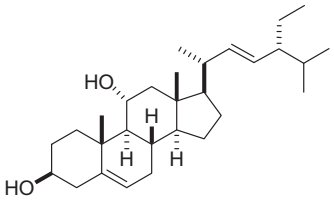
ABSTRACT

Two new stigmastane-type steroids, stigmasta-5,22*E*-diene-3β,11α-diol (**1**) and stigmasta-5,22*E*-diene-3β,7α,11α-triol (**2**), together with eight known compounds, were isolated from the resinous exudates of *Commiphora mukul*. Their structures were established by extensive analysis of their HR-MS, 1D- and 2D-NMR (COSY, HMQC, HMBC and NOESY) spectra. The isolates were evaluated for their antiproliferative activities against four human cancer cell lines. Compound **2** demonstrated inhibitory effects with IC_{50} values of 5.21, 9.04, 10.94 and 16.56 μM, respectively, against K562, MCF-7, PC3 and DU145 human cancer cell lines. Further study showed that **2** was able to enforce the PC3 cell cycle arrest in the G2/M phase, and induce the apoptosis of PC3 cells by activation of Bax, caspases 3 and 9, and by inhibition of Bcl-2. It was also found that **1** inhibited proliferation of PC3 cells via G0/G1 phase arrest of the cell cycle.

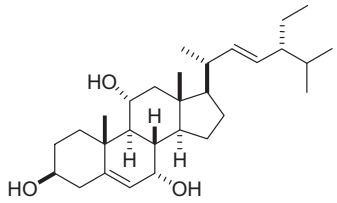
Commiphora mukul (Hook. ex Stocks) Engl., commonly known as *guggul*, is a shrub or small tree belonging to the family of Burseraceae, and distributed in northern Africa and central Asia. Its resin is an important component in Ayurvedic folk medicine, and used for the treatment of chronic inflammation, obesity, rheumatoid arthritis, fractures, intestinal parasitic infection, ulcer, etc.[1–4] Phytochemical investigation of *C. mukul* has reported a series of steroids, diterpenoids, triterpenoids and long-chain aliphatic tetrols.[5–13] The steroids guggulsterones have attracted lots of interests for their potent inhibition against human cancer cells, including leukemia, multiple myeloma, head and neck carcinoma, lung carcinoma, melanoma, breast carcinoma, ovarian carcinoma and kidney cancer.[14] They also exhibit the antiproliferative activities on the human prostate cancer LNCap and PC3 cells.[15,16]

Apoptosis is a form of programmed cell death, and enhancing apoptosis in malignancy are therapeutically valuable.[17] In prostate cancer PC3 cells, normal apoptotic mechanisms are maladjusted, and several apoptosis related proteins, covering p53, Bax, Bcl-2, IAP, etc., alter expression, which make the cancer cells resistant to apoptosis.[18] Hence enhancement of apoptotic process could be a significant strategy for the inhibition of PC3 cells, and for the treatment of human prostate cancer.

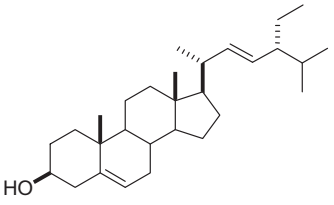
In our systematic investigation of anti-tumor (particularly anti-prostate tumor) constituents from the *Commiphora* genus and their



Stigmasta-5,22*E*-diene-3β,11α -diol (**1**)



Stigmasta-5,22*E*-diene-3β,7α,11α -triol (**2**)



Stigmasterol (**3**)

Figure 1. The structures of steroids (**1**–**3**) isolated from *C. mukul*.

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Table 1
^{13}C (600 MHz) and ^{1}H NMR (150 MHz) spectroscopic data of **1** and **2** in $CDCl_3$

Position	**1**		**2**	
	δ_C	δ_H (mult, *J*, Hz)	δ_C	δ_H (mult, *J*, Hz)
1α	39.3	1.17 m	38.9	1.17 m
1β		2.56 dt (13.2, 4.2)		2.61 dt (13.2, 4.2)
2α	31.9	1.58 m	31.6	1.63 m
2β		1.81 m		1.83 m
3	72.0	3.54 m	71.5	3.60 m
4	42.9	2.28 m	42.6	2.33 m
5	141.3		146.8	
6β	121.7	5.40 br d (5.4)	123.7	5.66 br d (5.4)
7αβ	32.0	1.97 m	65.3	3.85 br s
7β		1.58 m		
8	31.9	1.40 m	37.2	1.63 m
9	57.0	0.97 dd (10.2, 6.6)	55.7	0.96 m
10	38.3		38.9	
11β	69.4	4.05 m	69.3	4.09 m
12a	51.4	1.24 m	49.5	1.21 m
12b		2.28 m		2.33 m
13	43.0		42.8	
14	56.1	1.11 m	51.4	1.12 m
15a	29.2	1.11 m	29.2	1.12 m
15b		1.58 m		1.63 m
16aβ	24.4	1.24 m	24.1	1.27 m
16b		1.74 m		1.63 m
17	55.9	1.22 m	55.7	1.21 m
18	13.2	0.72 s	13.0	0.72 s
19	19.2	1.17 s	19.1	1.17 s
20	40.6	2.03 m	40.5	2.04 m
21	21.3	1.04 d (6.6)	21.2	1.05 d (6.6)
22	138.0	5.13 dd (15.6, 6.3)	137.7	5.14 dd (15.0, 8.4)
23	129.7	5.03 dd (15.6, 6.2)	129.8	5.04 dd (15.0, 8.4)
24	51.4	1.58 m	49.4	1.63 m
25	32.1	1.58 m	32.0	1.63 m
26	19.1	0.78 d (6.0)	18.1	0.79 d (4.2)
27	21.3	0.84 d (6.6)	21.2	0.85 d (4.2)
28a	25.5	1.17 m	25.5	1.17 m
28b		1.40 m		1.42 m
29	12.4	0.80 t (7.2)	12.4	0.81 t (4.8)

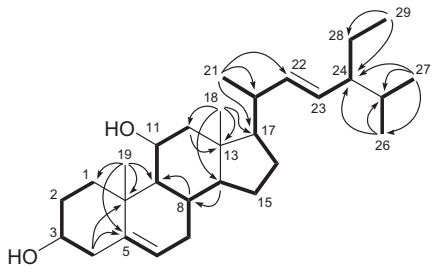

Figure 2. Selected ^{1}H–^{1}H COSY (—) and HMBC (H→C) correlations of **1**.

mechanism of action,[19–23] the resinous exudates of *C. mukul* were phytochemically studied to afford two new stigmastane-type steroids (**1**–**2**) (Fig. 1) and eight known compounds (**3**–**10**). The antiproliferative activities of isolates (**1**–**9**) were evaluated against human prostate cancer PC3 and DU145, human leukemia K562 and human breast cancer MCF-7 cell lines. Preliminary antiprolifirative mechanism of **1**–**3** (particularly **2**) targeting cell cycle arrest and induction of apoptosis on cancer cells has also been investigated.

The resin of *C. mukul* was purchased from Dixa AG medical herbs company, Switzerland in 2007. A voucher specimen (No. 20070930CM) has been deposited at the Laboratory of Natural

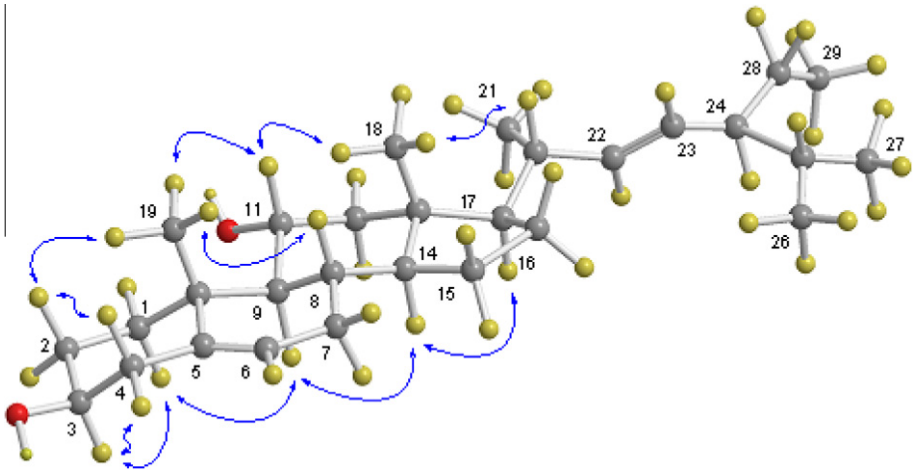

Figure 3. Selected NOESY (H↔H) correlations of **1**.