

## Secondary metabolites from the resins of *Aloe vera* and *Commiphora mukul* mitigate lipid peroxidation

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Oxidative stress is often considered detrimental for cellular processes and damaging for the lipid bi-layer. Counteracting such stresses with the aid of nature-based chemical constituents can be an ideal therapeutic approach. The current study aimed to investigate the chemical constituents of resins derived from the well-known *Aloe vera* and less known *Commiphora mukul* trees and their effect in mitigating the lipid peroxidation (LPO) process. The bio-guided isolation of bioactive fractions from both resins afforded 20 chemical constituents (17 from *A. vera* and 3 from *C. mukul*). These compounds belonged to anthraquinones, anthraquinone glycosides, quinones, coumarins, polypodane-type terpenoids and benzene derivatives. Major chemical constituents of the resins of *A. vera* and *C. mukul* were from the classes of quinones and terpenoids. Feroxidin (**4**, from *A. vera*) showed slightly higher inhibition ( $IC_{50} = 201.7 \pm 0.9 \mu\text{mol L}^{-1}$ ) than myrrhanone C (**18**, from *C. mukul*:  $IC_{50} = 210.7 \pm 0.0 \mu\text{mol L}^{-1}$ ) and methyl 3-(4-hydroxyphenyl) propionate from *A. vera* (**13**,  $IC_{50} = 232.9 \pm 0.2 \mu\text{mol L}^{-1}$ ) compared to the other compounds. Structure-activity relationship showed that the existence of hydroxyl, methoxy and ether groups might play a major role in countering oxidative stress. To the best of our knowledge, anti-LPO activities of compounds **1-4**, **14**, **18** and **20** are reported for the first time. Such chemical constituents with high anti-lipid peroxidation activity could be helpful in synthesizing candidate drugs.

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Indigenous knowledge of medicinal plant and recipes is still being practiced throughout the world, *e.g.*, in the Middle East (1, 2). Though there are numerous studies that elucidate the bioactive role of medicinal plants, their fractions and pure metabolites, little is known about pure metabolites from the resins and their anti-lipid peroxidation potentials.

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In the current study, we aimed to evaluate and understand the anti-lipid peroxidation potential of fractions and pure metabolites from economically and ecologically important resinous medicinal plants of Oman. In this regard, two resins of *Aloe vera* (*A. vera*) and *Commiphora mukul* (*C. mukul*) were selected because of their traditional uses and fewer studies of anti-lipid peroxidation. *A. vera* has been reported to be used in anti-aging, anticancer, anti-inflammatory, antibacterial, antioxidant, antifungal, antiviral and antiseptic treatments (3). In addition, it is employed for preparation of cosmetic products, skin lotions, purgatives, to treat arthritis, asthma, Crohn's disease, ulcerative colitis, ulcers, acne, psoriasis, eczema, frost-bite, burns, cold and sores (3, 4). Among its metabolites, previous investigations revealed isolation of two new C-glucosyl chromones with striking activities against the enzyme urease, DPPH antioxidant activity and cytotoxicity against the breast cancer cell line (5).

*Commiphora* (*Burseraceae*) contains approximately 190 species mostly distributed in southern Arabia, India and Sri Lanka (6). It has been reported that the gum resin of *C. mukul* Hook. was practiced in traditional medicines of India and many Arabian countries as an anti-inflammatory, anti-bacterial, anti-coagulant, anti-obese and anti-atherosclerosis agent (7). Interestingly, previously described compounds from the resin of *C. mukul* demonstrated anti-inflammatory and analgesic effects (6). Moreover, some isolates were used as pain killers in addition to their inhibitory potential towards nitric oxide production (6, 8). Our previous efforts on searching the bioactive components from *C. mukul* resulted in isolation of three compounds: myrrhanone C (18), myrrhanone B (19) and myrrhanol B (20), which exhibited antiproliferative activity against MDA-MB-231 (breast cancer cell lines) (8). Herein, we have isolated chemical constituents with anti-lipid peroxidation potential from the resins of two plants (*A. vera* and *C. mukul*). In the current study, an *in vitro* approach was adopted to initially screen the different fractions of the resins obtained from the plants and then follow them up with comprehensive chromatographic and spectroscopic techniques to obtain pure constituents.

## EXPERIMENTAL

### *General experimental procedures*

TLC (thin layer chromatography) plates were used under UV light at 254 and 366 nm; silica gel pre-coated Al sheets (60F-254, Merck, Germany) were used. Ceric sulphate spray was used as a dyeing reagent followed by heating (110–130 °C) through a heat gun. Bruker <sup>1</sup>H NMR (multinuclear and multidimensional) operating at 600 MHz (150 MHz for <sup>13</sup>C) with CryoProbe Prodigy (chemical shift,  $\delta$  in ppm, with tetramethyl silane, TMS, as internal standard, *J* value in Hz) was used (Bruker, USA). Bruker ATR Tensor 37 spectrophotometer was used for infrared spectra (cm<sup>-1</sup>) and a mass spectrometer (Waters Quattro Premier XE, Waters, USA) was used for the determination of molecular masses of the compounds. All solvents used for isolation were properly distilled.

### *Sample collection and fractionation*

Air dried ground materials of resins of *A. vera* (2016) and *C. mukul* (2014) were purchased from the local market (Souq) in Nizwa, Sultanate of Oman, and identified by the plant taxonomist Mr. Saif Al-Hatmi at the Oman Botanical Garden Muscat, Oman. Voucher

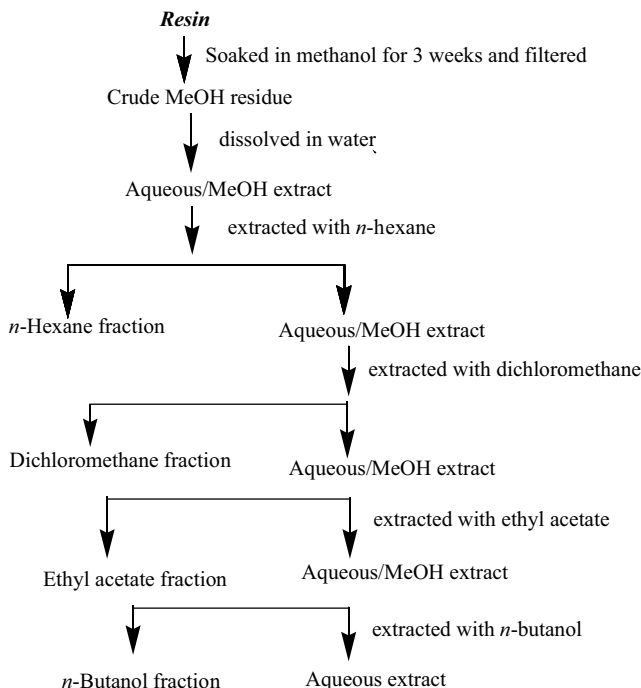


Fig. 1. Fractionation scheme for solvent-solvent extraction of the resins from *Commiphora mukul* and *Aloe vera*.

specimen of *A. vera* (No. AFS-08/2016) was deposited in the Oman Botanical Garden herbarium, Muscat, while *C. mukul* (No. CMS-03/2014) was deposited in the herbarium of the Department of Biological Sciences and Chemistry, University of Nizwa, Oman. General fractionation scheme for solvent-solvent fractionation of both resins is given in Fig. 1. Different fractions were then subjected to initial screening for anti-lipid peroxidation. Upon positive results, the extracts were subjected to column chromatography.

#### *Extraction, isolation and identification of compounds from A. vera resin (1–17)*

Air dried powdered material (1.2 kg) of *A. vera* resin was carefully extracted with methanol (3 L) at room temperature. Evaporation of methanol under reduced pressure at room temperature yielded the crude methanol extract, which was further fractionated into *n*-hexane, dichloromethane ( $\text{CH}_2\text{Cl}_2$ ), ethyl acetate (EtOAc), *n*-butanol and aqueous fractions (5). Dichloromethane fraction was subjected to silica gel column chromatography (CC) (0.063–0.210 mm, Merck), using *n*-hexane, *n*-hexane/ethyl acetate, ethyl acetate, ethyl acetate/methanol and pure methanol to afford ten fractions ( $F_{1-10}$ ). Fraction  $F_4$  (2.0 g) was subjected to further CC using EtOAc/*n*-hexane (70:30 to 90:10) as eluent to afford compounds 1–3 and 5–7. Similarly, fraction  $F_2$  (0.8 g), obtained on elution of the crude material with 30–40 % ethyl acetate/*n*-hexane, was re-chromatographed using ethyl acetate/*n*-hex-

ane (40:60 to 80:20) as eluent and provided compounds 8–10. Repeated CC of fraction F<sub>3</sub> using ethyl acetate-*n*-hexane (20:80 to 50:50) in gradient elution mode yielded compounds 4 and 11–13. Finally, fraction F<sub>1</sub> was subjected to further CC using ethyl acetate/*n*-hexane (10:90 to 20:80) as gradient eluent and provided compounds 14–17.

Compounds 1–17 were identified as 6'-*O*-coumaroylaloenin (1), aloeveraside A (2) and aloeveraside B (3) (5), feroxidin (4), aloinoside B (5), 10-hydroxyaloins A (6) and B (7), emodin (8), aloemodin (9), aloemodin-11-*O*-rhamnoside (10), 7-demethylsiderin (11) (9), 3-(4-hydroxyphenyl)propanoic acid (12), methyl 3-(4-hydroxyphenyl)propionate (13), 1-(2,4-dihydroxy-6-methylphenyl)ethanone (14), *p*-anisaldehyde (15), salicylaldehyde (16), *p*-cresol (17), resp., (Fig. 2), by 1D (<sup>1</sup>H and <sup>13</sup>C) and 2D (HSQC, HMBC, COESY and NEOSY) NMR and mass spectrometry.

### Extraction, isolation and identification of compounds from *C. mukul* resin (18–20)

*C. mukul* resin was finely ground and extracted with methanol (3.5 L) at r.t. Vaporization of the solvent under reduced pressure gave a crude methanol residue, which was fractionated into sub-fractions with *n*-hexane, CH<sub>2</sub>Cl<sub>2</sub>, EtOAc, *n*-butanol and water. The *n*-hexane fraction was subjected to silica gel column chromatography (0.063–0.210 mm, Merck), using the *n*-hexane/CH<sub>2</sub>Cl<sub>2</sub> (70:30) system as eluent, to give compound 18. Similarly, ethyl acetate fraction was subjected to silica gel column chromatography to afford compounds 19 and 20 using an ethyl acetate-*n*-hexane (30:70) system (8).

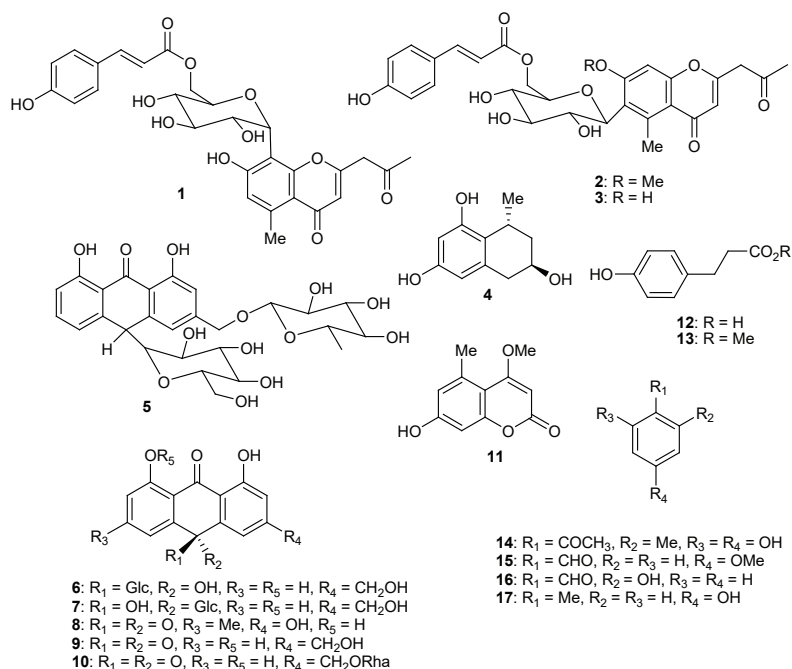


Fig. 2. Compounds isolated from *Aloe vera* resin (5, 9).

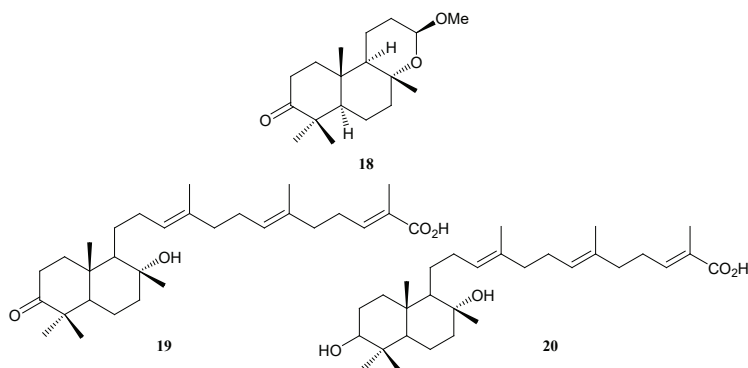


Fig. 3. Compounds isolated from *Commiphora mukul* resin (8).

Compounds 18–20 were identified as myrrhanone C (18), myrrhanone B (19) and myrrhanol B (20) (8) (Fig. 3) by 1D and 2D NMR spectroscopic techniques and mass spectrometry.

#### *In vitro anti-lipid peroxidation activity (LPO) of fractions and pure metabolites*

Isolated fractions and compounds in different concentrations were screened for inhibiting the LPO. This was performed using a modified method of TBARS (thiobarbituric acid reactive substances) (10). The LPO of liposome (50 mg mL<sup>-1</sup> phosphatidyl-choline, Sigma, Germany) was initiated by adding FeCl<sub>3</sub> (200 μL, 0.001 mmol L<sup>-1</sup>), KCl (200 μL, 300 mmol L<sup>-1</sup>) and test compounds (50 μL, 5 to 50 μg mL<sup>-1</sup>). This was followed by the addition of ascorbic acid (125 μL, 0.001 mol L<sup>-1</sup>) to the reaction mixture and incubation for 30 min (37 °C). Trichloroacetic acid and thiobarbituric acid (1 % TCA, 0.38 % TBA) were added to the final reaction mixture and the glass vials were kept in a water bath (95 °C) for 1 hour. Alteration in pink color was noted on ELISA at 535 nm. A control without pure compounds was employed as a negative control while butyl hydroxy toluene (BHT) was used as a positive control. All chemicals used were of Merck KgaA, Germany. Percent inhibition was noted. The experiment was repeated three times.

#### *Statistical analysis*

Data was analyzed by one-way ANOVA analysis in GraphPad Prism (v6.01, Benferoni test) with a specific IC<sub>50</sub> package, using non-linear regression (dose-response inhibition) diagnoses by *R*-square goodness-of-fit and D'Agostino-Pearson omnibus normality test. In addition, Duncan's multiple range (DMRT) test using *p* < 0.05 was also performed for the replicates through SAS (9.1; Cary, NC, USA).

## RESULTS AND DISCUSSION

#### *Phytochemical investigations of A. vera and C. mukul resins*

We have isolated and characterized 20 different compounds belonging to different classes such as polypodane-type triterpenes, chromones, anthrones, anthraquinones, anthraquinones glycosides and benzene derivatives.

### Anti-lipid peroxidation activity of pure chemical constituents

To assess the anti-lipid peroxidation potential of the twenty isolated compounds, they were initially screened. Compounds **1–4**, **6**, **9** and **12–17** from the resin of *A. vera*, and compounds **18** and **20** from *C. mukul* showed promising anti-lipid peroxidation activity, still lower than that of BHT (Table I). The lowest  $IC_{50}$  values were found for feroxidin (**4**) and myrrhanone C (**18**), followed by methyl 3-(4-hydroxyphenyl)propionate (**13**), 1-(2,4-dihydroxy-6-methylphenyl)ethanone (**14**) and *p*-anisaldehyde (**15**).

*Aloe vera* resin. – Compound **4** identified in *A. vera* exhibited significantly ( $p < 0.0079$ ) higher anti-LPO effect ( $IC_{50} = 201.7 \pm 0.9 \mu\text{mol L}^{-1}$ ) among all active constituents, though the inhibition percentage was significantly lower than that of the positive control (BHT:  $IC_{50} = 58.4 \pm 0.8 \mu\text{mol L}^{-1}$ ). Compound **13** also showed significantly ( $p < 0.0262$ ) higher inhibition ( $IC_{50} = 232.9 \pm 0.2 \mu\text{mol L}^{-1}$ ) compared to other compounds isolated from *A. vera* resin. The  $IC_{50}$  for compounds **14** and **15** was calculated as  $269.1 \pm 0.7$  and  $289.1 \pm 0.6 \mu\text{mol L}^{-1}$ , resp. On the other hand, the remaining compounds (**1–3**, **6**, **9**, **12**, **16** and **17**) showed lower anti-lipid peroxidation activity.

The promising lipid peroxidation inhibitory activity exhibited by the compounds isolated from *A. vera* may substantiate its use in traditional medicine. Our previous study reported the isolation of two active compounds, aloeverasides A (**2**) and B (**3**), from the

Table I. Anti-lipid peroxidation activity of isolated compounds

Compd.	$IC_{50}$ ( $\mu\text{mol L}^{-1}$ )
<b>1</b>	$476.4 \pm 0.9$
<b>2</b>	$469.5 \pm 0.4$
<b>3</b>	$432.1 \pm 0.6$
<b>4</b>	$201.7 \pm 0.9$
<b>6</b>	$762.3 \pm 0.1$
<b>9</b>	$801.8 \pm 0.8$
<b>12</b>	$868.1 \pm 0.9$
<b>13</b>	$232.9 \pm 0.2$
<b>14</b>	$269.1 \pm 0.7$
<b>15</b>	$289.1 \pm 0.6$
<b>16</b>	$701.8 \pm 1.0$
<b>17</b>	$713.9 \pm 2.1$
<b>18</b>	$210.7 \pm 0.0_1$
<b>20</b>	$522.4 \pm 0.3$
Control (BHT)	$58.4 \pm 0.83$

BHT – butyl hydroxy toluene (positive control)

<sup>a</sup> Mean  $\pm$  SEM,  $n = 3$ .

resin of *A. vera*, with breast cancer cell growth inhibition, urease inhibition and antioxidant activity (5).

*Commiphora mukul* resin. – Among the isolated compounds from *C. mukul*, compound **18** displayed the highest lipid peroxidation activity ( $IC_{50} = 210.7 \pm 0.01 \mu\text{mol L}^{-1}$ ), followed by compound **20** ( $IC_{50} = 522.4 \pm 0.2 \mu\text{mol L}^{-1}$ ). Activity of compound **18** can be attributed to the presence of methoxy or ether linkage, which is absent in the other two compounds (**19** and **20**) (12) isolated from *C. mukul* resin.

### Structure activity relationship

The presence of -OH groups in compound **4** may be a major feature of its promising anti-lipid peroxidation activity compared to the positive control (BHT). In addition, compound **13** showed four times higher activity than compound **12**, which may be due to the presence of the methyl group instead of hydrogen in the side-chain. Among the isolated compounds **1–3**, compound **3** showed slightly higher activity than **1** and **2**, which is correlated with one extra -OH group attached to the benzene ring at position C-7. Compounds **1** and **2** showed almost similar anti-lipid peroxidation activity probably because of the same functional groups.

Among phenolic compounds, the higher anti-LPO activity of compound **14** than that of **15–17** might be due to the presence of -OH groups attached in *ortho* and *para* positions with respect to the acetyl group. Higher activity of compound **15** than **16** can be due to the presence of the -OCH<sub>3</sub> group in *para* position. The presence of C-O-C (ether) and -OCH<sub>3</sub> groups in **18** is a prominent feature of its higher activity than **20**. Our previous study suggested that compounds **18–20** showed significantly higher anti-proliferative activity in case of breast cancer cell lines, whilst they also possessed moderate  $\alpha$ -glucosidase and urease enzyme inhibition activities (8). Such chemical structures can help scavenge the free radicals produced during the process of lipid peroxidation (11, 13). Overall, the current results suggest that the presence of -OH, ether and -OCH<sub>3</sub> group may enhance the anti-lipid peroxidation activity. Similar conclusions were drawn previously (13). Polyhydroxylated compounds, in particular flavones, have often been known to act as antioxidants (14).

### Screening for in vitro lipid peroxidation of different fractions from both resins

The *in vitro* LPO inhibition of different fractions of *A. vera* resin (expressed as concentration to exhibit 50 % inhibition) were as follows: EtOAc fraction of  $271.3 \pm 0.8 \mu\text{g mL}^{-1}$ , followed by *n*-butanol fraction with the value of  $289.6 \pm 0.4 \mu\text{g mL}^{-1}$  and *n*-hexane fraction with  $632.9 \pm 0.7 \mu\text{g mL}^{-1}$  (Table II). The anti-LPO effect of CH<sub>2</sub>Cl<sub>2</sub> fraction of *C. mukul*, expressed as concentration to exhibit 50 % inhibition, was  $210.4 \pm 0.8 \mu\text{g mL}^{-1}$ , followed by aqueous and EtOAc fraction with  $228.4 \pm 0.8 \mu\text{g mL}^{-1}$  and  $230.3 \pm 0.7 \mu\text{g mL}^{-1}$ , resp., whilst *n*-hexane fraction showed the value of  $436.4 \pm 0.9 \mu\text{g mL}^{-1}$ . Our results are in conformity with Ramesh *et al.* (2012), who studied the effects of *C. mukul* resin in lipid peroxidation and hepatic enzyme markers in diabetic rats (11).

## CONCLUSIONS

The current study reports the isolation and characterization of twenty known compounds from the resins of *A. vera* and *C. mukul*. Among the isolated compounds, fourteen

Table II. In vitro anti-lipid peroxidation activity of different fractions of plant resins

Extract code	IC <sub>50</sub> (μmol L <sup>-1</sup> )
<i>A. vera</i>	
AVHF	632.9 ± 0.7
AVDF	343.3 ± 0.8
AVEF	271.3 ± 0.8
AVBF	289.6 ± 0.4
AVWF	473.3 ± 0.8
<i>C. mukul</i>	
CMHF	436.4 ± 0.9
CMDF	210.4 ± 0.8
CMEF	230.3 ± 0.7
CMMF	362.1 ± 0.4
CMBF	353.4 ± 0.6
CMWF	228.4 ± 0.8

Fraction in solvent: BF – *n*-butanol, DF – dichloromethane, EF – ethyl acetate, HF – *n*-hexane, MF – methanol, WF – water

<sup>a</sup>Mean ± SEM, *n* = 3.

were found to be promising agents for LPO inhibition. Furthermore, activities of compounds 1–4, 14, 18 and 20 are reported here for the first time and could be promising sources of new potential antioxidant agents. From the assessment of the relationship of compound skeleton and structure with their potential to inhibit lipid peroxidation, it can be concluded that the presence and position of -OH, -OCH<sub>3</sub> and ether groups in phytochemicals might play a crucial role in anti-lipid peroxidation. Among isolated compounds, 4 and 18 can be potentially used for minimizing or preventing LPO, improving the nutritional quality and prolonging the shelf life of foods and pharmaceuticals. Furthermore, the present findings reveal that resin-based chemical constituents may offer an alternative for addressing lipid peroxidation and related ailments.

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