

The Anti-proliferative and Anti-bacterial Activity of Argan oil and Crude Saponin Extract from *Argania spinosa* (L.) Skeels

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ABSTRACT

Introduction: Argan oil is a well-known cosmeceutical that is commercially available. It is traditionally used for the treatment of acne and skin inflammation among others. The objective of this study was to assess the anti-proliferative and antibacterial activities of argan oil and a crude saponin extract from the argan tree (*Argania spinosa* (L.) Skeels) that is endemic to Morocco. **Materials and Methods:** The anti-proliferative activity of argan oil and the crude saponin extract was assessed by the 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) assay on A431; HaCat; HeLa; MCF-7 and UCT-Mel 1 cells. The antibacterial activity was evaluated by the broth microdilution method against two species of bacteria: *Cutibacterium acnes* and *Prevotella intermedia*. **Results:** The results of this study indicated that the argan oil sample did not inhibit the cell growth of the specified cell lines up to 1000µg/ml, while the crude saponin extract had low anti-proliferative activity. The minimal inhibitory concentration (MIC) values for both the argan oil and the crude saponin extract were found to be 500µg/ml against *Cutibacterium acnes*. No antibacterial activity from the argan oil or the crude saponin extract was evident against *Prevotella intermedia* up to a concentration of 12.5mg/ml. **Conclusion:** The results of this study indicated that argan oil and the crude saponin extract might have direct inhibitory effects on the growth and proliferation of *Cutibacterium acnes*. This finding supports the use argan oil as a treatment for acne vulgaris. **Key words:** Acne, Broth microdilution method, *Prevotella intermedia*, *Cutibacterium acnes*, XTT assay.

INTRODUCTION

Argan oil is a well-known substance extracted from the kernels of the fruit of the argan tree (*Argania spinosa* (L.) Skeels) from the Sapotaceae family. The argan tree is endemic to Southwestern Morocco where it is traditionally used, mainly for nutritional purposes, though many traditional cosmetic uses have been recorded. Its traditional cosmetic uses for dry skin, dry hair, psoriasis, eczema, wrinkles and to prevent hair loss are mainly attributed to its skin- and hair moisturizing effects. Furthermore, argan oil is used traditionally for acne, skin inflammation, joint pain and its ability to act as a choleric and hepatoprotective agent.¹⁻³ Due to the extensive cosmetic and pharmacological benefits that argan oil possess, the composition of argan oil has been comprehensively investigated. Studies on the composition of argan oil have reported that the oil is mainly composed of acylglycerides (99%) and unsaponifiable matter (1%). Unsaturated fatty acids such as oleic acid and linoleic acid comprise the greater part of the acylglycerides component. Although theories suggest that the high oleic- and linoleic acid content of argan oil could be responsible for its therapeutic effects, other oils consisting of high concentrations of

these fatty acids do not possess the same therapeutic effects. As such, the therapeutic activity of argan oil might rather be a consequence of the 1% unsaponifiable matter found within the oil. This unsaponifiable matter consists of a range of biologically active groups of compounds including carotenes (37%), tocopherols (8%), triterpene alcohols (20%), sterols (29%) and xanthophylls (5%).¹⁻³ Carotenes, tocopherols and xanthophylls are well known antioxidants, whereas the triterpene alcohols and sterols groups of compounds have been associated with anticancer and antimicrobial activity.⁴⁻⁸ The reported traditional uses and composition of argan oil warrants its evaluation for anti-proliferative and antibacterial activity. As such, the objective of the present study was to evaluate the *in vitro* anticancer and antibacterial activity of argan oil and its crude saponin extract.

MATERIALS AND METHODS

Materials

The argan oil and crude saponin extract were generous gifts from Prof. Charrouf from the Université

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Mohammed V-Agdal, Rabat, MAR. The human epidermoid carcinoma (A431) and human cervix adenocarcinoma (HeLa) cell lines were obtained from the European Collection of Cell Cultures (ECACC), England, UK. The pigmented human melanoma skin cancer (UCT-Mel 1) and human non-cancerous keratinocytes (HaCat) cell lines were kindly donated by Prof Davids, University of Cape Town, Cape Town, RSA. The human breast adenocarcinoma (MCF-7) cell line was a gracious gift from Dr. Van de Venter from the Nelson Mandela Metropolitan University, Port Elizabeth, RSA. Fetal bovine serum (FBS) and antibiotics were purchased from Separations (Pty) Ltd. (Randburg, Johannesburg, RSA). Tryptone soy (TS) agar and TS broth, anaerocult jars and anaerocult A strips were purchased from Merck (Pty) Ltd, Johannesburg, RSA. The bacterial strains, *Cutibacterium acnes* (ATCC 11827) (previously known as *Propionibacterium acnes*) and *Prevotella intermedia* (ATCC 25611), were purchased from Anatech Analytical Technologies, Johannesburg, RSA. PrestoBlue was purchased from Life Technologies, Johannesburg, RSA. The XTT cell proliferation kit II and all other chemicals and reagents were of analytical grade and were acquired from Sigma-Aldrich, Missouri, USA.

Collection and extraction

Hilali *et al.*⁹ has previously described the extraction of the argan oil. In brief, the argan oil was made from the hard-shelled argan seeds from ripened argan fruits collected between July and August 2015 from the Agadir argan forest. The argan oil was extracted by the use of a vegetable oil expeller. A study by Charrouf *et al.*¹⁰ defined the method utilized for the extraction and compound identification of the crude saponin extract. As indicated by Charrouf *et al.*¹⁰ the crude saponin extract contains oleanane saponins including arganine A-F and mi-saponin A.

Cell culturing

The A431, UCT-Mel 1 and HaCat cell lines were maintained in T₇₅ culture flasks containing Dulbecco's Modified Eagles Medium (DMEM). The MCF-7 and the HeLa cell lines were maintained in Eagle's Essential Medium (EMEM). All media were supplemented with 1% antibiotics (100 U/ml penicillin, 100µg/ml streptomycin and 250µg/L fungizone) and 10% heat-inactivated fetal bovine serum. The cells were grown at 37°C in a humidified incubator set at 5% CO₂. Cells were sub-cultured every 2-3 days after the cells had formed a confluent monolayer.

Cell proliferation assay

XTT cell proliferation kit II

The anti-proliferative activity of the samples was measured by the XTT method using the Cell Proliferation Kit II (Sigma-Aldrich, Missouri, USA). The assay was performed according to the method by Zheng *et al.*¹¹ The cells were seeded in complete growth media (100µl) in 96-well microtiter plates at a concentration of 1×10⁵ cells/ml and incubated for 24h at 37°C and 5% CO₂ to allow the cells to attach to the bottom of the wells. Stock solutions (20mg/ml) of the argan oil and crude saponin extract were prepared in dimethyl sulfoxide (DMSO) and serially diluted in complete growth media to obtain final concentrations ranging from 7.8-1000µg/ml and 3.1-400µg/ml, respectively. The control wells included vehicle treated cells exposed to 2% DMSO (highest concentration of DMSO used in the assay) and the positive control, Actinomycin D (Act D) at a concentration range between 3.91×10⁻⁴-0.05µg/ml. The microtiter plates were incubated for 72h after treatment. After the 72h incubation period, XTT reagent (50µl) was added to a final concentration of 0.3mg/ml and the plate was further incubated for 2h. Subsequently, the absorbance of the colour complex was read at 490nm with a reference wavelength set at 690nm using a BIO-TEK Power-Wave XS multi-well plate reader. The

assay was performed for a minimum of three experimental repeats and each experimental repeat was done in triplicate.

Statistical analysis

The mean values of the three independent experimental repeats were utilized to calculate the fifty percent inhibitory concentrations (IC₅₀) of the samples with GraphPad Prism 4 software. One-way Anova was used to evaluate the significant difference between the cell viability of the crude saponin extract and the vehicle control, DMSO, which was regarded as 100%. One-way Anova analysis (Tukey method) was done by using GraphPad prism 4 software.

Antibacterial assay

Microdilution broth assay

The microdilution broth method as described by Eloff¹² was used for the determination of the Minimum Inhibitory Concentration (MIC) against *Cutibacterium acnes* (ATCC 11827) and *Prevotella intermedia* (ATCC 25611) with slight modifications.

Cutibacterium acnes (ATCC 11827)

A stock concentration of the samples (2mg/ml) was serially diluted in a 96 well plate. The final concentrations of the samples ranged from 500-3.9µg/ml while Tetracycline (positive control) ranged from 100-0.78µg/ml. A bacterial suspension of *C. acnes* was adjusted to a 0.5 McFarland standard (1×10⁷ colony forming units per ml (CFU/ml)). For addition of the bacterial suspension, 100µl of a 72h culture of *P. acnes* was added to sample wells, bacterial control wells and solvent control wells. The bacterial culture was not added to the media control wells. Test plates were then incubated anaerobically for 72h at 37°C using Anaerocult A jars. After incubation, 20µl of PrestoBlue was added to all the wells. The MIC was determined as the lowest concentration where there was no color change.

Prevotella intermedia (ATCC 25611)

The samples were dissolved in 10% DMSO and serially diluted (100 µl) in a 96-well plate across four wells. The final concentrations of the samples ranged from 12500-100µg/ml while chlorhexidine gluconate (CHX, positive control) ranged from 12500-3800×10⁻⁴µg/ml. *P. intermedia* subcultures were inoculated in TS nutrient broth, to a density of 3×10⁸ CFU/ml which corresponds to a 1 McFarland Standard. Inoculated broth containing the bacterial suspension (100µl) was added to the plates. After 24h incubation at 37°C in anaerobic conditions, 20µl PrestoBlue was added. After 1h, the MIC was determined by observing a color change in the growth indicator, as the lowest concentration that showed no bacterial growth.

RESULTS

Anti-proliferative activity

The argan oil did not show any inhibitory activity against the cell proliferation of cell lines: A431, UCT-Mel 1, MCF-7, HeLa and HaCat up to a concentration of 1000µg/ml. The IC₅₀ values for the anti-proliferative activity of the saponin extract are shown in Table 1. Although no IC₅₀ value could be extrapolated for the crude saponin extract activity against the MCF-7 cell line, the extract did show anti-proliferative activity at a concentration of 400µg/ml as apparent from the dose response curve. The dose-response curves of the effect of the crude saponin extract on the cell viability of the different cells lines are given in Figure 1.

Antibacterial activity

The argan oil and saponin extract showed anti-bacterial activity at a concentration of 500µg/ml on the bacterium, *C. acnes*. No anti-bacterial activity on *P. intermedia* was observed up to a concentration of 12.5mg/ml

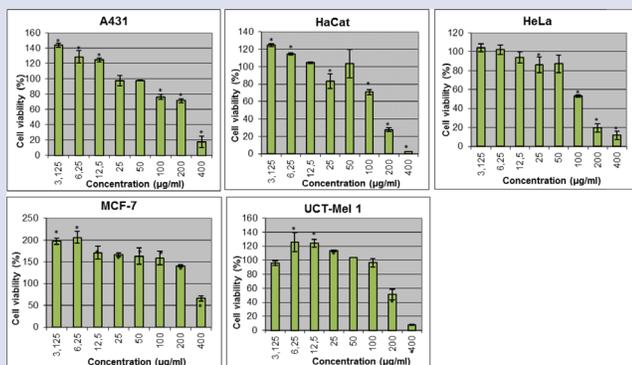


Figure 1: Dose response curves of the crude saponin extract on the cell lines A431; HaCat; HeLa; MCF-7; UCT-Mel 1 at concentrations ranging from 3.125- 400µg/ml. * P-values < 0.5.

Table 1: Effect of the crude saponin extract on the cell proliferation of various cell lines after 72h treatment.

Treatment	IC ₅₀ (µg/ml)				
	A431	UCT-Mel 1	MCF-7	HeLa	HaCat
Crude saponin extract	236.2±10.6	155.4±7.3	>400	126±5.9	100.5±5.5
Actinomycin D*	2.6×10 ⁻³ ± 2.6×10 ⁻³	4.7×10 ⁻³ ± 1.2×10 ⁻⁴	2.3×10 ⁻² ± 5.5	9.3×10 ⁻³ ± 6.0	7.7×10 ⁻³ ± 4.0×10 ⁻⁵

A431: Human epidermoid carcinoma cell line

UCT-Mel 1: Human pigmented malignant melanoma cell line

MCF-7: Human breast adenocarcinoma cell line

HeLa: Human cervical adenocarcinoma cell line

HaCat: Human keratinocyte cell line

IC₅₀: Fifty percent inhibitory concentration

*: Positive control

Table 2: The antibacterial effect of argan oil and crude saponin extract on *Cutibacterium acnes* and *Prevotella intermedia* after 72h of treatment.

Treatment	MIC (µg/ml)	
	<i>C. acnes</i>	<i>P. intermedia</i>
Argan oil	500	>12 500
Crude saponin extract	500	>12 500
Tetracycline ^A	1.6	0.39
Chlorhexidine gluconate ^B		

MIC: Minimum Inhibitory Concentration

^A: Positive control for *C. acnes*

^B: Positive control for *P. intermedia*

for both the argan oil and the saponin extract. The MIC values are shown in Table 2.

DISCUSSION

Anti-proliferative activity

The argan oil evaluated in this study did not show any anti-proliferative effect on the human cell lines: epidermoid carcinoma cells (A431);

pigmented melanoma skin cancer cells (UCT-Mel 1); breast adenocarcinoma cells (MCF-7); cervical cancer cells (HeLa) and non-cancerous skin keratinocytes (HaCat) up to a concentration of 1000µg/ml. The current study is the first to report the evaluation of argan oil against A431, HeLa and UCT-Mel 1 cell proliferation. Previously reported studies on the cytotoxic effect of argan oil have yielded varied results. A study by Aribi *et al.*¹³ indicated that argan oil has a strong anti-proliferative effect on human leukemia cell lines (JURKAT; MOLT-3 and DND41) at 100µg/ml after a 48h treatment. The same study also found that argan oil had no cytotoxic effect on murine immature T cells (preT2017 and M31), human embryonic kidney cells (HEK293) and HaCat cells at a concentration of 100µg/ml after a 72h treatment. Other studies have found that argan oil does not have any cytotoxic effects on the HTC rat hepatoma cell line up to a concentration of 100µg/ml after 6 and 21h treatment periods or on the B16 murine melanoma cell line at concentrations of 1/100; 1/1000 and 1/10000 v/v after a 48h treatment period.¹⁴⁻¹⁵ These results might indicate that argan oil has anti-proliferative activity specifically against human leukemia cells. Furthermore, the authors propose that this anti-proliferative activity against human leukemia cell lines might be the result of argan oil's ability to influence the expression and activity of the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway. Though theory is debatable since some studies found an increase in the expression and activity of ERK1/2, while another found a decrease.¹³⁻¹⁵ The crude saponin extract showed some anti-proliferative activity on the MCF-7 cell line at a concentration of 400µg/ml, while it was found to have statistically significant cell growth stimulating effects at lower concentrations (200-1.325µg/ml). The saponin extract was found to have significant cell growth inhibition against the A431 (100-400µg/ml), UCT-Mel 1 (200-400µg/ml); HeLa (100-400µg/ml) and (HaCat 100- 400µg/ml) cell lines. Again, statistically significant cell growth stimulatory activity was found on the A431 (12.5- 3.125µg/ml), HaCat (6.25-3.125µg/ml) and UCT-Mel 1 (25-6.25µg/ml) cell lines at lower concentrations. This finding suggests that the crude saponin extract might have potential wound healing properties and deserves further investigation. Although the crude saponin extract was found to inhibit cancerous cell proliferation (A431, HeLa and UCT-Mel 1) in a dose-dependent manner, the extract also inhibited the growth of the non-cancerous (HaCat) cell line at around the same range of concentrations (Figure 1). This might indicate that the saponin extract indiscriminately inhibits normal and cancerous cells of specific tissue origin. An unsaponifiable fraction of argan oil has been shown to have the capacity to inhibit the cell growth and proliferation of the cancerous cell lines, HT-1080 (human fibrosarcoma) and Moloney sarcoma virus (MSV)-transformed Madin-Darby canine kidney-invasive variant cells (MDCK)-(INV), in a dose-dependent manner at concentrations ranging between 1-12.5µg/ml.¹⁴ Fractions from argan oil have also been evaluated for their anti-proliferative effects on human prostate cancer cell lines, DU145; LNCaP and PC3.¹⁶⁻¹⁷ A tocopherol fraction of argan oil showed good anti-proliferative activity on the DU145 and LNCaP cell lines with IC₅₀ values below 30µg/ml, whereas the saponin fraction had an IC₅₀ value of 24.24 ± 2.84µg/ml on the PC3 cell line and a sterol fraction had an IC₅₀ value of 25.07 ± 2.74µg/ml on the DU145 cell line. An extract from the fruit of *Argania spinosa* has been evaluated against the MCF-7 human breast adenocarcinoma cell line. The results found by Babilli and colleagues¹⁸ showed that the ethyl acetate extract had an IC₅₀ value of 42µg/ml, whereas the petroleum ether and decoction extracts did not show any activity up to concentration of 100µg/ml. It would also seem that given fractions from argan oil do have anti-proliferative activity against specific cancerous cell lines as indicated by other studies, whereas the oil itself might not have anti-proliferative activity at these low concentrations evaluated. Furthermore, it can be said that the fruit of the argan tree does have an effect on the MCF-7 cell line in crude extract form when extracted with ethyl acetate,

even though the oil, which is also obtained from the fruit of the Argan tree, was found to be inactive against the MCF-7 cell line up to a concentration of 1000µg/ml in this study. Additionally, argan oil has been suggested to have chemopreventive activity due to its antioxidant rich composition and its ability to act as an UV protectant.¹⁸⁻²⁰

Antibacterial activity

The argan oil and saponin extract inhibited the growth of *C. acnes* at a MIC value of 500µg/ml, whereas no inhibition of bacterial growth was observed against *P. intermedia* up to the highest concentration (12500µg/ml) tested. No published results on the inhibition activity of argan oil and the crude saponin extract against *C. acnes* and *P. intermedia* have been reported to date. The antibacterial activity against *C. acnes* found in this study indicates that argan oil and the saponin extract have a direct inhibitory effect on the growth and proliferation of *C. acnes*. Although this activity of the argan oil is only facilitated a high concentration of 500µg/ml, the *in vitro* cell proliferative assay indicated that the argan oil does not have any anti-proliferative effects on the skin keratinocyte (HaCat) cell line up to a concentration of 1000µg/ml. Furthermore, argan oil has been used for many years as a topical agent both traditionally and commercially. Argan oil has also been shown to be useful as an additive acne treatment by the evaluation of its sebum-reducing efficacy in a clinical study of 17- to 50-year-old volunteers with oily facial skin. The findings of the clinical study revealed that argan oil had the capacity to reduce greasiness and improve the appearance of facial skin when applied for four weeks, twice daily, in the form of a cream preparation containing argan oil.²¹ Since the growth and survival of *C. acnes* are facilitated by excessive sebum production, the anti-sebum activity of argan oil would be very relevant in the treatment regime for acne vulgaris.²² Although tea tree oil has higher growth inhibitory activity for *C. acnes* and is considered the gold-standard of natural oils for anti-acne activity, side effects such as burning, stinging, scaling, itching, redness and dryness have been reported.²³⁻²⁴ Furthermore, it was discovered that a crude argan saponin extract have anti-5α-reductase activity, which could also be potentially beneficial for anti-acne activity.²⁵⁻²⁷ It has also been reported that argan oil together with hydrogen peroxide (H₂O₂) has antibacterial activity against methicillin resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Moreover, the studies indicated that treatment with argan oil alone did not yield any or had very low antibacterial activity against methicillin resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*, respectively.²⁸⁻²⁹ Although the antibacterial activity of argan oil may be improved with the addition of H₂O₂, H₂O₂ exerts severe toxicity when administered by topical and oral administration routes.³⁰ A study by Stojkovic and colleagues³¹ found that the naturally occurring compounds, caffeic acid, *p*-coumaric acid and rutin, present in argan oil could inhibit *Staphylococcus aureus* growth and proliferation. The available research suggests that the compounds present in argan oil and other crude extracts of the argan tree can be considered for further evaluation of their antibacterial activity against *C. acnes* and *P. intermedia*. Besides, argan oil itself can be used as a multi-targeted treatment for acne since it can reduce both the growth of *P. acnes* and sebum. Apart from the antibacterial activity of argan oil, studies have also shown that argan oil can be used in nano-emulsions and as a lipid carrier to help improve the skin permeability of other drugs when topically administered.³²⁻³⁴ Furthermore, two studies by Boucetta *et al.*³⁵⁻³⁶ have found no side effects via topical application of argan oil. As such, argan oil seems to be capable of effectively permeating the skin without causing any side effects.

CONCLUSION

The results of this study indicated that the crude saponin extract had low anti-proliferative activity on the cancerous cell lines and the non-

cancerous keratinocytes (HaCat) cell line. The argan oil and crude saponin extract showed moderate inhibitory activity against *Cutibacterium acnes*. These results indicated that argan oil and the crude saponin extract might have a direct inhibitory effect on the growth and proliferation of *Cutibacterium acnes*. This finding supports the use argan oil as a treatment for acne vulgaris.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

ABBREVIATIONS

Act D: Actinomycin D; **ATCC:** American Type Culture Collection; **CFU:** Colony forming units; **CHX:** Chlorhexidine gluconate; **CO₂:** Carbon dioxide; **DMEM:** Dulbecco's Modified Eagle Media; **DMSO:** Dimethyl sulfoxide; **ECACC:** European Collection of Authenticated Cell Cultures; **EMEM:** Eagle's Minimum Essential Medium; **ERK1/2:** Extracellular signal-regulated kinase 1/2; **FBS:** Fetal bovine serum; **H₂O₂:** Hydrogen peroxide; **IC₅₀:** Fifty percent inhibitory concentration; **MAR:** Morocco; **MIC:** Minimum Inhibitory Concentration; **RSA:** Republic of South Africa; **TS:** Tryptone soy; **UK:** United Kingdom; **USA:** United States of America; **UV:** Ultraviolet; **XTT:** 2,3-bis-(2-methoxy-4-nitro-5-sulphophenyl)-2H-tetrazolium-5-carboxanilide.

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GRAPHICAL ABSTRACT



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SUMMARY

- The *Argania spinosa* crude saponin extract showed dose-dependent anti-proliferative activity on the A431; HaCat; HeLa and UCT-Mel 1 cell lines with IC_{50} values ranging between 100.5 ± 5.5 to $236.2 \pm 10.6 \mu\text{g/ml}$.
- Argan oil did not show any anti-proliferative activity on the A431; HaCat; HeLa; MCF7 and UCT-Mel 1 cell lines up to a concentration of $1000 \mu\text{g/ml}$.
- The argan oil and crude saponin extract did not show growth inhibition against the *Prevotella intermedia* bacteria up to a concentration of $12500 \mu\text{g/ml}$.
- The argan oil and crude saponin extract showed growth inhibition against *Cutibacterium acnes*, causal agent of acne, at an MIC value of $500 \mu\text{g/ml}$. This finding validates, to some extent, the use of argan oil for the treatment of acne in traditional and commercial use.



Prof. Zoubida Charrouf: Prof Charrouf is Professor at the Faculty of Science, University Mohammed V, In Rabat and President of Ibn Al Baytar Association in Morocco. She specializes in the phytochemistry of Moroccan medicinal plants and their metabolites for cosmetics and nutraceuticals. Prof Charrouf founded the first women's cooperatives for the production and marketing of argan oil in Morocco and has contributed to the recognition of argan oil as a cosmetic and culinary ingredient, as well as a functional food. She has won several national and international awards and has authored more than 130 publications on argan and its derivatives and more than 300 papers, conferences, and presentations.



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