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Evaluation Of The Cytotoxic Activity Of Searsia Rhemanniana Crude Extracts Against The Human Prostate Cancer Cell Line DU145

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Abstract
Background: *Prostate cancer is the second most common cancer among men globally and the leading cancer in African men. Current treatments are often inaccessible or limited by resistance. Natural products, particularly from underexplored plants like Searsia rhemanniana, offer a promising alternative for anticancer drug discovery.*
Objective: *To evaluate the cytotoxic activity of crude extracts of S. rhemanniana against the human prostate cancer cell line DU145.*
Methods: *Extracts were prepared using methanol, dichloromethane, and water. DU145 cells were treated with various extract concentrations, and cytotoxicity was assessed using the MTT assay. IC_{50} values were calculated from dose-response curves generated in GraphPad Prism (n=4).*
Results: *Among the nine extracts tested, three (samples 3, 6, and 8) demonstrated IC_{50} values below 100 µg/mL, indicating significant cytotoxicity. The remaining samples showed moderate to negligible effects. R^2 values from nonlinear regression confirmed reliable curve fitting.*
Conclusion: *Searsia rhemanniana exhibits promising antiproliferative activity, justifying further research into its potential as a source of new anticancer agents.*
Keywords: *Searsia rhemanniana, prostate cancer, DU145, cytotoxicity, MTT assay, IC_{50}*

INTRODUCTION

Prostate cancer represents a significant global health burden, with increasing incidence, mortality, and disability-adjusted life years (DALYs) observed over the past three decades. The Global Burden of Disease Study indicates that from 1990 to 2019, incident cases rose by 116.11%, deaths by 108.94%, and DALYs by 98.25% (Zhang et al., 2023; Dumps & Speliotes, 2023). Prostate cancer is indeed a significant global health burden, particularly in major BRICS countries, where incidence and prevalence are rising. Tailored health policies are essential to address the diverse characteristics of this disease burden effectively (Zhang et al., 2024). It ranks as the fourth most diagnosed cancer worldwide when considering both sexes and is the second most frequently diagnosed cancer among men in 2020 an estimated 1.4 million men were diagnosed with prostate cancer globally, accounting for approximately 7.3 % of all cancers in men (Kral et al.,2025). The disease presents an even more critical concern in Africa, where prostate cancer is the leading cancer affecting men, with rising incidence and mortality rates attributed to late diagnosis and limited access to effective treatment options (Jalloh et al.,2024). The primary therapeutic approach for advanced prostate cancer involves androgen deprivation therapy (ADT), which aims to suppress the activity of intraprostatic testosterone and its more potent derivative, dihydrotestosterone (DHT) (Reiss et al.,2024). While ADT initially yields positive responses, the emergence of therapy-resistant tumor clones often leads to castration-resistant prostate cancer (CRPC), characterized by disease progression, metastasis, and increased mortality (Maoping et al.,2023). Surgical intervention, particularly radical prostatectomy, is commonly employed in the early stages of solid tumors. However, this approach may not fully prevent recurrence or metastatic spread, especially in advanced cases (Bernal et.al.,2024). For patients with metastatic disease, first-line chemotherapy typically includes a combination of docetaxel and prednisone, administered over at least six cycles. Although these regimens can offer palliative relief and temporary disease control, they have shown limited impact on improving overall survival rates (Zhao et al.,2023). In resource-limited settings, 5-fluorouracil (5-FU), with or without cisplatin, is often recommended as a cost-effective alternative, although its efficacy remains constrained (Bosland et al.,2023).

Early detection of prostate cancer (PCa) remains a cornerstone of reducing disease-specific morbidity and mortality (Wei et al.,2023). Despite advances in imaging and biomarker technologies, the optimal

screening approach continues to evolve, particularly in balancing the benefits of early diagnosis against the harms of overdiagnosis and overtreatment (van Harten et al.,2024). Key screening modalities include prostate-specific antigen (PSA) testing, digital rectal examination (DRE), and multiparametric magnetic resonance imaging (mpMRI), often integrated into risk-adapted screening protocols (Navarro et al.,2024). Prostate-specific antigen (PSA) testing is the most widely used tool for the early detection of PCa. PSA is a serine protease secreted by prostatic epithelial cells, and elevated serum levels may indicate prostate malignancy, benign prostatic hyperplasia, or inflammation (Merriel et al.,2022). PSA screening has been shown to reduce PCa specific mortality, particularly in men aged 55–69 years, as demonstrated by the European Randomized Study of Screening for Prostate Cancer (ERSPC) (Bouras 2024). However, this benefit must be weighed against the risks of false positives, unnecessary biopsies, and treatment of indolent tumours. The major limitations of PSA testing include poor specificity and the inability to differentiate between aggressive and indolent disease (Duffy 2020). Elevated PSA levels (>4 ng/mL) can occur in the absence of cancer, and low levels can still be present in high-grade tumours. To mitigate this, derivatives such as PSA density, PSA velocity, and the free-to-total PSA ratio have been employed, albeit with limited sensitivity (Balazs et al.,2021). Digital rectal examination (DRE) is often used in conjunction with PSA testing, although its sensitivity is highly operator dependent. It can detect asymmetries or nodules suggestive of malignancy, particularly in the posterior prostate. However, its standalone value is limited, and DRE is not recommended as a primary screening tool due to poor reproducibility and low sensitivity for early-stage disease (Matsukawa et al.,2024).

The introduction of multiparametric magnetic resonance imaging (mpMRI) has significantly improved the accuracy of prostate cancer detection. mpMRI enables visualization of suspicious lesions using a combination of T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) sequences (Palumbo et al.,2020). When used as a triage test following elevated PSA levels, mpMRI can guide targeted biopsies and reduce the detection of clinically insignificant cancers (Getaneh et al.,2021). Risk-adapted screening strategies integrate clinical factors such as age, race, family history, PSA levels, and imaging findings to personalize screening intervals and biopsy decisions (Remmers et al.,2020). Emerging tools like the Prostate Health Index (PHI), 4Kscore, and genomic risk calculators further enhance risk stratification by distinguishing between indolent and clinically significant disease (Ferro et al.,2020). One of the principal challenges in prostate cancer screening is overdiagnosis, the detection of cancers that would not have become clinically significant within a man's lifetime (Dunn et al.,2022).

Overdiagnosis can lead to overtreatment, exposing patients to unnecessary surgical or radiation-related complications such as urinary incontinence, erectile dysfunction, and bowel dysfunction (Sloan 2020). Population-based studies have estimated that up to 50% of screen-detected prostate cancers may be over diagnosed, particularly among older men and those with low-grade, low-volume tumours (de Vos et al.,2023). This has prompted a paradigm shift towards active surveillance for patients with low-risk disease, thereby minimizing harm while preserving the opportunity for curative intervention if the cancer progresses (Detti et al.,2021). In resource-limited settings, the risks of overdiagnosis may be compounded by poor follow-up infrastructure and limited access to advanced diagnostics like mpMRI or genomic testing (Yadav et al.,2022). Therefore, the development of context-specific screening algorithms remains a critical research and policy priority. Given, the limitations of current treatment modalities and the rising burden of prostate cancer, especially in low- and middle-income regions, there is a growing need to explore alternative and complementary therapeutic strategies, including those derived from natural products and traditional medicines.

For this study, Searsia rhemanniana plant belonging to species within the genus Searsia, which is part of the Anacardiaceae family was selected a due to less scientific reports regarding its medicinal potential. This genus, previously classified under Rhus, encompasses over 250 species, many of which are recognized for their medicinal properties and biological activities. Research indicates that Searsia species, including S. rhemanniana, contain various phytochemicals such as terpenoids and flavonoids, which exhibit significant antioxidant and enzyme inhibition activities (Koki et al., 2022). But there is a gap to futhrer analyse this plant medical

MATERIALS AND METHODS

Plant material

The plant material was authenticated as Searsia rhemanniana by botanists from the botanical garden in Kwazulu-Natal, South Africa. Following verification, the purchased plant material was thoroughly cleaned

with distilled water to remove soil and debris. The plant was then separated into its major anatomical parts: roots, bulbs, and leaves. Each plant component was dried in a ventilated oven at a temperature range of 30–60°C for five days to ensure gradual dehydration and preservation of phytochemicals. Once fully dried, the material was coarsely ground using a hammer mill and stored at room temperature in airtight containers until required for extraction.

Extract preparation

Plant material was ground into a fine powder using an IKA grinder (IKA Labortechnik, Germany) at the Central University of Technology laboratory. Then powdered material was then taken to the bioassaix (invitro screening for drugs) lab for further processing. At bioassay (invitro screening for drugs) lab powdered plant material was subjected the extraction of compounds using methanol (MeOH), dichloromethane (DCM), and water (H_2O) at a ratio of approximately 1:4 (w/v). The maceration was placed on a shaker (Labcon, Lab Design Engineering, Maraisburg, South Africa) for 72 hours. Following extraction, the mixture was filtered through Whatman No. 1 filter paper (Merck Chemicals (Pty) Ltd, Wadeville, South Africa) using a vacuum filtration system (Merck Chemicals (Pty) Ltd, Wadeville, South Africa). This process was repeated until the filtrate was clear. The organic solvents (MeOH and DCM) were removed under reduced pressure using a BÜCHI Rotovapor (Labotec (Pty) Ltd, Halfway House, South Africa), and the resulting extracts were dried at room temperature under a fume hood and stored at 4°C. The aqueous extract was frozen at -80°C and subsequently freeze-dried to a powder, then stored at 4°C.

In vitro IC_{50} determination of extracts against prostate cancer cell line DU145

Sample Preparation

Test samples were reconstituted in DMSO to a stock concentration of 100 mg/mL. Samples were sonicated if solubility issues arose and stored at 4°C until use.

Cell Line Maintenance

The human prostate cancer cell line DU145 (ATCC) was used for cytotoxicity testing. Cells were cultured in 10 cm dishes containing complete medium (RPMI supplemented with 10% FBS and penicillin/streptomycin) and maintained at 37°C in a humidified incubator with 5% CO_2.

Cytotoxicity Assay – MTT

Cells were seeded into 96-well plates at a density of 4,000 cells per well in 100 µL of complete medium and incubated overnight to allow attachment. The next day, treatments were prepared in complete medium at concentrations of 7.8, 15.625, 31.25, 62.5, 125, and 250 µg/mL, and applied to the cells. Melphalan (30 µM) served as a positive control. Following a 48-hour incubation period, treatments were removed, and 100 µL of MTT solution (0.5 mg/mL in complete medium) was added to each well. After a further 3-hour incubation, the medium was replaced with 100 µL of DMSO to solubilize the formazan crystals. Absorbance was measured at 540 nm using a BioTek® PowerWave™ XS spectrophotometer (Winooski, VT, USA).

RESULTS

The cytotoxic effects of nine plant-derived samples were evaluated against DU145 human prostate cancer cells using the MTT assay. IC_{50} values (the concentration required to inhibit 50% of cell viability) were calculated using non-linear regression analysis in GraphPad Prism (version X), based on dose-response curves generated from four independent experiments (n = 4). The graphical representation of the dose-response curves is shown in Figure 1.

IC_{50} determination among the nine samples tested, six produced measurable IC_{50} values, while the remaining three (Samples 1, 4, and 7) failed to reach 50% inhibition of cell viability in at least three of the four replicates and were therefore considered non-determinable (ND). This indicates a lack of significant cytotoxic activity at the concentrations tested.

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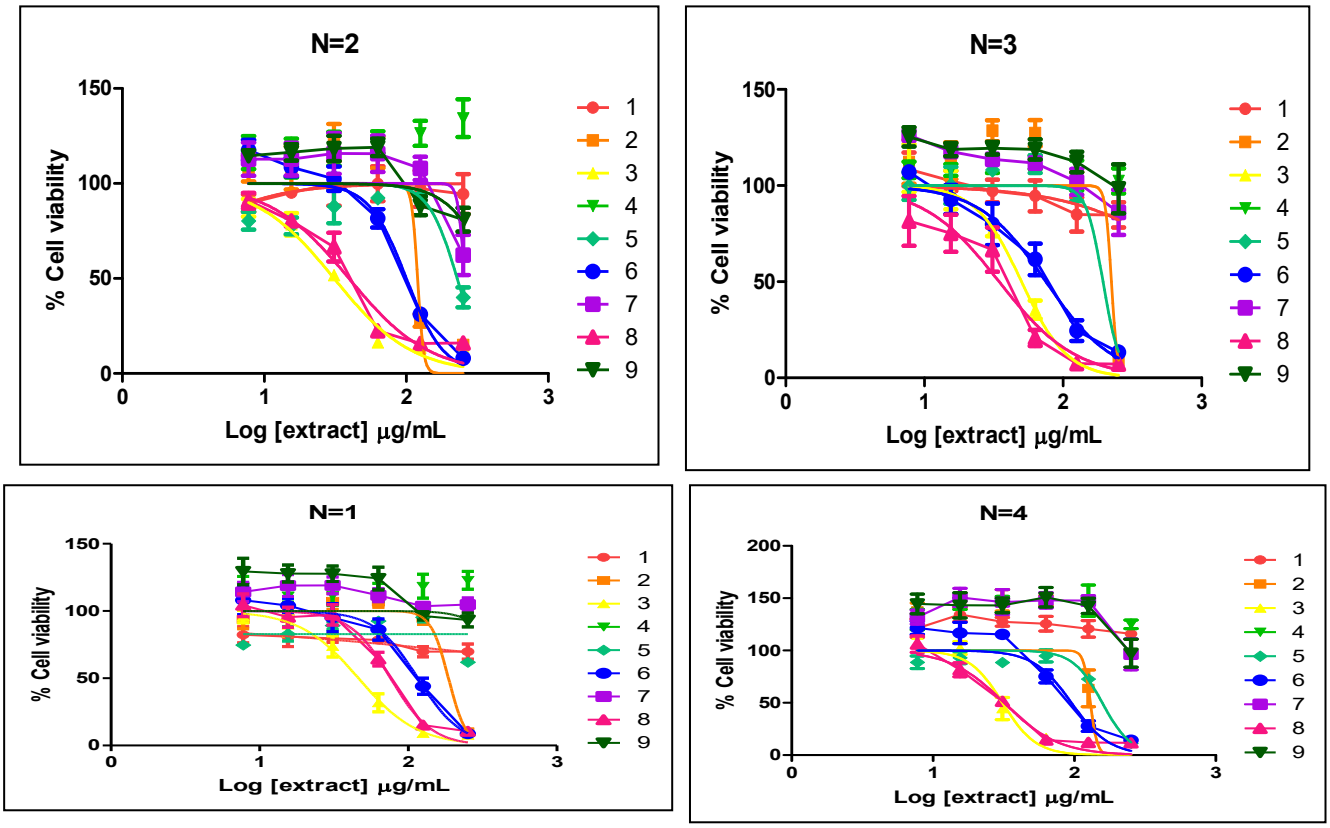

Figure 1: Determination of IC_{50} value for tested samples against DU145 cells (n=4).

The average IC_{50} values and corresponding standard deviations for each sample are summarized in **Table I**, along with R^2 values that reflect the goodness of fit for the regression models used. Samples 2, 3, 5, 6, and 8 demonstrated IC_{50} values below 250 µg/mL, with sample 3 showing the highest potency (mean IC_{50} = 39.63 µg/mL ± 10.07), followed by Sample 8 (45.55 µg/mL ± 20.66). These values fall within the physiologically relevant range for crude plant extracts, suggesting potential for further antiproliferative investigation. **Table I** shows the resulting IC_{50} values (µg/mL) and corresponding R^2 values for samples tested against DU145 cells, indicating the accuracy of the data.

Table I: IC_{50} values of selected samples and resulting R^2 values.

Sample	N=1	N=2	N=3	N=4	Average	Stdev
1	8493	ND	1165	ND		
2	186.5	120.2	223.6	130	165.08	48.75
3	46.27	31.03	50.21	31.01	39.63	10.07
4	ND	ND	ND	ND		
5	ND	228.7	194.3	157.6	193.53	35.56
6	108.3	100.3	75.32	95.36	94.82	14.05
7	ND	258.2	ND	ND		
8	76.18	39.51	34.62	31.88	45.55	20.66
9	477.7	418.5	ND	ND		

ND: Not determined; % inhibition did not reach 50%.

The R^2 values for the curve-fitting analysis, shown below, support the reliability of the IC_{50} estimates for most samples. Higher R^2 values (close to 1.0) indicate strong model fit. Notably, samples 3, 6, and 8 displayed consistently high R^2 values across replicates, reinforcing confidence in their IC_{50} estimations.

Table II: R^2 values for dose-response curve fitting for each sample.

R^2 values

Sample	N=1	N=2	N=3	N=4
1	0.5151	0.06554	0.4557	

2	0.9588	0.8852	0.7953	0.4891
3	0.9762	0.9555	0.9654	0.9153
4				
5		0.4919	0.9523	0.9225
6	0.963	0.95	0.9538	0.8824
7		0.5049		
8	0.9703	0.9445	0.9006	0.9544
9	-0.9684	0.1114		

The results indicate that Samples 3, 6, and 8 show promising cytotoxic potential, with consistent IC_{50} values and reliable curve fits.

DISCUSSION

This study evaluated the cytotoxic effects of crude extracts derived from Searsia rhemanniana on the DU145 human prostate cancer cell line. The resulting IC_{50} values demonstrated that certain extracts possess strong antiproliferative activity, suggesting that S. rhemanniana contains bioactive compounds with potential therapeutic relevance. Among the nine samples tested, Sample 3, Sample 6, and Sample 8 showed pronounced cytotoxic effects, with IC_{50} values below 100 µg/mL (39.63 µg/mL, 94.82 µg/mL, and 45.55 µg/mL, respectively). These results align with the established criterion for cytotoxic significance in crude extracts. Sample 3 displayed low variability across replicates and high R^2 values (>0.9), indicating a strong and consistent dose-response effect. This is the first report, to our knowledge, demonstrating the cytotoxicity of Searsia rhemanniana against prostate cancer cells. However, related species in the Anacardiaceae family, such as Searsia chirindensis and Searsia pyroides, have previously demonstrated antibacterial, antioxidant, and anti-inflammatory activity (Nyagumbo et al.,2022). These bioactivities are often linked to polyphenolic and flavonoid constituents, which may similarly be responsible for the cytotoxic effects observed in this study. Sample 2 exhibited moderate cytotoxicity (IC_{50} = 165.08 µg/mL), which may still be biologically relevant given the unrefined nature of the extract. Sample 5 had an IC_{50} of 193.53 µg/mL, also pointing to some level of activity. While these values exceed the threshold of 100 µg/mL, they suggest potential for enhanced potency after fractionation or isolation of active constituents. The observed variability in response could reflect differences in the phytochemical composition of the various extracts, extraction solvents, or plant parts used. Inconsistent results in Samples 1, 4, 7, and 9, where IC_{50} values could not be reliably calculated, are likely due to insufficient bioactive concentrations or suboptimal solubility and bioavailability in the test system. Prostate cancer remains a leading cause of cancer-related morbidity and mortality worldwide, with especially high incidence in sub-Saharan Africa (Badal et al.,2020). Current treatment regimens such as androgen deprivation, surgery, and chemotherapeutics like docetaxel are often inaccessible, costly, and associated with resistance and relapse. This creates a pressing need for affordable, plant-based therapies (Sekhoacha et al.,2022). The cytotoxic activity of S. rhemanniana crude extracts observed in this study positions the species as a potential source of novel antiproliferative agents. Previous ethnobotanical surveys report the use of Searsia species in traditional medicine for ailments ranging from inflammation to infections (Koki et al.,2022), which supports their pharmacological potential.

CONCLUSION

The current study demonstrates that crude extracts of Searsia rhemanniana possess notable cytotoxic activity against DU145 human prostate cancer cells, particularly samples 3, 6, and 8, which exhibited IC_{50} values below the 100 µg/mL threshold considered physiologically relevant. These findings suggest that S. rhemanniana contains bioactive compounds with potential anticancer properties. Given the urgent need for affordable cancer therapeutics in resource limited settings, this plant may offer a promising foundation for novel drug discovery.

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