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Review Article

Review of the Pharmacological Properties and Phytochemical Profile of *Ptaeroxylon obliquum* (Thunb.) Radlk

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ABSTRACT

Introduction: *Ptaeroxylon obliquum* (Thunb.) Radlk. That is a medium tree native to South Africa. It has been traditionally used for centuries to treat a wide range of disorders. **Objectives:** This study reviews the pharmacological profile of South African *Ptaeroxylon obliquum* (Thunb.) Radlk., including its ethnobotanical use, anti-inflammatory, anti-microbial, and anti-proliferative bioactivities, with the aim of encouraging additional research in this field. **Materials and Methods:** Scientific literature, review articles, and online databases were examined to investigate traditional therapeutic applications of *P. obliquum*. A subsequent search was carried out to identify studies examining the pharmacological properties of *P. obliquum*. **Results:** The review highlighted the therapeutic properties of *P. obliquum,* including significant antimicrobial activity against a panel of bacterial and fungal pathogens. This species also has anti-inflammatory properties, including inhibition of COX-2, reducing pro-inflammatory cytokine secretion, and modulation of NF-KB transcription pathways. Additionally, anti-proliferative activity has been observed against specific cancer cell lines, although relatively few studies have explored this potential. **Conclusion:** Whilst *Ptaeroxylon obliquum* has promising pharmacological properties, including antibacterial, antifungal, anti-inflammatory and anticancer effects, its mechanisms of action, and toxicity have been relatively poorly studied. Future studies are required to identify the active compounds, evaluate the therapeutic efficacy *in vivo,* and expand research into its anticancer potential.

Keywords: Traditional Medicine, Sneezewood, Rutaceae, Anti-inflammatory activity, Antibacterial activity, Anticancer activity.

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INTRODUCTION

Ptaeroxylon obliquum (Thunb.) Radlk., commonly known as sneezewood, is a deciduous shrub or medium-sized tree native to a wide range of southern African countries, including South Africa, Angola, Botswana, Mozambique, Namibia, Eswatini, Tanzania, and Zimbabwe.[1,2] The tree can grow up to 15 M tall and is notable for its medicinal and ethnoveterinary applications, particularly in South Africa, where it is frequently used in the Eastern Cape province.[1,2] *Ptaeroxylon obliquum* has demonstrated efficacy in treating a variety of ailments, including tuberculosis (TB), parasitic infections in both humans and animals, bacterial and fungal infections, inflammatory diseases, and conditions such as rheumatism, arthritis, and liver diseases.[3,4] Its ethnoveterinary uses are especially prominent, as it is employed in the treatment of contagious pleuropneumonia and parasitic infections in cattle and goats.[3,4] Traditionally, the leaves, stem, bark, roots, and twigs are utilized in remedies for vaginal infections, sinusitis, malaria, heart disease, hypertension, colic, and even ritual sacrifices.[3] The extensive ethnopharmacological relevance and diverse applications of this plant underscore its significance in both human and veterinary medicine.[3]

Within South Africa, traditional medicine, largely based on plant therapies, is a primary source of healthcare, particularly in rural areas where access to modern medical facilities may be limited.[3] Indigenous plants are integral to local healing practices, offering remedies for various ailments, from infections to chronic conditions.[3] Many South Africans rely on these plant-based treatments for their daily health needs, often utilizing them in the form of teas, extracts, or topical applications.[3,4] The pharmaceutical industry has also turned to plants for drug development, recognizing their potential in treating various diseases. For example, the anti-malarial drug artemisinin was derived from the plant *Artemisia annua* L., whilst the heart

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medication digoxin comes from the foxglove plant *Digitalis purpurea* L.[5,6] These examples highlight the valuable contributions of plants in creating effective pharmaceuticals, demonstrating their enduring role in modern medicine.

MATERIALS AND METHODS

This review summarises current knowledge on *P. obliquum*, a plant traditionally utilised in South African medicine for managing various health conditions, including inflammation and cancer, as well as treating bacterial and fungal infections. The online scientific databases Google Scholar, PubMed, Elsevier, ScienceDirect and Scopus were searched to identify relevant original scientific literature. Additional publications were identified by reviewing references cited in previously identified publications. The online databases were searched using the terms "*Ptaeroxylon obliquum*", "anti-bacterial properties", "anti-inflammatory properties", "anti-cancer properties", "anti-proliferative activity", "anti-fungal properties", "traditional use", "natural healing", "natural remedies", "ethnobotany", "anti-microbial", "alternative medicine", "South African". All terms were searched both independently, as well as in combinations.

Eligibility criteria

Abstracts of published articles were examined to determine their relevance, followed by detailed evaluation based on predefined inclusion and exclusion criteria.

Inclusion criteria

The studies considered for inclusion in the review were:

- Studies involving *Ptaeroxylon obliquum* (Thunb.) Radlk. Where the plant identity was dubious, the study was not included herein,
- Studies examining the pharmacological properties of *Ptaeroxylon obliquum*,
- Ethnobotanical studies that focused solely on *Ptaeroxylon obliquum* (Thunb.) Radlk,
- Manuscripts written in English and published prior to February 2025.

Exclusion criteria

The studies excluded from this review were:

- Studies that included pharmacological profile of plant species from different species, or where the species identity was not clearly defined,
- To avoid misinterpretation, studies that were written in non-English languages were excluded,
- Studies that focused on treatments of conditions other than bacterial, fungal, inflammation and cancer.

RESULTS AND DISCUSSION

Antibacterial properties

Antimicrobial resistance (AMR) occurs when microorganisms, including bacteria, fungi, viruses, and parasites, evolve to resist the effects of previously effective drugs.[7-9] This resistance arises primarily through genetic mutations or the acquisition of resistance genes from other microorganisms via horizontal gene transfer.[7-9] These adaptations allow the pathogens to survive and proliferate despite the presence of antimicrobial agents. Overuse and misuse of antimicrobial drugs in both healthcare and agriculture contribute significantly to AMR. Inappropriate prescribing, such as using antibiotics for viral infections, incomplete courses of treatment, or the use of suboptimal doses, can expose microorganisms to drugs for prolonged periods, thereby increasing the likelihood of resistance.[10] Furthermore, the widespread use of antimicrobial agents in agriculture, where they are often used for infection prophylaxis in healthy animals, further drives the emergence of resistant strains, which can spread to humans through the food chain, direct contact, or environmental exposure.[7-10] The development of novel antimicrobial compounds is essential to combat the growing global threat of AMR. Existing antimicrobials are becoming increasingly ineffective against resistant strains, leading to infections that are harder to treat,

Table 1: Antibacterial properties of *Ptaeroxylon obliquum* extracts.

Bacterial strains	Extract Type	MIC (µg/mL)	References
Escherichia coli	Methanolic	64	13
	Ethanolic	64	
	Chloroform	128	
	Acetone	32	
	Fractionated hexane-acetone	80	14
	Fractionated chloroform-acetone	240	
	Fractionated 30% H_2O in MeOH-acetone	630	
	Fractionated butanol-acetone	1250	

Bacterial strains	Extract Type	MIC (µg/mL)	References
Staphylococcus aureus	Methanolic	32	13
	Ethanolic	32	
	Chloroform	8	
	Acetone	16	
	Fractionated hexane-acetone	40	14
	Fractionated chloroform-acetone	240	
	Fractionated 30% H_2O in MeOH-acetone	320	
	Fractionated butanol-acetone	630	
Pseudomonas mirabilis	Methanolic	64	13
	Ethanolic	32	
	Chloroform	8	
	Acetone	16	
Proteus vulgaris	Methanolic	32	13
	Ethanolic	32	
	Chloroform	64	
	Acetone	32	
Pseudomonas aeruginosa	Methanolic	128	13
	Ethanolic	64	
	Chloroform	128	
	Acetone	64	
	Fractionated hexane-acetone	160	14
	Fractionated chloroform-acetone	80	
	Fractionated 30% H_2O in MeOH-acetone	630	
	Fractionated butanol-acetone	1250	
Streptococcus pneumoniae	Methanolic	64	13
	Ethanolic	32	
	Chloroform	16	
	Acetone	16	
Streptococcus sonnei	Methanolic	4	13
	Ethanolic	4	
	Chloroform	8	
	Acetone	4	
Mycobacterium tuberculosis	Acetone	313	4
	Fractionated hexane-acetone	620	
	Fractionated 30% H_2O in MeOH-acetone	625	
Mycobacterium fortuitum	Fractionated hexane-acetone	20	4
	Fractionated chloroform-acetone	630	
	Fractionated 30% H_2O in MeOH-acetone	40	
	Fractionated butanol-acetone	320	

Bacterial strains	Extract Type	MIC (µg/mL)	References
Mycobacterium smegmatis	Fractionated hexane-acetone	20	4
	Fractionated chloroform-acetone	630	
	Fractionated 30% H_2O in MeOH-acetone	320	
	Fractionated butanol-acetone	1250	
Enterococcus faecalis	Fractionated hexane-acetone	80	14
	Fractionated chloroform-acetone	320	
	Fractionated 30% H_2O in MeOH-acetone	320	
	Fractionated butanol-acetone	1250	

prolonged illness, and, in some cases, death.[9] With fewer new antimicrobial drugs being introduced to clinical use, the situation is becoming critical and safe and effective new therapies are urgently needed.[10]

When developing new compounds for antimicrobial therapy, it is imperative to identify the lowest effective concentration to inhibit microbial growth while maintaining minimal toxicity to mammalian cells.[11,12] Authors from previous studies have evaluated the minimum inhibitory concentration (MIC) of *P. obliquum* against selected bacterial and fungal species. *Ptaeroxylon obliquum* extracts have shown to possess antibacterial activity, although substantial variation in potency was apparent, depending on the extraction method and solvent system used (Table 1).[4,13,14]

Notably, methanolic, ethanolic and acetone extracts showed the most potent antibacterial properties, with noteworthy minimum inhibitory concentration (MIC) values across most bacterial strains.[13] Those extracts exhibited potent activity against *S. sonnei*, with MIC values of 4 µg/mL for methanolic, 4 µg/mL for ethanolic, 8 µg/mL for chloroform, and 4 µg/mL for acetone extracts.[14] In contrast, fractionated extracts, such as hexane-acetone and butanol-acetone fractions, exhibited higher MIC values, possibly due to the absence of specific phytochemicals that are necessary for bacterial inhibition. Alternatively, the extracts may contain compounds that potentiate the inhibitory activity of the antibacterial compounds, and these may have been separated during the extraction process.[15] Indeed, several previous studies have reported on the antibacterial potentiating activity of some plant compounds.[4,13,14] However, this remains to be examined for *P. obliquum* and further study is required.

The antimicrobial activity of *P. obliquum* extracts against *Mycobacterium* spp. varies across species and extract types. An acetone extract exhibited good activity against *Mycobacterium tuberculosis* (MIC=313 µg/mL), whilst fractionated extracts also showed noteworthy (albeit lower) activity, with MIC values ranging from 620-625 µg/mL.[4] In contrast, fractionated acetone extracts have demonstrated high activity (20 µg/mL) against *Mycobacterium fortuitum* and *Mycobacterium smegmatis*. However, their susceptibility decreased as the extracts were fractionated. For example, the chloroform-acetone had noteworthy activity (630 µg/mL), whilst the butanol-acetone ranged from good to moderate activity (320-1250 µg/mL) towards those bacteria.[4] These variations suggest that different solvent fractions influence antimicrobial efficacy, which may be due to differences in compound solubility, extraction efficiency, and interaction with bacterial cell wall structures.[4] Notably, extracts demonstrated higher MIC values against *M. tuberculosis*, a slow-growing pathogen, than the rapidly growing *M. fortuitum* and *M. smegmatis*, indicating that species-specific factors such as cell wall permeability and intrinsic resistance mechanisms influence susceptibility to these plant-derived extracts.

Future phytochemical analyses are required to identify the active antimicrobial compounds in the extracts. Additionally, combination studies are required to evaluate whether these extracts (or individual components) may also enhance the efficacy of conventional antibiotics. Despite the promising earlier results, further investigations are required to determine whether the extracts inhibit bacteria via bactericidal or bacteriostatic effects. Additionally, whilst *in vitro* MIC values provide useful insights into antimicrobial potential, *in vivo* efficacy and pharmacokinetics remain unexplored and should be assessed in future studies. The fact that some mycobacterial species exhibited susceptibility to fractionated extracts narrows the search to identify the specific bioactive molecules responsible for the observed effects, and further isolation and characterization studies are warranted.[4] The variation in MIC values across different bacterial strains and solvent extracts emphasises the importance of selecting appropriate extraction methods to maximize antimicrobial efficacy. Whilst fractionation did not enhance antimicrobial activity in most cases, further refinement of purification techniques could help isolate specific bioactive compounds with enhanced potency.[4,13,14] Overall, this study highlights the potential of *Ptaeroxylon obliquum* extracts in combating microbial infections and provides a foundation for future research into their therapeutic applications.

Table 2: Antifungal properties of *Ptaeroxylon obliquum* leaf extracts.[4]

Fungal species	Extract type	MIC (µg/mL)
Aspergillus fumigatus	Acetone	240
	Hexane fraction	180
	CHL_3 fraction	120
	30% H_2O in MeOH fraction	160
	Butanol fraction	1250
	Water fraction	2500
Candida albicans	Acetone	320
	Hexane fraction	400
	CHL3 fraction	320
	30% H_2O in MeOH fraction	940
	Butanol fraction	2500
	Water fraction	>2500
Cryptococcus neoformans	Acetone	480
	Hexane fraction	200
	CHL_3 fraction	240
	30% H_2O in MeOH fraction	480
	Butanol fraction	1250
	Water fraction	>2500

CHL_3=chloroform, MeOH =methanol.

Antifungal properties

Notably, chloroform and hexane extracts demonstrated the most potent antifungal properties (compared to other solvents), with consistently low minimum inhibitory concentration (MIC) values reported (Table 2).[4] For *Aspergillus fumigatus*, the chloroform fraction showed the strongest activity (120 µg/mL), followed by the hexane fraction (180 µg/mL), whilst the water fraction was the least effective (2500 µg/mL).[4] A similar trend was observed when the extracts were screened against *Candida albicans*, where the acetone and chloroform extracts exhibited the highest antifungal potency (320 µg/mL). In contrast, the water extracts had negligible activity (>2500 µg/mL).[4] Notably, *Cryptococcus neoformans* was most susceptible to the hexane extract (200 µg/mL), with moderate activity observed for the chloroform and acetone extracts (240-480 µg/mL).[4] The butanol and water fractions consistently showed the weakest antifungal properties across all fungal species.[4] These findings highlight the importance of solvent selection in optimizing antifungal efficacy, with non-polar and semi-polar solvents, such as chloroform and hexane, yielding the most promising results.[4] The variability in MIC values across different fungi also suggests that there is species-specific susceptibility to *Ptaeroxylon obliquum* extracts, warranting further investigation into their mechanisms of action and potential clinical applications.

Fungal infections are a significant global health concern, with some species causing widespread and severe infections. *Candida albicans* for example, is a major opportunistic pathogen responsible for both vaginal and oral infections.[16] Therefore, given its clinical importance, studying the antifungal activity of *Ptaeroxylon obliquum* against *C. albicans* is highly relevant. Similarly, *Aspergillus* spp. are responsible for severe respiratory infections, particularly in individuals with underlying lung diseases or weakened immune systems, leading to conditions such as aspergillosis, which can be fatal if untreated.[17] However, whilst these studies provide valuable insights into antifungal activity, an important gap remains regarding the efficacy of *P. obliquum*, particularly against dermatophyte fungi, which causes cutaneous infections such as ringworm and tinea. These fungal infections are common worldwide and can significantly impact skin health, particularly in warm and humid climates.[18] Future research should explore the plant's potential antifungal properties against dermatophytes, as this could provide new insights into plant-derived treatments for superficial fungal infections.

Anti-inflammatory activities

Inflammation is the natural response to injury, infection, or harmful stimuli, and it plays a critical role in protecting tissues and promoting healing.[4] It is a complex biological process that involves immune cells, blood vessels, and molecular mediators such as cytokines and prostaglandins.[4,19] Inflammation typically manifests through redness, swelling, heat, pain, and loss of function in the affected area.[19,20] Acute inflammation is a protective response that helps to eliminate pathogens and begin tissue repair.[19,20] However, when inflammation becomes chronic, it can contribute to a wide range of diseases, including arthritis, cardiovascular disease, cancer, and neurodegenerative conditions.[19,20]

The ability to control and modulate inflammation is essential for treating these chronic inflammatory diseases. The anti-inflammatory drugs that are commonly used to manage these conditions, including nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, have toxicities and limitations.[21] These medications may have significant side effects, including gastrointestinal issues, immunosuppression, or long-term organ damage.[4,21] Therefore, developing new drugs with anti-inflammatory properties is crucial for improving the safety and effectiveness of treatment options. Novel anti-inflammatory compounds could specifically target the pathways responsible for chronic inflammation without causing the harmful side effects associated with existing therapies. As such, new drugs may offer more precise control over the immune response, reducing tissue damage and promoting healing more efficiently. Additionally, they could help manage a broader range of conditions, from

autoimmune diseases to inflammatory infections, significantly improving patient outcomes and quality of life.

The 15-lipoxygenase (15-LOX) enzyme plays a crucial role in leukotriene biosynthesis, catalysing the initial conversion of arachidonic acid into biologically active leukotrienes.[22,23] These molecules act as potent mediators in inflammatory and allergic responses, making 15-LOX inhibition a relevant strategy in addressing inflammation-related conditions.[22,23] Acetone crude extracts and five fractions derived from *P. obliquum* demonstrated weak inhibitory effects on 15-LOX activity, with IC_{50} values of 1.61 mg/mL for the crude extract and between 2.55 and 12.43 mg/mL for the fractions (Table 3).[22] Interestingly, fractionating the crude extract resulted in diminished 15-LOX inhibitory properties, as all fractions displayed IC_{50} values exceeding the 1.61 mg/mL observed in the crude extract.[22] Lipoxygenase inhibition was primarily linked to non-polar compounds, while the water extract exhibited minimal activity.[22] It is possible that fractionation separated non-polar 15-LOX inhibitors from higher polarity potentiating compounds, although this remains to be tested.

Among the tested samples, three isolated compounds from the non-polar fraction demonstrated significant inhibitory activity, with IC_{50} values ranging from 7.4 to 13.9 µg/mL.[22] These values were comparable to those determined for quercetin, the positive control, which had an IC_{50} of 2.1 µg/mL. The mixture of lupeol and β-amyrin, as well as eranthin, displayed the strongest inhibitory effects, with IC_{50} values of 7.4 µg/mL and 7.5 µg/mL, respectively.[22]

The COX inflammatory pathway plays a crucial role in the synthesis of prostaglandins that regulate inflammation.[24] COX enzymes exit in two primary forms COX-1 and COX-2. COX-1 is constitutively expressed and is involved in maintaining normal

Table 3: Inhibitory effects of *Ptaeroxylon obliquum* extracts on NO production in LPS-induced RAW 264.7 cells, their viability against murine RAW 264.7 macrophages, and IC_{50} values of 15-LOX.[22]

Samples	Concentration (µg/mL)	NO inhibition (%)	Cell Viability (%)	15-LOX IC_{50} (µg/mL)
Crude extract	100	80.7	1.7	1610
	30	77.8	47.6	
	10	69.7	48.5	
	2	36.9	50.2	
Hexane fraction	100	80.5	2.1	2550
	30	79.4	51.9	
	10	72.8	53.5	
	2	41.3	66.8	
Chloroform fraction	100	83.3	2.7	3030
	30	83.2	44.2	
	10	80.9	49.2	
	2	44.2	53.3	
30% in H_2O in MeOH fraction	100	83.7	14.6	5240
	30	79.2	55.2	
	10	71.4	59.9	
	2	29.4	61.3	
Butanol fraction	100	82.2	44.8	6550
	30	77.3	54.5	
	10	48.8	58.1	
	2	9.8	63.0	
Water fraction	100	76.1	40.7	12430
	30	55.5	43.6	
	10	36.3	43.5	
	2	9.8	49.5	
Obliquumol	20	85.2	33.2	13.9
	5	82.9	59.7	
	2	81.8	65.0	
	0.5	64.0	67.0	

Samples	Concentration (µg/mL)	NO inhibition (%)	Cell Viability (%)	15-LOX IC_{50} (µg/mL)
Lupeol and β-amyrin mixture	20	74.2	55.0	7.4
	5	49.0	62.2	
	2	26.5	65.0	
	0.5	12.9	74.5	
Eranthin	20	85.0	38.9	7.5
	5	84.0	50.8	
	2	82.4	55.3	
	0.5	71.7	89.1	
Quercetin	20	72.5	48.2	2.1
	5	63.2	77.1	
	2	42.0	81.9	
	0.5	11.0	92.4	

MeOH=methanol; LOX=lipoxygenase.

physiological functions such as gastrointestinal protection. In contrast, COX-2 is induced in response to inflammation and contributes to pain and swelling.[24] Thus, inhibition COX-2 is a major target for anti-inflammatory drugs, including nonsteroidal anti-inflammatory drugs (NSAIDS). Studies screening *P. obliquum* demonstrated 73% inhibition of COX-1 activity by ethanol extracts at a concentration of 50 µg/mL.[24] Furthermore, the bark extracts of *P. obliquum* were evaluated for its COX-2 inhibition activity against LPS-stimulated RAW 264.7 macrophage cells. In the LPS control group, COX-2 concentrations reached up to 11.5 ng/mL. In contrast, ethanol extracts of *P. obliquum* exhibited a COX-2 concentration of 3 ng/mL, which was approximately 3.8-fold more potent than the control.[25] However, the aqueous extract demonstrated a COX-2 concentration of 13 ng/mL, indicating a lesser degree of inhibition compared to the ethanol extract.[25]

The study findings suggest that the ethanol extracts of *P. obliquum* effectively suppresses inflammation by significantly downregulating COX-2 activity.[25] This indicates a promising anti-inflammatory potential, as COX-2 inhibition is a key target for managing pain and swelling.[25] However, the observed inhibition of COX-1 by 73% raises concerns regarding gastrointestinal (GI) safety. Since COX-1 is essential for production of prostaglandins that are essential for maintaining gastric mucosa protection, its suppression can increase the risk of adverse effects such as stomach ulcers and gastric bleeding.[25] Thus, the potential impact on GI health must be carefully considered in clinical applications.

Nitric oxide (NO) serves as a key mediator in the pathogenesis of rheumatoid arthritis and other inflammation-related diseases.[26,27] Therefore, the suppression of NO production is an important target for treating such conditions.[26] To evaluate the anti-inflammatory potential of *P. obliquum*, crude extracts, fractions, and isolated compounds have been screened in previous studies in LPS-induced RAW 264.7 macrophage cells. This assay allowed for the concurrent assessment of their cytotoxicity, ensuring that any observed anti-inflammatory effects were not merely a consequence of cytotoxic action.[22]

The tested samples displayed high NO inhibition (compared to the untreated controls) in the induced cells. However, the results suggested that the significant inhibition observed might have been influenced by the cytotoxic effects of the crude extract, fractions, and isolated compounds (Table 3).[22] Cytotoxicity was present across all tested concentrations, with the highest recorded cell viability reaching only 66.8%.[22] The crude extract, along with the hexane and chloroform fractions, resulted in cell viability levels below 3%, whilst the 30% H_2O in MeOH fraction produced 14.6% cell viability at the highest tested concentration.[22] The crude extract inhibited NO production by 77.8% at a concentration of 30 µg/mL, although it had a corresponding cell viability of only 47.6%. A similar trend was observed in all five fractions, where high inhibition percentages at 30 µg/mL and 10 µg/mL were accompanied by poor cell viability.[22]

The isolated bioactive compound obliquumol exhibited NO inhibition levels ranging from 85.2% to 81.8% at concentrations of 20 to 2 µg/mL, with cell viability values between 33.2% and 67%. The mixture of lupeol and β-amyrin demonstrated 74.2% inhibition, with 55% cell viability at the highest tested concentration.[22] Eranthin showed the most promising activity among the tested samples, achieving 71.1% NO inhibition with 89.1% cell viability at a concentration of 0.5 µg/mL. The positive control, quercetin, maintained cell viability between 77.1% and 92.4% at concentrations ranging from 5 to 0.5 µg/mL.[22]

The anti-inflammatory effects of *P. obliquum* were further examined by evaluating its effects on nuclear factor kappa B (NF-KB) modulation, cytokine suppression, and chemokine regulation. These studies utilised murine RAW 264.7 macrophages and human dermal fibroblast (HDF) cells to assess both cytotoxicity and immunomodulatory effects.[24,28,29]

NF-KB is a transcription factor that regulates the expression of pro-inflammatory genes, including those encoding cytokines such as interleukin-6 (IL-6), tumour necrosis factor-α (TNFα), and interleukin-1 β (IL-1β).[28] Activation of NF-KB is a marker of chronic inflammatory disease, making it an important therapeutic target.[28] Whilst direct inhibition of NF-KB by *P. obliquum* was not explicitly measured, studies have shown that *P. obliquum* ethanol bark extracts significantly diseased IL-6 secretion by up to 33-fold compared to the LPS-stimulated control.[28] This significant suppression suggests potential interference with NF-KB signalling, likely mediated by bioactive compounds such as β-sitosterol, a plant sterol known to inhibit IL-6 production in immune cells.[28]

Cytokines are small signalling proteins that regulate immune responses, whilst chemokines play a role in immune cell migration to inflammation sites.[28] Ethanol bark extracts of *P. obliquum* significantly inhibit the production of IL-6, IL-1B and TNF-α. Additionally, it also regulates secretion of monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein -2 (MIP-2), which are chemokines involved in recruiting immune cells to sites of inflammation.[28] Thus, the downregulation of these factors by the extract would be expected to decrease inflammation, although this remains to be explored in *in vivo* systems.

Finally, previous studies have reported experiments using RAW 264.7 macrophages and human dermal fibroblast (HDF) cells (Table 3).[29] RAW 264.7 macrophages are commonly used in inflammation studies due to their role in producing cytokines in response to lipopolysaccharide (LPS) stimulation, mimicking an inflammatory response.[29] In contrast, HDF cells are used to evaluate cytotoxicity, as fibroblasts are essential for wound healing and tissue repair.[29] Thus, that study demonstrated that the extract was not only effective against the screened inflammatory biomarkers, but is was also relatively nontoxic, thereby indicating its safety for therapeutic use. Notably, the aqueous *P. obliquum* extract exhibited minimal toxicity, whilst the ethanol extract displayed higher toxicity at elevated concentrations, emphasizing the need for dose optimization in future therapeutic applications.[29] The extracts (and purified components) should be evaluated against other cell lines, as well as *in vivo*, before it is recommended for therapeutic use.

Anti-proliferative activities

Cancer is a group of diseases characterized by uncontrolled cell growth and division, leading to the formation of tumours and the potential spread of malignant cells to other parts of the body.[30] This uncontrolled growth is often driven by genetic mutations that disrupt the normal regulation of cell cycle processes, apoptosis, and DNA repair mechanisms.[30,31] Cancer can affect virtually any part of the body and is often associated with genetic predisposition, environmental exposures, and lifestyle choices. If left untreated, cancer can lead to significant tissue damage and metastasis.[30-32]

The development of new compounds for cancer treatment is critical since chemotherapy, radiation therapy, and surgery often have significant side effects and limitations.[33] For example, chemotherapy not only targets cancer cells, but also damages healthy cells, leading to adverse effects including nausea, fatigue, and immunosuppression.[33] Moreover, many cancers develop resistance to conventional treatments over time, rendering them less effective. Novel cancer drugs are needed to target specific molecular pathways involved in tumour growth and metastasis, thereby offering more precise and less toxic treatment options.

The primary goal of cancer therapy is to develop compounds that selectively target cancer cells while minimizing toxicity to normal cells.[34,35] Therefore, when identifying potential leads for cancer treatment, it is essential to assess the selective toxicity of extracts, fractions, or compounds against cancer cells.[30] Authors from previous studies have evaluated whether *P. obliquum* from geographically different locations exhibited selective activity against cancer cells.[30] In that study, samples with an SI values >2 were considered to possess selective toxicity against the tested cancer cell line.[30] Furthermore, according to the guidelines of the US National Cancer Institute, extracts are considered to exhibit significant *in vitro* antiproliferative activity against cancer cells if their 50% inhibitory concentration (IC_{50}) is below 20 µg/mL.[30] Extracts with IC_{50} values between 20 µg/mL and 50 µg/mL are classified as moderately toxic, those ranging from 50 µg/mL to 200 µg/mL are deemed less toxic, and extracts with IC_{50} values exceeding 200 µg/mL are regarded as non-toxic.[30,36-38]

Acetone extracts derived from *P. obliquum* demonstrated selective cytotoxic activity against HepG2 and HeLa cancer cell lines, with selective index values reaching up to 14 (Table 4). The Hatfield acetone extract exhibited the highest cytotoxicity, with an IC_{50} value of 8.4 µg/mL against HepG2 cells, with the highest recorded SI value of 14. This indicates that the extracts were approximately seven times more toxic to cancer cells compared to normal Vero cells.[30]

The choice of solvent for extraction is critical as it dictates the class and polarity of the compounds isolated. The extractant used significantly affects the biological activity of *P. obliquum* extract, particularly in relation to its effects on both normal and cancer cell lines. Furthermore, the antiproliferative activity and possibly the phytochemical composition of *P. obliquum*, were influenced by its geographical location.[30] However, relatively little research has been conducted on the antiproliferative properties of *P. obliquum*. One possible reason for this limited exploration is that *P. obliquum* does not appear have traditional uses in cancer treatment, which makes it less likely to be prioritised for cancer screening compared to other well documented medical plants that has traditional use in cancer therapy. Additionally,

Table 4: Cytotoxicity and selectivity of the extracts, fractions, and isolated compound from *P. obliquum* leaves.[30]

Extracts	IC_{50} (µg/mL)								
	MCF7	SI	HEPG2	SI	A549	SI	HELA	SI	VERO
Walter Sisulu									
Acetone	197.3 ± 26.5	0.6	14.5 ± 0.2	8.6	147.4 ± 9.6	0.8	87.2 ± 9.6	1.4	126.1 ± 4.5
Water (cold)	487.8 ± 11.9	0.9	832.1 ± 42.1	0.5	353.1 ± 59.5	1.3	946.6 ± 104.9	0.5	449.5 ± 0.8
Water (hot)	418.7 ± 175.4	0.5	455 ± 24.1	0.5	830 ± 60.9	0.3	911.6 ± 56.6	0.2	214.3 ± 15.1
UP Hatfield									
Acetone	194.7 ± 27.2	0.6	8.6 ± 0.8	14.2	64.1 ± 20.4	1.9	34.8 ± 6.9	3.5	122.1 ± 6.1
Water (cold)	>1000	0.3	754.6 ± 22.2	0.7	>1000	0.2	>1000	0.4	535.3 ± 20.5
Water (hot)	666.7 ± 109.6	1.5	372.2 ± 8.3	2.74	490.8 ± 17.1	2.1	>1000	1	>1000
Nelspruit									
Acetone	269.8 ± 33.2	0.4	248.4 ± 38.9	0.40	374.7 ± 8.4	0.27	>1000	0.07	100.3 ± 0.8
Water (cold)	>1000	0.7	246 ± 4.6	3.61	916.5 ±137.1	1.00	>1000	0.71	961.5 ± 19.2
Water (hot)	658 ± 162.1	0.5	550.9 ± 70.4	0.56	136.6 ± 17.8	2.4	>1000	0.18	322.5 ± 85.9
$CHCl_3$ fraction	284.2 ± 38.4	1.0	33.5 ± 3	8.5	218.9 ± 9	1.3	824.5 ± 139.1	0.34	284.2 ± 68.1

SI = safety index, calculated by toxicity/IC_{50}. The locations in the extracts column indicate the source of the plant material tested. UP Hatfield = University of Pretoria, Hatfield campus; Walter Sisulu = Walter Sisulu Botanical Gardens in Johannesburg; Nelspruit = the Lowveld Botanical Gardens on Mbombela (formerly called Nelspruit). IC_{50} results indicate the Mean result ± Standard Deviation.

in some of the cytotoxicity studies, Vero cells (a money kidney epithelial cell line) were used for comparison.[30] This may not be the most appropriate control for evaluating selective anticancer activity as they are non-human cells and therefore do not provide the most relevant insights into how a compound might affect human cancerous versus non-cancerous cells. A more appropriate approach in future studies would be to compare cancer lines directly to human-derived non-cancerous cells, such as human dermal fibroblast (HDF), which would offer a better representation of selective toxicity towards malignant cells while minimising harm to normal human tissue. Thus, expanding research on *P. obliquum* to include diverse human cancer cell lines alongside non-cancerous human controls will help clarify potential as an anticancer compound.

CONCLUSION

Ptaeroxylon obliquum has significant pharmacological potential, particularly for its antimicrobial, anti-inflammatory and anti-proliferative activities. Its extracts exhibit strong antibacterial and antifungal properties, although their efficacy varies based on extraction methods and solvent selection. Notably, only a limited number of bacterial pathogens have been tested to date and further studies are needed to evaluate a broader range of bacterial pathogens. Similarly, only a small subset of fungal species have been investigated, and a more extensive studies should be conducted to include additional fungal strains. Furthermore, there are limited studies against any viruses or parasites, representing a major gap in understanding their potential antiviral or antiparasitic activities. The plant's anti-inflammatory effects are evident through COX-2 inhibition, modulation of NF-KB signalling, and cytokine suppression, highlighting its potential for managing inflammatory conditions. Furthermore, its anti-proliferative properties suggest selective cytotoxic activity against certain cancer cell lines, warranting further investigation into its mechanisms and potential therapeutic applications. However, substantial gaps remain in our understanding of its active compounds, toxicity, and clinical relevance. Notably (with the exception of the anticancer studies, and some of the anti-inflammatory studies), the majority of studies that have screened *P. obliquum* extracts for activity have not evaluated their toxicity in parallel. Even where toxicity has been tested, it generally has been tested against one, or a limited panel of cells. Furthermore, the cell line(s) tested has not always been the most appropriate, and an extended cell panel should be examined. Following those studies and pending their outcome, *in vivo* preclinical studies may be required before the extracts (or pure components) are deemed to be safe for therapeutic use. Future research should also focus on mechanistic studies, bioactive compound identification, and optimisation of extraction methods to harness its full medicinal potential.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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