Alfred Maroyi /J. Pharm. Sci. & Res. Vol. 11(8), 2019, 3072-3079

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Review of medicinal uses, phytochemistry and pharmacological properties of *Protorhus longifolia*

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Abstract

Protorhus longifolia is a medium to large tree widely used as herbal medicine in southern Africa. This study was aimed at providing a critical review of the biological activities, phytochemistry and medicinal uses of *P. longifolia*. Documented information on the botany, biological activities, medicinal uses and phytochemistry of *P. longifolia* was collected from several online sources which included BMC, Scopus, SciFinder, Google Scholar, Science Direct, Elsevier, Pubmed and Web of Science. Additional information on the botany, biological activities, phytochemistry and medicinal uses of *P. longifolia* was gathered from pre-electronic sources such as book chapters, books, journal articles and scientific publications sourced from the University library. This study showed that the bark, fruits, gum, latex and leaves of *P. longifolia* are used are used as depilatories and herbal medicine for hemiphlegic paralysis, internal bleeding, magical purposes, skin problems, gastro-intestinal problems and ethnoveterinary medicine. Phytochemical compounds identified from the seeds and stem bark of *P. longifolia* include alkaloids, cardiac glycosides, flavonoids, phenols, saponins, sterols, tannins, terpenoids and triterpenes. Ethnopharmacological research revealed that *P. longifolia* extracts and compounds have acetylcholinesterase inhibitory, antibacterial, anti-Listeria, antimycobacterial, antifungal, anticoagulant, anti-hypertensive, antihyperlipidemic, antihyperglycemic, anti-inflammatory, antioxidant, anti-platelet, cardioprotective and cytotoxicity activities. Future studies should focus on conducting detailed phytochemical, pharmacological, toxicological and clinical evaluations of *P. longifolia* crude extracts as well as compounds isolated from the species.

Keywords: Anacardiaceae, ethnopharmacology, herbal medicine, indigenous pharmacopeia, *Protorhus longifolia*

INTRODUCTION

Protorhus longifolia (Bernh.) Engl. is a medium to large evergreen tree belonging to the Anacardiaceae, commonly known as the cashew or sumac family. The family Anacardiaceae includes economically important fruit tree species such as cashews (*Anacardium occidentale* L.), staghorn sumac (*Rhus typhina* L.), mangos (*Mangifera indica* L.), pistachios (*Pistacia vera* L.), pink peppercorns (*Schinus terebinthifolia* L.) and marula (*Sclerocarya birrea* (A. Rich.) Hochst.). The genus *Protorhus* Engl. comprises about 20 species which are mainly trees and shrubs primarily distributed in Madagascar with *P. longifolia* recorded in South Africa and Swaziland.[1-3] Most of these *Protorhus* species are characterized by wood that is durable, resistant to termites and fungal attack, and therefore, used as a general purpose timber for furniture, construction, joinery, flooring, panelling, moulding and railway sleepers.[3] The bark, fruits and leaves of the species are eaten by birds, game and livestock.[1] In the Eastern Cape province in South Africa, the leaves of *P. longifolia* are used as wild spinach and/or pot-herb or wild fruit or as famine food.[4,5] The bark and leaves of the species are used as herbal medicines in South Africa and Swaziland, playing an important role in the primary health care of local communities. *Protorhus longifolia* is heavily traded in Gauteng,[6,7] KwaZulu-Natal[7] and the Eastern Cape[8-11] provinces in South Africa and also unsustainably harvested in the Eastern Cape province.[8] It is against this background that this study was undertaken aimed at appraising the medicinal uses, phytochemistry and biological activities of *P. longifolia*.

Taxonomy and description of *Protorhus longifolia*

The generic name *Protorhus* is based on the Greek words "protos" meaning "first" and "rhus", now *Searsia* F.A. Barkley, another genus of the family and possibly meant in the sense of "approaching the Searsia genus" in morphological characteristics. The specific name "*longifolia*" is derived from Latin words meaning "long leaves".[12] Synonym associated with *P. longifolia* include *Anaphrenium longofolium* Bernh., *Heeria longifolia* Bernh. ex C. Krauss and *Rhus longifolia* (Bernh.) Sond.[2,13] *Protorhus longifolia* is commonly known as "purple currant", "red beech" and "red Cape beech" in English. *Protorhus longifolia* is a medium to large evergreen tree growing up to 18 metres in height with a trunk diameter of one metre.[12] The bark is dark brown in colour, smooth to rough and characterized by milky latex. The leaves are simple, opposite to sub-opposite or spirally arranged, linear-oblong to narrowly elliptic in shape, hairless, upper surface dark green and glossy while the under surface is paler green with conspicuous parallel lateral veins. Flowers are greenish white to yellow in colour, occurring in dense, many-flowered, short, terminal heads or panicles. The fruit is an asymmetrically oblong, fleshy one-seeded drupe and becoming purple-mauve when ripe. *Protorhus longifolia* has been recorded in South Africa and Swaziland in coastal and montane forests, forest margins, open woodland and along river banks at an altitude ranging from 12 metres to 1980 metres above sea level.[2,13]

Medicinal uses of *Protorhus longifolia*

The bark, fruits, gum, latex and leaves of *P. longifolia* are used as depilatories and herbal medicines for hemiphlegic paralysis, internal bleeding, magical purposes, skin problems, gastro-intestinal problems and ethnoveterinary medicine (Table 1, Figure 1). The leaves of *P. longifolia* are mixed with those of *Clerodendrum glabrum* E. Mey. and *Psidium guajava* L. as herbal medicine for diarrhoea and dysentery.[14,15] The bark of *P. longifolia* is mixed with

bark of *Hippobromus pauciflorus* Radlk. as ethnoveterinary medicine for heartwater and diarrhoea in cows.[15-19]

Phytochemical composition of *Protorhus longifolia*

Mosa et al.[35] identified saponins, tannins, flavonoids, alkaloids, terpenoids and cardiac glycosides from the stem bark of *P. longifolia* while Mhlongo et al.[36] identified flavonoids, cardiac glycosides, phenols and sterols from the seed extracts of the species. Triterpenes which included 3-oxo-5α-lanosta-8,24-dien-21-oic acid,[37] 3β-hydroxylanosta-9,24-dien-24-oic acid,[37] 3β-hydroxylanosta-9,24-dien-21-oic acid,[38-42] methyl-3β-hydroxylanosta-9,24-dienoate,[39] methyl-3β-hydroxylanosta-9,24-dien-21-oate[38,40,42-47] have been identified from the stem bark of the species (Table 2). Some of the pharmacological activities associated with the species could be attributed to the documented phytochemical compounds.

The following biological activities have been reported from the bark, leaf, seed and triterpene compounds isolated from *P. longifolia*: acetylcholinesterase inhibitory,[48] antibacterial,[36,37,42,49-52] anti-Listeria,[40] antimycobacterial,[53,54] antifungal,[49-52] anticoagulant,[41] anti-hypertensive,[31] antihyperlipidemic and antihyperglycemic,[38,43,44,46,47,55] anti-inflammatory,[37,41] antioxidant,[35-37,48,49,56], anti-platelet,[35,37,49,56] cardioprotective[45] and cytotoxicity[35,37,49,53,54,56] activities.

Acetylcholinesterase inhibitory activities

Amoo et al.[48] evaluated acetylcholinesterase inhibitory properties of aqueous leaf extract of *P. longifolia* using colorimetric assay with galanthamine at 20 µM as a positive control. Acetylcholinesterase inhibition (%) at 1.0 mg/ml was 40.1% to 51.8%. These results suggest that *P. longifolia* extracts deserve further investigation as they may provide secondary metabolites which can act as natural acetylcholinesterase inhibitors required for the treatment of neurodegenerative disorders.

Biological activities of *Protorhus longifolia*

Table 1: Medicinal uses of *Protorhus longifolia*

Medicinal use	Plant parts	Country	References
Blood purifier	Bark	South Africa	Mhlongo and Van Wyk[20];
Respiratory problems (chest pains and tuberculosis)	Bark	South Africa and Swaziland	Long[21]; Madikizela et al.[22]
Depilatories	Bark, gum and latex	South Africa and Swaziland	Palmer and Pitman[12]; Long[21]; Watt and Breyer-Brandwijk[23]; Hutchings et al.[24]
Emetic	Bark	South Africa	Cocks and Dold[25]; Zukulu et al.[26]
Gastro-intestinal problems (biliousness, diarrhoea and inability to defecate)	Bark	South Africa	Mhlongo and Van Wyk[20]; Zukulu et al.[26]; Appidi et al.[27]
Diarrhoea and dysentery	Leaves mixed with those of *Clerodendrum glabrum* E. Mey. and *Psidium guajava* L.	South Africa	Bisi-Johnson et al.[14]; Stark et al.[15]
Heartburn	Bark	South Africa	Hutchings et al.[24]; Pujol[28]
Hemiphlegic paralysis	Bark	South Africa	Palmer and Pitman[12]; Hutchings et al.[24]; Gerstner[29]; Netshiluvhi[30]
High blood pressure	Bark and leaves	South Africa	Balogun and Ashafa[19]; Duncan et al.[31]
Internal bleeding	Bark	South Africa	Balogun and Ashafa[19]; Hutchings et al.[24]; Pujol[28]
Magical purposes (good luck and ward off evil spirits)	Bark	South Africa	Palmer and Pitman[12]; Hutchings et al.[24]; Zukulu et al.[26]; Netshiluvhi[30]
Perfume	Fruits	South Africa	Palmer and Pitman[12]
Skin problems (acne, bruise, cuts, dermatophytoses, eczema, ringworm, sunlight protection, warts and wounds)	Bark and leaves	South Africa	Mhlongo and Van Wyk[20]; Otang et al.[32]; Mwangi et al.[33]; Sagbo and Mbeng[34]
Teething problems in babies	Bark	South Africa	Zukulu et al.[26]
Urinary system problem (inability to urinate)	Bark	South Africa	Mhlongo and Van Wyk[20]
Ethnoveterinary medicine			
Diarrhoea in cows	Bark mixed with bark of *Hippobromus pauciflorus* Radlk.	South Africa	Stark et al.[15]; Dold and Cocks[16]; McGaw and Eloff[17]; Chinsembu[18]; Balogun and Ashafa[19]
Heartwater	Bark mixed with bark of *Hippobromus pauciflorus*	South Africa	Dold and Cocks[16]; McGaw and Eloff[17]; Chinsembu[18]
Heartwater	Bark	South Africa	Cocks and Dold[25]
Paratyphoid in cattle	Bark	South Africa	Cocks and Dold[25]

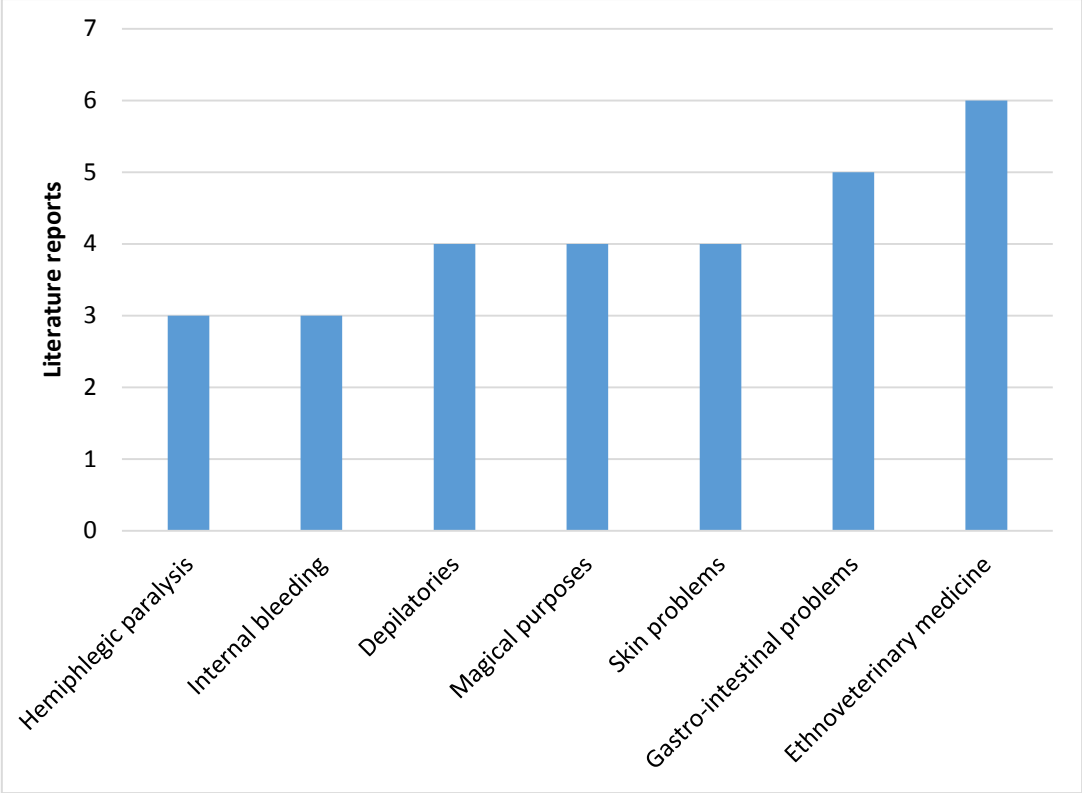

Figure 1. Medicinal applications of *Protorhus longifolia* derived from literature records

Table 2: Phytochemical composition of *Protorhus longifolia*

Phytochemical composition	Value	Plant part	Reference
3-oxo-5α-lanosta-8,24-dien-21-oic acid	-	Stem bark	Mosa et al.[37]
3β-hydroxylanosta-9,24-dien-24-oic acid	-	Stem bark	Mosa et al.[37]
3β-hydroxylanosta-9,24-dien-21-oic acid	-	Stem bark	Mosa et al.[38]; Mosa et al.[39]; Penduka et al.[40]; Mosa et al.[41]; Penduka et al.[42];
Condensed tannins (% in dry matter)	0.4 – 0.7	Leaves	Amoo et al.[48]
Free gallic acid (µg gallic acid equivalents/g dry weight)	1901.4 – 2398.8	Leaves	Amoo et al.[48]
Gallotannins (µg gallic acid equivalents/g dry weight)	2726.2 – 4039.9	Leaves	Amoo et al.[48]
Iridoids (µg harpagoside equivalents/g dry weight)	1034.4 – 7787.2	Leaves	Amoo et al.[48]
Methyl-3β-hydroxylanosta-9,24-dienoate	-	Stem bark	Mosa et al.[39]
Methyl-3β-hydroxylanosta-9,24-dien-21-oate	-	Stem bark	Mosa et al.[38]; Penduka et al.[40]; Mosa et al.[43]; Machaba et al.[44]; Mosa et al.[45]; Mabhida et al.[46]; Mabhida et al.[47]
Total flavonoids (mg catechin equivalents/g dry weight)	10.1 – 18.3	Leaves and stem bark	Mosa et al.35; Amoo et al.48
Total phenolics (mg gallic acid equivalents/g dry weight)	51.8 – 114.4	Leaves and stem bark	Mosa et al.35; Amoo et al.48

Antibacterial activities

Suleiman[49], Suleiman et al.[50] and Suleiman et al.[51] evaluated the antibacterial activities of the hexane, acetone, dichloromethane and methanol leaf extracts of *P. longifolia* against *Enterococcus faecalis, Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus* using the bioautographic procedure. The extracts exhibited activities against the tested pathogens.[49-51] Suleiman[49] and Suleiman et al.[52] evaluated the antibacterial activities of the hexane, dichloromethane, acetone and methanol leaf extracts of *P. longifolia* against *Staphylococcus aureus, Enterococcus faecalis, Escherichia coli* and *Pseudomonas aeruginosa* using a two-fold serial microdilution method with gentamicin (0.1 mg/ml) as a positive control. The extracts exhibited activities with minimum inhibitory concentration (MIC) values ranging from 0.08 mg/ml to 2.5 mg/ml and total activities ranging from 25.0 ml/g to 1913.0 ml/g.[49,52] Mosa et al.[37] evaluated the antibacterial activities of triterpene compounds 3β-hydroxylanosta-9,24-dien-21-oic acid and methyl-3β-hydroxylanosta-9,24-dienoate isolated from the stem bark of *P. longifolia* against *Streptococcus viridians, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Salmonella* spp., and *Proteus mirabilis* using disk

diffusion and micro-dilution methods with ampicillin and neomycin as positive controls. The compounds exhibited activities against all tested pathogens with zone of inhibition ranging from 8.0 mm to 16.0 mm which was comparable to 8.0 mm to 14 mm exhibited by the positive control. The MIC and minimum bactericidal concentration (MBC) values against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Salmonella* spp. and *Proteus mirabilis* ranged from 0.2 mg/ml to 1.3 mg/ml and 1.3 mg/ml to 5.0 mg/ml, respectively.[37] Penduka et al.[42] evaluated antibacterial activities of triterpenes 3β-hydroxylanosta-9, 24-dien-21-oic acid and methyl-3β-hydroxylanosta-9, 24-dien-21-oate isolated from *P. longifolia* stem bark against *Escherichia coli, Bacillus cereus, Enterococcus avium, Enterococcus casseliflavus, Enterococcus faecalis, Enterococcus gallinarum, Enterococcus hirae, Vibrio fluvialis, Vibrio parahaemolyticus* and *Vibrio vulnificus* using the micro-broth dilution assay with ciprofloxacin as a positive control. The checkerboard method was used to determine the antibiotic triterpene interactions while the cytosolic lactate dehydrogenase test was used to determine the membrane damaging potentials of the compounds in comparison to 3% Triton X-100. Both compounds exhibited activities against tested bacteria with zone of inhibition ranging from 7 mm to 28 mm which was comparable to 18 mm to 34 mm exhibited by the positive control. The MIC and MBC values ranged from 1.25 mg/ml to 10 mg/ml and 1.25 mg/ml to >10.0 mg/ml, respectively. The interaction of the compounds with ciprofloxacin ranged between indifference and antagonism. The compound methyl-3β-hydroxylanosta-9, 24-dien-21-oate showed minimal membrane damaging potential with the levels of cytosolic lactate dehydrogenase released ranging from 1.0% to 36.0% in comparison to 3% Triton X-100 against *Escherichia coli* and *Vibrio vulnificus*.[42] Mhlongo et al.[36] evaluated the antibacterial activities of hexane, ethyl acetate, chloroform, methanol, ethanol and water seed extracts of *P. longifolia* against *Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Enterococcus faecalis* and *Pseudomonas aeruginosa* using disc diffusion and micro dilution methods with neomycin (50 µg/ml) as a positive control. The extract exhibited activities against all the tested pathogens with the exception of *Enterococcus faecalis* with zone of inhibition ranging from 7 mm to 16 mm which was comparable to 7 mm to 15 mm exhibited by the positive control. The MIC values ranged from 62.5 µg/ml to 200 µg/ml while MIC values exhibited by the control ranged from 62.5 µg/ml to 100 µg/ml.[36]

Anti-*Listeria* activities

Penduka et al.[40] evaluated anti-Listeria activities of triterpenes 3β-hydroxylanosta-9,24-dien-21-oic acid and methyl-3β-hydroxylanosta-9,24-dien-21-oate isolated from *P. longifolia* stem bark against *Listeria monocytogenes, Listeria ivanovii* and *Listeria grayi* using the broth microdilution assay with penicillin G, ampicillin, neomycin and gentamicin as positive controls. The chequerboard method was used to assess the interactions between the compounds and conventional antibiotics ampicillin, neomycin, gentamicin and penicillin G. Both compounds exhibited activities against tested pathogens with MIC and MBC values of 0.2 mg/ml and >1.5 mg/ml, respectively. The interactions involving 3β-hydroxylanosta-9,24-dien-21-oic acid were mainly additive with ampicillin and synergistic with neomycin, gentamicin and penicillin G. The interactions involving methyl-3β-hydroxylanosta-9, 24-dien-21-oate were mainly antagonistic with ampicillin, indifferent with neomycin, ranging from synergistic to indifference with gentamicin and synergistic with penicillin G.[40]

Antimycobacterial activities

Kabongo-Kayoka et al.[53] evaluated antimycobacterial activities of acetone leaf extracts of *P. longifolia* using a microdilution assay against the pathogenic *Mycobacterium bovis*, multidrug resistant *Mycobacterium tuberculosis*, avirulent strain, H37Ra *Mycobacterium tuberculosis, Mycobacterium fortuitum, Mycobacterium smegmatis* and *Mycobacterium aurum* with ciprofloxacin, rifampicin, isoniazid and streptomycin as positive controls. The extracts demonstrated activities with MIC values ranging from 0.07 mg/ml to 0.11 mg/ml and total activities ranged from 1186 ml/g to 2264 ml/g.[53] Madikizela and McGaw[54] evaluated the antimycobacterial activities of acetone, 70% ethanol, water and hot water bark and leaf extracts of *P. longifolia* against *Mycobacterium fortuitum, Mycobacterium smegmatis, Mycobacterium bovis, Mycobacterium gordonae, Mycobacterium aurum* and *Mycobacterium tuberculosis* using microdilution assay with isoniazid, streptomycin and rifampicin as positive controls. The acetone and 70% ethanol leaf extracts were active against all tested *Mycobacterium* strains with MIC values ranging from 0.08 mg/ml to 1.25 mg/ml while water and hot water bark and leaf extracts were active against non-pathogenic Mycobacterium strains only with MIC values ranging from 0.16 mg/ml to 2.5 mg/ml.[54]

Antifungal activities

Suleiman,[49] Suleiman et al.[50] and Suleiman et al.[51] evaluated the antifungal activities of the hexane, acetone, dichloromethane and methanol leaf extracts of *P. longifolia* against *Aspergillus fumigatus, Candida albicans, Cryptococcus neoformans, Microsporum canis* and *Sporothrix schenckii* using the bioautographic procedure. The extracts exhibited activities against the tested pathogens.[49-51] Suleiman[49] and Suleiman et al.[52] evaluated the antifungal activities of the hexane, dichloromethane, acetone and methanol leaf extracts of *P. longifolia* against *Aspergillus fumigatus, Candida albicans, Candida neoformans, Microsporum canis* and *Sporothrix schenckii* using a two-fold serial microdilution method with amphotericin B (0.16 mg/ml) as a positive control. The extracts exhibited activities with MIC values ranging from 0.2 mg/ml to 2.5 mg/ml and total activities ranging from 37.0 ml/g to 729.0 ml/g.[49,52] Mhlongo et al.[36] evaluated antifungal activities of hexane, ethyl acetate, chloroform, methanol, ethanol and water seed extracts of *P. longifolia* against *Candida albicans, Candida krusei*

and *Candida parapsilosis* using disc diffusion and micro dilution methods with amphotericin B (20 µg/ml) as a positive control. Only methanol extract exhibited activities against *Candida albicans* with zone of inhibition ranging from 7 mm to 9 mm which was comparable to 9 mm to 12 mm exhibited by the positive control.[36]

Anticoagulant activities

Mosa et al.[41] evaluated the anticoagulant activities of a lanosteryl triterpene 3β-hydroxylanosta-9,24-dien-21-oic acid isolated from *P. longifolia* stem bark using tail bleeding time assay using adult Sprague Dawley rats. The authors also evaluated the effect of the compound on the malate dehydrogenase, citrate synthase and heat shock protein 70 system using malate dehydrogenase and citrate synthase aggregation suppression assay. The compound significantly increased bleeding time in rats by up to 7 minutes as compared to 2.5 minutes observed in the normal control group. The compound also improved the activities of heat shock protein 70 on malate dehydrogenase and citrate synthase aggregation suppression.[41]

Anti-hypertensive activities

Duncan et al.[31] evaluated the anti-hypertensive activities of aqueous and ethanolic leaf extracts of *P. longifolia* by using the angiotensin-converting enzyme (ACE) assay. The aqueous and ethanolic extracts exhibited 64.0% and 77.0% ACE inhibitory activities, respectively.[31]

Antihyperlipidemic and antihyperglycemic activities

Mosa et al.[38] evaluated the antihyperlipidemic activities of triterpene compounds 3β-hydroxylanosta-9,24-dien-21-oic acid and methyl-3β-hydroxylanosta-9,24-dien-21-oate isolated from the stem bark of *P. longifolia* on selected lipid digestive enzymes (pancreatic lipase and cholesterol esterase), hormone-sensitive lipase (HSL), their ability to bind bile acids, glucose uptake in C2C12 muscle cells and 3t3-l1 adipocytes and triglyceride accumulation in 3T3-L1 adipocytes. The compounds inhibited the activities of the pancreatic lipase, cholesterol esterase and HSL enzymes with half maximal inhibitory concentration (IC_{50}) values ranging from 0.04 mg/mL to 0.31 mg/mL which were comparable to IC_{50} values of 0.01 mg/mL to 0.16 mg/mL exhibited by the positive controls, orlistat and simvastatin. The compounds showed a high affinity for secondary bile acids and both compounds stimulated glucose uptake in C2C12 muscle cells and 3T3-L1 adipocytes. The compound 3β-hydroxylanosta-9,24-dien-21-oic acid significantly reduced triglyceride accumulation in mature differentiated 3T3-L1 adipocytes.[38] Machaba et al.[44] evaluated anti-hyperlipidemic activities of triterpene methyl-3β-hydroxylanosta-9, 24-dien-21-oate isolated from the stem bark of *P. longifolia* in high fat diet induced hyperlipidemic Sprague Dawley rats. The rats were orally treated with 100 mg/kg and 200 mg/kg body weight of the compound for 15 days and blood samples were collected for biochemical assays. Significant lowering of total serum cholesterol levels (7.5 mmol/L) and low-density lipoprotein cholesterol (4.5 mmol/L) with an increase in high-density lipoprotein cholesterol (47.3 mmol/L), and decrease in atherogenic index and coronary risk index were observed.[44] Mosa et al.[43] evaluated the in vivo antihyperglycemic activities of a lanosteryl triterpene compound methyl-3β-hydroxylanosta-9,24-dien-21-oate isolated from *P. longifolia* stem bark in a streptozotocin (STZ)-induced diabetes rat model. The Sprague Dawely rats were orally administered with 100 mg/kg body weight of the compound daily for 14 days and an oral glucose tolerance test was also performed. The rat were euthanized and biochemical analysis of antioxidant status, some glycolytic enzymes and glycogen content were conducted on serum and liver samples, respectively. The compound exhibited hypoglycemic activities by reducing blood glucose levels by 37% and the compound also improved glucose tolerance in the diabetic rats. Relatively higher hepatic glycogen content, hexokinase and glucokinase activities with a decrease in glucose-6-phosphatase activities were observed in the diabetic group treated with the compound in comparison with the control group. The compound also increased antioxidant status of the diabetic rats, increased the activities of superoxide dismutase and catalase, but decreased the malondialdehyde content.[43] Mabhida et al.[46] evaluated antihyperlipidemic activities of lanosteryl triterpene methyl-3β-hydroxylanosta-9,24-dien-21-oate isolated from *P. longifolia* stem bark by assessing the glucose tolerance in a high-fat diet and STZ-induced type 2 diabetes rat model. The compound was effective in improving the glucose tolerance and antioxidant effect in the diabetic rats, and also reduced elevated interleukin-6 levels and improved pancreatic beta cell ultrastructure. Mabhida et al.[46] concluded that the compound demonstrated strong potential to improve pancreatic beta cell ultrastructure by attenuating impaired glucose tolerance, reducing oxidative stress and inflammation. Mabhida et al.[47] evaluated the molecular mechanisms associated with antihyperglycemic activities of the lanosteryl triterpene methyl-3β-hydroxylanosta-9,24-dien-21-oate isolated from *P. longifolia* stem bark in streptozotocin-induced type 1 diabetic male Sprague Dawley rats. The type 1 diabetic rats were treated daily with a single oral dose of 100 mg/kg body weight for 28 days and the blood, skeletal muscle and pancreases were collected for biochemical, protein expression and histological analyses. Treatment of the diabetic rats with the compound significantly lowered the blood glucose levels by 67% which was comparable to the metformin treated group (69%), which served as the positive control. Treatment of the rates with the compound caused an increase in serum glutathione, superoxide dismutase, catalase and C-peptide levels, while their serum levels of interleukin-6 and malondialdehyde were reduced.[47] Mabhida et al.[55] evaluated the molecular mechanisms associated with antihyperglycemic activities of the lanosteryl triterpene methyl-3β-hydroxylanosta-9,24-dien-21-oate isolated from *P. longifolia* stem bark in streptozotocin-induced type 2 diabetic male Sprague Dawley rats. The rats received a daily oral single dose of 100 mg/kg body of the compound for 28 days and skeletal muscle was collected for protein expression analysis.

Treatment of the diabetic rats with the compound showed marked reduction in fasting plasma glucose levels, stimulated the insulin signaling pathway by reducing the expression of $IRS1^{Ser307}$ and increased p-AKT/p-GSK-3β expression. These results suggest that the anti-hyperglycemic effect of methyl-3β-hydroxylanosta-9,24-dien-21-oate could be associated with its ability to improve cellular glucose uptake in muscle tissue from type 2 diabetes mellitus.[55]

Anti-inflammatory activities

Mosa et al.[37] evaluated the anti-inflammatory activities of triterpene compounds 3-oxo-5α-lanosta-8,24-dien-21-oic acid and 3β-hydroxylanosta-9,24-dien-24-oic acid isolated from the stem bark of *P. longifolia* using the carrageenan-induced rat paw edema model. The compound 3β-hydroxylanosta-9,24-dien-24-oic acid exhibited anti-inflammatory activities in a concentration and time dependent fashion as it reduced the rat paw oedema volume.[37] Mosa et al.[41] evaluated the anti-inflammatory activities of a lanosteryl triterpene 3β-hydroxylanosta-9,24-dien-21-oic acid isolated from *P. longifolia* stem bark using the cotton pellet-induced granuloma model in adult Sprague Dawley rats. Granuloma formation was assessed following seven days of oral administration of the compound at 50 mg/kg and 250 mg/kg body weight. The granuloma formation decreased by up to 40.3% and the compound inhibited the aggregation of proteins.[41]

Antioxidant activities

Suleiman[49] and Suleiman et al.[56] evaluated the antioxidant activities of methanol leaf extracts of *P. longifolia* using 1,1′-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging and 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) assays with L-ascorbic acid as a positive control. The extracts exhibited activities with half maximal effective concentration (EC_{50}) value of 6.6 μg/mL in the DPPH assay, which was comparable to EC_{50} value of 1.6 μg/mL exhibited by the positive control. In the ABTS assay, the extract exhibited Trolox equivalent antioxidant capacity (TEAC) value 1.4.[49,56] Mosa et al.[35] evaluated the antioxidant activities of hexane, chloroform, ethyl acetate, methanol and water bark extracts of *P. longifolia* using DPPH radical scavenging assay, ABTS radical scavenging assay, reducing power and chelating activity on Fe2+ with butylated hydroxytoluene (BHT) and ascorbic acid as positive controls. The extracts exhibited activities with IC_{50} valuaes for DPPH, ABTS and Fe^{2+} chelating ranging from 0.07 mg/ml to >5.0 mg/ml.[35] Mosa et al.[37] evaluated the antioxidant activities of triterpene compounds 3-oxo-5α-lanosta-8,24-dien-21-oic acid and 3β-hydroxylanosta-9,24-dien-24-oic acid isolated from the stem bark of *P. longifolia* using DPPH and ABTS free radical scavenging and reduction potential assays. Both compounds exhibited poor (<20%) antioxidant activity as they weakly scavenged DPPH and ABTS radicals, and had low reduction potentials.[37] Amoo et al.[48] evaluated the antioxidant activities of aqueous leaf extract of *P. longifolia* using the DPPH free radical scavenging and β-carotenelinoleic acid model assays after long-term storage in comparison with freshly collected materials. The DPPH results showed EC_{50} values of 2.2 μg/ml to 2.3 μg/ml while the antioxidant activity of 90.9% and 72.9% at 200 μg/ml was exhibited using the β-carotenelinoleic acid model assay.[48] Mhlongo et al.[36] evaluated the antioxidant activities of hexane, ethyl acetate, chloroform, methanol, ethanol and water seed extracts of *P. longifolia* using DPPH-radical scavenging, hydrogen peroxide (H_2O_2) and ABTS+ assays. The methanol extract had the highest DPPH scavenging activity of 95% at 200 μg/ml, while hexane extract had the lowest DPPH scavenging activity of 16% at 25 μg/ml as compared to the standard control which exhibited 96% at 200 μg/ml. The water extract exhibited the highest H_2O_2 scavenging ability of 90% at 200 μg/ml, the same activity exhibited by the positive control, while hexane extract had the lowest H_2O_2 scavenging activity of 22% at 25 μg/ml. The reducing power exhibited by the extracts increased with increasing dosage. In ABTS+ assay, aqueous extract had the highest ABTS+ scavenging activity of 96% at 200 μg/ml while hexane had the lowest ABTS+ scavenging activity of 17% at 25 μg/ml.[36]

Anti-platelet activities

Suleiman[49] and Suleiman et al.[56] evaluated the antiplatelet activities of methanol leaf extracts of *P. longifolia* using the *in vitro* platelet aggregation assay with aspirin as a positive control. The extract exhibited activities with EC_{50} value of 0.2 μg/mL which was higher than the EC_{50} value of 0.04 μg/mL exhibited by the positive control.[49,56] Mosa et al.[35] evaluated the anti-platelet activities of hexane, chloroform, ethyl acetate, methanol and water bark extracts of *P. longifolia* using blood platelets, enzyme treated platelets, anti-platelet aggregation activity and tannin removal. The extracts exhibited a concentration dependent anti-platelet aggregation inhibitory activities induced by thrombin, adenosine diphosphate (ADP) and epinephrine with the highest activity exhibited by the hexane extract with IC_{50} of 0.59 mg/ml.[35] Mosa et al.[37] evaluated the anti-platelet activities of chloroform stem bark extract of *P. longifolia*, triterpene compounds 3-oxo-5α-lanosta-8,24-dien-21-oic acid and 3β-hydroxylanosta-9,24-dien-24-oic acid isolated from the species on thrombin, ADP, epinephrine and arachidonic acid induced rat platelet aggregation. The crude extract exhibited IC_{50} value of 0.67 mg/ml while the compound 3-oxo-5α-lanosta-8,24-dien-21-oic acid and 3β-hydroxylanosta-9,24-dien-24-oic acid exhibited IC_{50} values of 0.99 mg/ml and 1.04 mg/ml on the thrombin-induced platelet aggregation, respectively and a mixture of the two compounds exhibited IC_{50} value of 0.88 mg/ml. The compound 3β-hydroxylanosta-9,24-dien-24-oic acid (3 mg/ml) exhibited anticoagulant activities on whole blood.[37]

Cardioprotective activities

Mosa et al.[45] evaluated the cardioprotective activities of a lanosteryl triterpene methyl-3β-hydroxylanosta-9,24-dien-21-oate isolated from *P. longifolia* stem bark in an isoproterenol-induced myocardial injury in hyperlipidemic Sprague Dawely rats. The rats were orally administered

with 100 mg/kg of the compound for 15 days and the hearts and blood tissues were collected and used for histology and biochemical assays. The compound exhibited a cardioprotective effect as it minimized myocardial injury, few lesions of acute hyaline degeneration and reduced fat deposition were observed in the heart tissue of the compound pretreated rats. The lactate dehydrogenase activity was decreased in the blood of the pretreated rats (44.1 mU/mL) in comparison to the untreated (64.8 mU/mL) group. Increased glutathione content and catalase activity along with lower levels of malondialdehyde in the pretreated rats (120.8 nmol/μL) in comparison to untreated rats (143.6 nmol/μL) were observed.[45]

Cytotoxicity activities

Suleiman[49] and Suleiman et al.[56] evaluated the cytotoxicity activities of methanol leaf extracts of K. wilmsii against the Vero monkey kidney cell line using the 3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide (MTT) assay with berberine chloride as a positive control and hemagglutination assay. The agglutination occurred at 1.3 mg/mL and the extract exhibited hemagglutination assay titer value of 0.8 implying low toxicity.[49,56] Mosa et al.[35] evaluated the cytotoxicity activities of hexane, chloroform, ethyl acetate, methanol and water bark extracts of *P. longifolia* using the brine shrimp lethality bioassay. The median lethal concentration (LC_{50}) values of the extract was very low, 36 700 μg/ml.[35] Mosa et al.[37] evaluated the cytotoxicity activities of triterpene compounds 3-oxo-5α-lanosta-8,24-dien-21-oic acid and 3β-hydroxylanosta-9,24-dien-24-oic acid isolated from the stem bark of P. longifolia against human embryonic kidney (HEK293) and human hepatocellular carcinoma (HepG2) cell lines using the MTT cell proliferation assay. The compound 3β-hydroxylanosta-9,24-dien-24-oic acid exhibited weak activities with IC_{50} 8520 μg/ml and 7960 μg/ml against HEK293 and HepG2, respectively.[37] Kabongo-Kayoka et al.[53] evaluated cytotoxicity activities of leaf extracts of *P. longifolia* using the MTT assay against Vero African monkey kidney cells, cancer liver cells and mouse macrophage cells. The extracts exhibited low toxicity against the three cell lines with the LC_{50} values ranging from 0.62 mg/mL to >1.0 mg/mL.[53] Madikizela and McGaw[54] evaluated the cytotoxicity activities of acetone, 70% ethanol, water and hot water bark and leaf extracts of P. longifolia against Vero monkey kidney and bovine dermis cells using the MTT assay. The bark ethanol extract showed selective toxicity towards Vero cells with LC_{50} value of 0.04 mg/ml while water extract was slightly toxic against both Vero and bovine dermis cells with LC_{50} values of 0.06 mg/ml and 0.01 mg/ml, respectively.[54]

CONCLUSION

The present review summarizes the botany, medicinal uses, phytochemistry and pharmacological properties *P. longifolia*. Based on presented information, there is not yet enough data correlating the ethnomedicinal uses of the species with its phytochemical and pharmacological properties. Detailed studies on the pharmacokinetics, *in vivo* and clinical research involving both extracts and compounds isolated from the species are required. Therefore, future research should focus on the molecular modes or mechanisms of action, pharmacokinetics and physiological pathways for specific extracts of the species including identification of the bioactive compounds of the species and their associated pharmacological activities. Future research should also include the identification of any side effects and/or toxicity associated with usage of *P. longifolia* extracts or compounds isolated from the species.

Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this paper.

Acknowledgements

The author acknowledges financial support from GMRDC, University of Fort Hare

REFERENCES

[1] Von Teichman, I., *Bot. Bull. Academia Sinica* 1991, 32, 121-128.
[2] Palgrave, M.C., *Keith Coates Palgrave Trees of Southern Africa*, Struik Publishers, Cape Town 2002.
[3] Lemmens, R.H.M.J., in: Lemmens, R.H.M.J., Louppe, D., Oteng-Amoako, A.A. (Eds.), *Plant Resources of Tropical Africa 7(2): Timber 2*, PROTA Foundation, Wageningen 2012, pp. 549-550.
[4] Shava, S., *South. Afr. J. Environ. Ed.* 1999, 19, 85-97.
[5] Shava S. *The Use of Indigenous Plants as Food by a Rural Community in the Eastern Cape: An Educational Exploration*, MSc Dissertation, Rhodes University, Grahamstown 2000.
[6] Williams, V.L., Balkwill, K., Witkowski, E.T.F., *Bothalia* 2001, 31, 71-98.
[7] Cunningham, A.B., *African Medicinal Plants: Setting Priorities at the Interface Between Conservation and Primary Health Care*, People and Plants Working Paper 1, UNESCO, Paris 1993.
[8] Dold, A.P., Cocks, M., *Traffic Bull.* 2001, 19, 11–13.
[9] Dold, A.P., Cocks, M.L., *S. Afr. J. Sci.* 2002, 98, 589-597.
[10] Dold, A.P., Cocks, M.L., *Quest* 2004, 1, 16-17.
[11] Keirungi, J., Fabricius, C., *S. Afr. J. Sci.* 2005, 101, 497-501.
[12] Palmer, E., Pitman, P., *Trees of southern Africa covering all known indigenous species in the Republic of South Africa, South West Africa, Botswana, Lesotho and Swaziland*, AA Balkema, Cape Town 1972.
[13] Germishuizen, G., Meyer, N.L., *Plants of Southern Africa: An Annotated Checklist*, Strelitzia 14, National Botanical Institute, Pretoria 2003.
[14] Bisi-Johnson, M.A., Obi, C.L., Kambizi, L., Nkomo, M., *Afr. J. Biotechnol.* 2010, 9, 1245-1254.
[15] Stark, T.D., Mtui, D.J., Balemba, O.B., *Animals* 2013, 3, 158-227.
[16] Dold, A.P., Cocks, M.L., S. Afr. J. Sci. 2001, 97, 375–379.
[17] McGaw, L.J., Eloff, J.N., J. Ethnopharmacol. 2008, 119, 559–574.
[18] Chinsembu, K.C., in Chinsembu, K.C., Cheikhyoussef, A., Mumbengegwi, D., Kandawa-Schulz, M., Kasanda, C.D., Kazembe, L. (Eds.), *Indigenous Knowledge of Namibia*, University of Namibia, Windhoek 2015, pp. 115-134.
[19] Balogun, F,O., Ashafa, A.O.T., *Planta Med.* 2019, 85, 312–334.
[20] Mhlongo, L.S., Van Wyk, B.-E., S. Afr. J. Bot. 2019, 122, 266–290.
[21] Long, C., Swaziland's Flora: SiSwati Names and Uses. Mbambane, Swaziland: Swaziland National Trust Commission; 2005. Available at: http://www .sntc.org.sz/index.asp [Accessed on 14 June 2019].
[22] Madikizela, B., Kambizi, L., McGaw, L.J., S. Afr. J. Bot. 2017, 109, 231–236.
[23] Watt, J.M., Breyer-Brandwijk, M.G., *The Medicinal and Poisonous Plants of Southern and Eastern Africa*, Livingstone, London 1962.
[24] Hutchings, A., Scott, A.H., Lewis, G., Cunningham, A.B., *Zulu Medicinal Plants: An Inventory*, University of Natal Press, Pietermaritzburg, 1996.
[25] Cocks, M., Dold, A.P., J. Ethnobiol. 2006, 26, 60-81.

[26] Zukulu, S., Dold, T., Abbott, T., Raimondo, D., *Medicinal and Charm Plants of Pondoland*, South African National Biodiversity Institute, Pretoria 2012.
[27] Appidi, J.R., Grierson, D.S., Afolayan, A.J., *Pakistan J. Biol. Sci.* 2008, 11, 1961–1963.
[28] Pujol, J., *Natur Africa: The Herbalist Handbook*, Jean Pujol Natural Healers Foundation, Durban 1990.
[29] Gerstner, J., *Bantu Stud.* 1941, 15, 277-301.
[30] Netshiluvhi, T.R., *Aspects of Seed Propagation of Commonly Utilised Medicinal Trees of Kwazulu-Natal*, MSc Dissertation, University of Natal, Durban 1996.
[31] Duncan, A.C., Jäger, A.K., Van Staden, J., *J. Ethnopharmacol.* 1999, 68, 63–70.
[32] Otang, W.M., Grierson, D.S., Ndip, R.N., *J. Med. Pl. Res.* 2012, 6, 2071-2080.
[33] Mwinga J.L., Makhaga, N.S., Aremu, A.O., Otang-Mbeng, W., *S. Afr. J. Bot.* 2019, https://doi.org/10.1016/j.sajb.2019.03.038.
[34] Sagbo, I.J., Mbeng, W.O., *Indian J. Pharmacol.* 2019, 51, 140-149.
[35] Mosa, R.A., Lazarus, G.G., Gwala, P.E., Oyedeji, A.O., Opoku, A.R., *J. Nat. Prod.* 2011, 4, 136–146.
[36] Mhlongo, N.Y., Naidu, K.S.B., Himakar, R.K., Cheriti, S.A., Govender, P., *Curr. Trends Biotechnol. Pharm.* 2018, 12, 128-138.
[37] Mosa, R.A., Oyedeji, A.O., Shode, F.O., Singh, M., Opoku, A.R., *Afr. J. Pharm. Pharmacol.* 2011, 5, 2698-2714.
[38] Mosa, R.A., Naidoo, J.J., Nkomo, F.S., Mazibuko, S.E., Muller, C.J.F., Opoku, A.R., *Planta Med.* 2014, 80, 1685-1691.
[39] Mosa, R.A., Nhleko, M.L., Dladla, T.V., Opoku, A.R., *Med. Pl. Res.* 2014, 8, 686-702.
[40] Penduka, D., Mosa, R., Simelane, M., Basson, A., Okoh, A., Opoku, A., *Ann. Clin. Microbiol. Antimicrob.* 2014, 13, 37.
[41] Mosa, R.A., Cele, N.T., Opoku, A.R., *J. Med. Pl. Res.* 2015, 9, 613–619.
[42] Penduka, D., Gasa, N.P., Hlongwane, M.S., Mosa, R.A., Osunsanmi, F.O., Opoku, A.R., *Afr. J. Trad. Compl. Alt. Med.* 2015, 12, 180-188.
[43] Mosa, R.A., Cele, N.D., Mabhida, S.E., Shabalala, S.C., Penduka, D., Opoku, A.R., Molecules 2015, 20, 13374–13383.
[44] Machaba, K.E., Cobongela, S.Z.Z., Mosa, R.A., Oladipupo, L.A., Djarova, T.G., Opoku, A.R., *Lipids Health Dis.* 2014, 13, 1–7.
[45] Mosa, R.A., Hlophe, N.B., Ngema, N.T., Penduka, D., Lawal, O.A., Opoku, A.R., *Pharm. Biol.* 2016, 54, 3244–3248.
[46] Mabhida, S.E., Mosa, R.A., Penduka, D., Osunsanmi, F.O., Dludla, P.V., Djarova, T.G., Opoku, A.R., *Molecules* 2017, 22, 1252.
[47] Mabhida, S.E., Johnson, R., Ndlovu, M., Sangweni, N.F., Louw, J., Opoku, A., Mosa, R.A., *BMC Compl. Alt. Med.* 2018, 18, 265.
[48] Amoo, S.O., Aremu, A.O., Moyo, M., Van Staden, J., *BMC Compl. Alt. Med.* 2012, 12, 87.
[49] Suleiman, M.M., *The in Vitro and in Vivo Biological Activities of Antifungal Compounds Isolated from Loxostylis alata A. Spreng. ex Rchb. Leaf Extracts*, PhD Thesis, University of Pretoria, Pretoria 2009.
[50] Suleiman, M.M., McGaw, L.J., Picard, J., Naidoo, V., Eloff, J.N., *Afr. J. Trad. Compl. Alt. Med.* 2009, 6, 324-325.
[51] Suleiman, M.M., McGaw, L.J., Naidoo, V., Eloff, J.N., *Afr. J. Trad. Compl. Alt. Med.* 2010, 7, 64-68.
[52] Suleiman, M.M., McGaw, L.J., Naidoo, V., Eloff, J.N., *S. Afr. J. Bot.* 2010, 76, 64-71.
[53] Kabongo-Kayoka, P.N., Eloff, J.N., Obi, C.L., McGaw, L.J., *Phytother. Res.* 2016, 30, 2001–2011.
[54] Madikizela, B., McGaw, L.J., *J. Ethnopharmacol.* 2018, 224, 250–260.
[55] Mabhida, S.E., Johnson, R., Ndlovu, M., Louw, J., Opoku, A., Mosa, R.A., *Diabetol. Metab. Syndr.* 2019, 11, 27.
[56] Suleiman, M.M., Bagla, V., Naidoo, V., Eloff, J.N., *Pharm. Biol.* 2010, 48, 643-650.