Medicinal Uses, Biological and Chemical Properties of Wild Plum (*Harpephyllum caffrum*): An Indigenous Fruit Plant of Southern Africa

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Abstract: *Harpephyllum caffrum* is a fruit plant widely used as herbal medicine throughout its distributional range in southern Africa. This study was aimed at providing a critical review of the biological activities, phytochemistry and medicinal uses of *H. caffrum*. Documented information on the botany, biological activities, medicinal uses and phytochemistry of *H. caffrum* was collected from several online sources which included BMC, Scopus, SciFinder, Google Scholar, Science Direct, Elsevier, Pubmed and Web of Science. Additional information on *H. caffrum* 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 and roots of *H. caffrum* are used as blood purifier and emetic, and as herbal medicine against asthma, wounds, bone fractures, sprains and skin problems. Phytochemical compounds identified from the fruits, leaves and stem bark of *H. caffrum* include cardanols, fatty acid esters, flavonoids, phenolics and triterpenoids. Ethnopharmacological research revealed that *H. caffrum* extracts and compounds have *in vitro* and *in vivo* pharmacological activities such as acetylcholinesterase, analgesic, antibacterial, anticonvulsant, antimycobacterial, antifungal, anti-HIV, anti-inflammatory, antioxidant, antipyretic, melanogenesis and antityrosinase, hypoglycaemic and hypotensive, hepatoprotective and cytotoxicity activities. *Harpephyllum caffrum* should be subjected to detailed phytochemical, pharmacological and toxicological evaluations aimed at correlating its medicinal uses with its phytochemistry and pharmacological activities of the species.

Keywords: Anacardiaceae, ethnopharmacology, *Harpephyllum caffrum*, herbal medicine, indigenous pharmacopeia.

INTRODUCTION

Harpephyllum caffrum Bernh. is a member of the cashew, mango, sumac or Anacardiaceae family. The genus *Harpephyllum* Bernh. ex Krauss consists of a single species, *H. caffrum* recorded in riverine and coastal forests in South Africa and Swaziland at an altitude ranging from 15 m to 1400 m above sea level [1-3]. The generic name "*Harpephyllum*" is based on the Greek word meaning "sickle" and "leaf" in reference to the shape of the lateral leaflets [4]. The specific name "*caffrum"* is derived from the Hebrew word "*kafri*" meaning "person living on the land", and the name was often applied to plants indigenous to the eastern parts of South Africa in the previous centuries [4]. *Harpephyllum caffrum* is a small to medium-sized evergreen tree reaching a height of up to 15 metres [2,4]. The trunk is usually clean and straight with a neat, round smallish, compact and spreading crown. The bark maybe silvery-white with small, raised, crosswise ridges or brown and cracking into segments. The fruits of *H. caffrum* are oblong in shape, fleshy and bright red when ripe [1,2]. The fruits of *H. caffrum* are used as a snack, non-alcoholic beverage, alcoholic beverage and sweet preserve in South Africa and Swaziland [1,2,4-20]. *Harpephyllum caffrum* is widely cultivated in South Africa as a decorative tree along streets and as a general ornamental tree [2,16,21]. Based on the importance of *H. caffrum* as a source of edible fruits and ornamental tree, the species has been introduced in several countries including Egypt and the Negev Desert in Israel [16,17,21]. Van Wyk [17] argued that the fruits of *H. caffrum* have commercial potential in South Africa in the production of a wide diversity of food products and additives such as dried fruits, jam, processed into fruit juices, sweets, jellies, liqueurs and novel flavours. Research by Mosina *et al*. [22,23], Mosina and Maroyi [24] showed that *H. caffrum* is widely cultivated and/or maintained in home gardens in the Limpopo province in South Africa as an ornamental and medicinal plant. *Harpephyllum caffrum* is also sold in informal herbal medicine markets in the Gauteng and KwaZulu-Natal provinces in South Africa [25-30]. It is within this context that the current study was undertaken aimed at reviewing the medicinal uses, phytochemistry and biological activities of *H. caffrum*.

Medicinal Uses of *Harpephyllum caffrum*

The bark, fruits and roots of *H. caffrum* are used as blood purifier and emetic, and as herbal medicine

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Table 1: Medicinal Uses of *Harpephyllum caffrum*

Medicinal use	Parts used	References
Asthma	Root	[31,32]
Backache	Bark	[33]
Blood purifier	Bark	[15,16,19,29,34-36]
Bone fractures	Bark	[16,19,35]
Chest problems	Bark	[15]
Chronic cough	Root	[32]
Convulsions	Bark	[36]
Diarrhoea	Bark	[33]
Emetic	Bark	[19,33,34]
Epilepsy	Bark	[36]
Headache	Root	[32]
Malaria	Root	[37]
Menstrual problems	Bark and roots	[15]
Pain	Bark	[36]
Skin problems (acne, eczema, pimples, rash and skin cuts)	Bark and fruits	[14-16,19,29,30,35,36,38-47]
Sprains	Bark	[14,19,35,44]
Wounds	Bark and fruits	[43,46]
Ethnoveterinary medicine		
Anthelmintics in goats	Bark	[48]

against asthma, wounds, bone fractures, sprains and skin problems (Table **1**, Figure **1**). Other minor uses supported by single literature records include backache, chest problems, chronic cough, convulsions, diarrhoea, epilepsy, headache, malaria, menstrual problems, pain and ethnoveterinary medicine (Table **1**).

Nutritional and Phytochemical Composition of *Harpephyllum caffrum*

The fruits of *H. caffrum* are a good source of minerals such as calcium, copper, iron, magnesium, manganese, phosphorus, zinc and classic nutrients such as carbohydrates, proteins, fats and vitamins

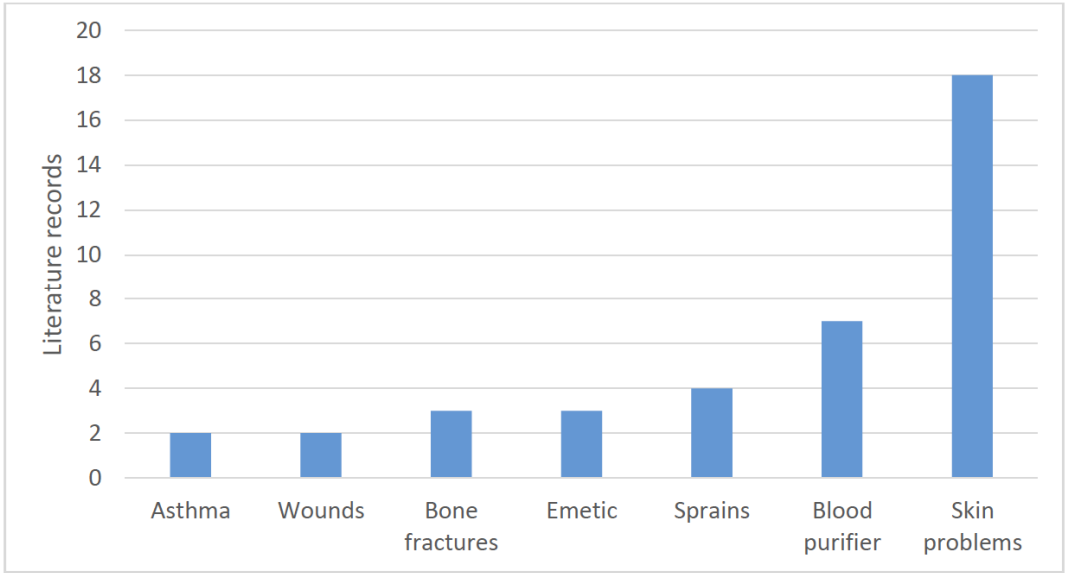

Figure 1: Medicinal applications of *Harpephyllum caffrum* derived from literature records.

(Table **2**). Cardanols, fatty acid esters, flavonoids, phenolics and triterpenoids have been isolated from the fruits, leaves and stem bark of *H. caffrum* (Table **3**). Some of these phytochemical compounds may be responsible for the biological activities associated with the species.

Table 2: Nutritional Composition of *Harpephyllum caffrum* Fruits (after Wehmeyer [8] and Moodley *et al*. [49]

Nutritional composition	Values
Ash (g/100g)	0.8
Calcium (mg/100g)	47.0 – 115.8
Carbohydrates (g/100g)	9.1
Chromium (mg/20 g dry mass)	0.1
Cobalt (mg/20 g dry mass)	0.003
Copper (mg/100g)	0.1 – 0.4
Crude fibre (g/100g)	1.7
Energy kj/100g	172.0
Fat (g/100g)	0.2
Iron (mg/100g)	0.6 – 2.9
Magnesium (mg/100g)	23.7 – 26.4
Manganese (mg/20 g dry mass)	0.2
Moisture (g/100g)	87.5
Nickel (mg/20 g dry mass)	0.08
Phosphorus (mg/100g)	13.3
Potassium (mg/100g)	254.0
Protein (g/100g)	0.7
Sodium (mg/100g)	5.7
Thiamin (mg/100g)	0.1
Vitamin C (mg/100g)	70.7
Zinc (mg/20 g dry mass)	0.1 - 0.3

Pharmacological Properties of *Harpephyllum caffrum*

Pharmacological studies on *H. caffrum* leaf and stem bark extracts and compounds isolated from the species exhibited potent *in vitro* and *in vivo* pharmacological activities such as acetylcholinesterase [53], analgesic [21,36], antibacterial [21,40,45,57-61], anticonvulsant [36], antimycobacterial [62], antifungal [21,40,55,58-60,63-65], anti-HIV [66], anti-inflammatory [21,39,54,59,67], antioxidant [50,51,53,56,61,67], antipyretic [21], melanogenesis and antityrosinase [68,69], hypoglycaemic and hypotensive [70], hepatoprotective [21] and cytotoxicity [21,51,55,67,69] activities.

Acetylcholinesterase Activities

Moyo *et al*. [53] evaluated the inhibition of acetylcholinesterase activities of dichloromethane, methanol and petroleum ether leaf and stem bark extracts of *H. caffrum* using the micro-plate assay with galanthamine as a positive control. The extracts inhibited acetylcholinesterase in a dose-dependent manner with the half maximal inhibitory concentration (IC_{50}) values of methanol stem bark and leaf extracts being 0.02 mg/ml and 0.1 mg/ml, respectively [53].

Analgesic Activities

Ojewole and Amabeoku [36] evaluated the analgesic activities of stem bark aqueous extracts of *H. caffrum* by administering 50 mg/kg to 800 mg/kg body weight extract using hot-plate and acetic acid analgesic test methods. The extract exhibited dose-dependent and significant analgesic activities against thermally and chemically-induced nociceptive pain in mice [36]. Shabana *et al*. [21] evaluated the analgesic activities of leaf ethanol extracts of *H. caffrum* by assessing the minimum voltage required for adult male albino rats to emit a cry after one and two hour of oral administration of 50 mg/kg, 75 mg/kg and 100 mg/kg body weight of the extract. The extract exhibited analgesic activities [21].

Antibacterial Activities

McGaw *et al*. [57] evaluated the antibacterial activities of aqueous, ethanol and hexane bark extracts of H. caffrum against *Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus aureus* using the disc-diffusion assay with neomycin (5 μg) as the positive control. All extracts were active against *Bacillus subtilis* with minimum inhibitory concentration (MIC) values ranging from 0.1 mg/ml to 1.6 mg/ml, however, only ethanol extract was active against the rest of the tested pathogens with MIC values ranging from 1.6 mg/ml to 3.1 mg/ml [57]. Buwa and Van Staden [40,58] evaluated antibacterial activities of water and ethanol bark extracts of *H. caffrum* against *Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus aureus* using the microplate method with neomycin as a positive control. The extracts exhibited activities with MIC values ranging from 0.1 mg/ml to 1.6 mg/ml [40,58]. Moyo *et al*. [59] evaluated antibacterial activities of dichloromethane, ethanol and petroleum ether leaf and twig bark of *H. caffrum* against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli* and *Klebsiella pneumoniae* using the micro-dilution assay with

Table 3: Phytochemical Composition of *Harpephyllum caffrum*

Phytochemical composition	Plant parts	References
1-hydroxy-3-[(Z)-12'-nonadecenyl] benzene	Stem bark	[50]
1-hydroxy-3-[(Z)-12'-heptadecenyl] benzene	Stem bark	[50]
1-hydroxy-3-heptadecanyl benzene	Stem bark	[50]
1-hydroxy-3-pentadecanyl benzene	Stem bark	[50]
1,3-di-O-galloyl glucose	Leaves	[51]
2,3-di-Ogalloyl glucose	Leaves	[51]
3-acetyl methyl betulinate	Leaves	[21]
3,3″-dimethoxy ellagic acid 4-O-glucoside	Leaves	[51]
3,3′,4-trimethoxyellagic acid	Leaves	[51]
3-methoxyellagic acid 4-O-β- galactopyranoside	Leaves	[51]
3-methoxy gallic acid	Leaves	[51]
3-methoxy gallic acid 5-sodium sulfate	Leaves	[51]
Apigenin-7-glucoside	Leaves	[52]
Apigenin-7-O-α-glucoside	Leaves	[21]
Betulonic acid	Leaves	[21]
(+)-catechin	Fruits and stem bark	[50]
eicosanyl-trans-p-coumarate	Stem bark	[50]
Ethyl gallate	Leaves	[21]
Gallic acid	Leaves	[21,51,52]
Gallotannins (mg GAE/g)	Leaves and stem bark	[53]
Gentesic acid 2-O-glucoside	Leaves	[51]
Gentesic acid 5-O-glucoside	Leaves	[51]
Hendecane	Leaves	[21]
Kaempferol	Leaves	[21,51,52]
Kaempferol 3-rhamnoside	Leaves	[52]
Kaempferol 3-galactoside	Leaves	[52]
Kaempferol-3-O-α-rhamnoside	Leaves	[21]
Kaempferol-3-O-β-(2″-sulphatogalactopyranside)	Leaves	[51]
kaempferol 3-O-galactoside	Leaves	[51]
Kaempferol-3-O-β-galactoside	Leaves	[21]
kaempferol 3-O-rhamnoside	Leaves	[51]
Lupenone	Leaves	[21]
Lupeol	Fruits and leaves	[21,50]
Methyl gallate	Leaves	[21,52]
Methyl linoleate	Leaves	[21]
p-hydroxybenzoic acid	Leaves	[51]
Proanthocyanidins (%)	Leaves and stem bark	[53]
Protocatechuic acid	Leaves	[51,52]
Quercetin	Leaves	[21,51,52]
Quercetin 3-arahinoside	Leaves	[52]
Quercetin 3-glucoside	Leaves	[52]

(Table 3). Continued.

Phytochemical composition	Plant parts	References
Quercetin 3-O-arabinopyranoside	Leaves	[51]
Quercetin-3-O-β-arabinoside	Leaves	[21]
Quercetin 3-O-galactoside	Leaves	[51]
Quercetin 3-O-rhamnoside	Leaves	[21,51]
Quercetin 3-rhamnoside	Leaves	[52]
Quercetin 3-O-β-(2″-sulphatogalactopyranoside)	Leaves	[51]
β-sitosterol	Fruits	[50]
Total flavonoid content (mg QE/g)	Leaves	[54,55]
Total flavonoids (mg CE/g)	Leaves and stem bark	[53]
Total phenolic content (mg GAE/g)	Leaves	[54,55]
Total phenolics (mg GAE/g)	Leaves and stem bark	[53,56]

neomycin (100 μg/ml) as a positive control. The extracts exhibited activities with MIC values ranging from 0.2 mg/ml to 6.3 mg/ml while the minimum bacterial concentration (MBC) values ranging from 1.6 mg/ml to >12.5 mg/ml [59]. Shabana *et al*. [21] evaluated antibacterial activities of leaf ethanol extracts of *H. caffrum* against *Bacillus subtilis*, *Streptococcus faecalis*, *Staphylococcus aureus, Escherichia coli*, *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae* with ofloxacin as a positive control. The extracts exhibited activities against all tested pathogens with zone of inhibition ranging from 12 mm to 16 mm against 33 mm to 42 mm exhibited by the control [21]. Mabona *et al*. [60] evaluated antibacterial activities of aqueous and dichlomethane : methanol (1:1) bark and leaf extracts of *H. caffrum* using the microtiter plate dilution technique against dermatologically relevant pathogens such as *Brevibacillus agri, Propionibacterium acnes, Pseudomonas aeruginosa, Staphylococcus aureus* and *Staphylococcus epidermidis* with ciprofloxacin as the positive control and acetone and dimethyl sulfoxide (DMSO) as negative controls. The extracts showed activities with MIC values ranging from 0.2 mg/ml to 2.0 mg/ml [60]. Sharma and Lall [61] evaluated antibacterial activities of ethanol leaf extracts of *H. caffrum* against *Propionibacterium acnes* using a microdilution assay. The extract exhibited activities with MIC values of 125 μg/mL [61]. Kambizi [45] evaluated antibacterial activities of aqueous bark extracts of *H. caffrum* against *Staphylococcus aureus*, *Staphylococcus epidermis*, *Bacillus cereus*, *Micrococcus kristinae*, *Streptococcus faecalis, Escherichia coli*, *Pseudomonas aeruginosa*, *Shigella flexneri*, *Klebsiella pneumoniae* and *Serratia marcescens* using agar diffusion method. The extract was active against all tested pathogens with the exception of *Micrococcus kristinae* with MIC values ranging from 1.0 mg/mL to 1.0 mg/mL [45].

Anticonvulsant Activities

Ojewole and Amabeoku [36] evaluated the anticonvulsant activities of stem bark aqueous extracts of *H. caffrum* by administering 50 mg/kg to 800 mg/kg body weight extract intraperitoneally against pentylenetetrazole (PTZ, 90 mg/kg) and picrotoxin (PCT, 10 mg/kg) induced seizures in Balb C mice. The 100 mg/kg to 800 mg/kg body weight extract exhibited dose-dependent activities and significantly delayed the onset of seizures and profoundly antagonized PTZ and PCT-induced seizures [36].

Antimycobacterial Activities

Kabongo-Kayoka *et al*. [62] evaluated antimycobacterial activities of leaf extracts of *H. caffrum* 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 0.1 mg/ml to 0.2 mg/ml [62].

Antifungal Activities

Buwa and Van Staden [40,58] evaluated antifungal activities of water and ethanol bark extracts of *H. caffrum* against *Candida albicans* using the microplate

method with neomycin as a positive control. The extracts exhibited activities with MIC values ranging from 1.0 mg/ml to 2.9 mg/ml [40,58]. Moyo *et al*. [59] evaluated antifungal activities of dichloromethane, ethanol and petroleum ether leaf and twig bark of *H. caffrum* against *Candida albicans* using the micro-dilution assay with amphotericin B (0.25 mg/ml) as a positive control. The extracts exhibited activities with the MIC values ranging from 3.1 mg/ml to 4.7 mg/ml while the minimum fungicidal concentration (MFC) values ranged from 3.1 mg/ml to 6.3 mg/ml [59]. Mahlo *et al*. [63,64] evaluated antifungal activities of acetone, methanol, hexane and dichloromethane leaf extracts of *H. caffrum* against *Aspergillus fumigatus* using micro-dilution assay with amphotericin B and 100% acetone as positive and negative controls, respectively. The extracts exhibited activities against all tested fungi species with MIC values ranging from 0.02 mg/mL to 2.50 mg/mL [63,64]. Shabana *et al*. [21] evaluated antifungal activities of leaf ethanol extracts of *H. caffrum* against *Candida albicans* and *Aspergillus flavus* using the agar diffusion method with fluconazole as a positive control. The extract exhibited activities against *Candida albicans* with zone of inhibition of 12 mm against 10 mm exhibited by the positive control [21]. Mabona *et al*. [60] evaluated antifungal activities of aqueous and dichlomethane : methanol (1:1) bark and leaf extracts of *H. caffrum* using the microtiter plate dilution technique against dermatologically relevant pathogens such as *Candida albicans, Microsporum canis* and *Trichophyton mentagrophytes* with amphotericin B as the positive control and acetone and DMSO as negative controls. The extracts showed activities with MIC values ranging from 0.3 mg/ml to 4.0 mg/ml [60]. Mahlo *et al*. [65] evaluated antifungal activities of acetone, methanol, hexane and dichloromethane leaf extracts of *H. caffrum* against *Aspergillus niger, Aspergillus parasiticus, Colletotricum gloeosporioides, Fusarium oxysporum, Penicillium expansum, Penicillium janthinellum* and *Trichoderma harzianum* using micro-dilution assay with amphotericin B and 100% acetone as positive and negative controls, respectively. The extracts exhibited activities with MIC values ranging from 0.2 mg/ml to 2.5 mg/ml and total activities ranging from 10 ml/g to 407 ml/g [65]. Mongalo *et al*. [55] evaluated antifungal activities of aqueous and organic leaf extracts of *H. caffrum* against *Furasium verticillioides, Fusarium oxysporum, Fusarium graminearum, Aspergillus parasiticus, Aspergillus flavus* and *Aspergillus ochraceous* using micro-dilution assay with amphotericin B as a positive control. The extracts exhibited activities with MIC values ranging from 0.02 mg/ml to 4.7 mg/ml [55].

Anti-HIV Activities

Mkhize [66] evaluated anti-HIV activities of dichloromethane and methanol leaf and stem extracts of *H. caffrum* using *in vitro* non-radioactive HIV-RT colorimetric ELISA assay and cell-based 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenyloamino)carbonyl]-2*H*-tetrazolium hydroxide (XTT) assay. The leaf extract exhibited inhibition of the recombinant HIV-RT at an average of 81% at a concentration of 500 μg/mL [66].

Anti-Inflammatory Activities

Jäger *et al*. [39] evaluated anti-inflammatory activities of aqueous and ethanolic leaf extracts of *H. caffrum* in an *in vitro* assay for cyclooxygenase (COX) inhibitors with indomethacin (0.5μg) as the positive control. The ethanolic extract showed inhibition of 93% which was higher than 66.5% inhibition exhibited by the indomethacin control [39]. Moyo *et al*. [59] evaluated anti-inflammatory activities of dichloromethane, ethanol and petroleum ether leaf and twig bark of *H. caffrum* by assessing the ability of extracts to inhibit cyclooxygenase-1 and -2 (COX-1 and COX-2) enzymes. For all extracts, petroleum ether and dichloromethane fractions showed high COX-1 enzyme inhibition of 90.7% to 99.8% and 69.0% to 92.6% inhibition against COX-2 enzyme [59]. Adebayo *et al*. [54] evaluated the anti-inflammatory activities of acetone leaf extracts of *H. caffrum* by assessing the ability of extracts to inhibit 15-lipoxygenase (15-LOX) enzyme with quercetin as a positive control. The extract exhibited activities with IC50 value of 40.0 μg/mL which was higher than IC_{50} value of 8.8 μg/mL exhibited by the positive control [54]. Twilley *et al*. [67] evaluated anti-inflammatory activities of ethanol leaf extracts of *H. caffrum* using the cyclooxygenase-2 (COX-2) assay. At 10 μg/ml, the extract exhibited COX-2 inhibition of 77.5% and IC_{50} value of 6.4 μg/ml [67]. Shabana *et al*. [21] evaluated the acute anti-inflammatory activities of leaf ethanol extracts of *H. caffrum* using carrageenan-induced paw edema models in doses of 50 mg/kg, 75 mg/kg and 100 mg/kg body weight of adult male albino rats. The extract exhibited activities approximated to be 80% of that of indomethacin at the experimental dose level [21].

Antioxidant Activities

Moyo *et al*. [53] evaluated antioxidant activities of dichloromethane, methanol and petroleum ether leaf and stem bark extracts of *H. caffrum* using the 2,2-diphenyl-1-picryhydrazyl (DPPH) free radical

scavenging, ferric-reducing power, β-carotene/linoleic acid model assays with ascorbic acid and butylated hydroxytoluene (BHT) as positive controls. The extracts exhibited activities with half maximal effective concentration (EC50) values in the DPPH ranging from 4.3 μg/ml to 6.9 μg/ml which was comparable to 6.9 μg/ml exhibited by the control, ascorbic acid. A dose dependent linear curve was obtained for all extracts in the ferric-reducing power assay. Similarly, the extracts exhibited high antioxidant activities comparable to BHT based on the rate of β-carotene bleaching of 84.1% to 93.9% [53]. Nawwar *et al*. [51] evaluated the antioxidant activities of aqueous methanol leaf extracts and the compound kaempferol 3-O-β-(2″-sulphatogalactopyranoside) isolated from *H. caffrum* using the DPPH free radical scavenging and oxygen radical absorbance capacity (ORAC) assays with ascorbic acid as a positive control. The ORAC assay demonstrated antioxidant capacity of both the crude extract and the compound kaempferol 3-O-β-(2″-sulphatogalactopyranoside), while the crude extract completely inhibited DPPH absorbance at a concentration of 77 μl exhibiting 94.2% inhibition which was comparable to 98.3% exhibited by ascorbic acid, the positive control. The IC50 values of the extract and ascorbic acid were 8.4 μg/ml and 1.8 μg/ml, respectively [51]. Moodley *et al*. [50] evaluated antioxidant activities of the compounds β-sitosterol, lupeol, (+)-catechin, 1-hydroxy-3-[(Z)-12'-nonadecenyl] benzene, 1-hydroxy-3-[(Z)-12'-heptadecenyl] benzene, 1-hydroxy-3-heptadecanyl benzene, 1-hydroxy-3-pentadecanyl benzene and eicosanyl-trans-p-coumarate using the ferric reducing antioxidant power (FRAP) and DPPH free radical scavenging assays with ascorbic acid as the positive control. The results showed the reducing power of all compounds which increased with increasing concentration. In DPPH, at 250 μg/mL, β-sitosterol and lupeol showed no activities, while (+)-catechin exhibited scavenging ability of 97.9%, eicosanyl-trans-p-coumarate (29.7%) and the rest of the compounds exhibited 15.3% [54]. Sharma and Lall [61] evaluated antioxidant activities of ethanol leaf extracts of *H. caffrum* using the DPPH free radical scavenging assay with vitamin C as a positive control. The extract exhibited activities with EC_{50} value of 2.6 μg/mL which was comparable to EC_{50} value of 2.0 μg/mL which was exhibited by the positive control [61]. Makhafola *et al*. [56] evaluated the antioxidant activities of methanolic leaf extracts of *H. caffrum* using the DPPH free radical scavenging assay with ascorbic acid as the positive control. The extract exhibited activities with EC_{50} value of 1.5 μg/mL, which was comparable to EC_{50} value of 2.3 μg/mL exhibited by ascorbic acid, the positive control [56]. Twilley *et al*. [67] evaluated antioxidant activities of ethanol leaf extracts of *H. caffrum* using the DPPH radical scavenging and nitric oxide (NO) radical scavenging assays with ascorbic acid as a positive control. The extract exhibited good DPPH scavenging activities with an IC_{50} value of 2.4 μg/ml while NO scavenging activities exhibited IC_{50} value of 248.0 μg/ml [67].

Antipyretic Activities

Shabana *et al*. [21] evaluated the antipyretic activities of leaf ethanol extracts of *H. caffrum* by assessing the rise of temperature of adult male albino rats at zero time and after one and two hours of oral administration of 50 mg/kg, 75 mg/kg and 100 mg/kg body weight of the extract. The extract exhibited antipyretic activities [21].

Melanogenesis and Antityrosinase Activity

Lall *et al*. [68] evaluated the antityrosinase activities of ethanol bark and leaf extracts of *H. caffrum* using the tyrosinase enzyme assay with L-tyrosine and L-DOPA as substrates with kojic acid as a positive control. The leaf and bark extracts showed inhibition of the enzyme by 90% and 92% at 0.25 mg/ml, respectively when using L-tyrosine as substrates. The leaf extracts at a concentration of 0.5 mg/ml had an inhibitory effect of 70% on tyrosinase when L-DORA was used as a substrate. Lall *et al*. [68] evaluated the effect of bark and leaf extracts on melanin production and their cytotoxicity on melanocytes *in vitro*. The IC_{50} values for both extracts was found to be 0.002 mg/ml for melanocyte cells. The bark and leaf extracts showed 26% and 20% reduction respectively in the melanin content of melanocyte cells at a concentration of 0.006 mg/ml [68]. Mapunya *et al*. [69] evaluated the melanogenesis and antityrosinase activities of ethanol bark and leaf extracts of H. caffrum using the tyrosinase enzyme assay with L-tyrosine and L-DOPA as substrates with kojic acid as a positive control. The leaf and bark extracts showed inhibition of the enzyme by 90% and 92% at 500 μg/mL, respectively when using L-tyrosine and L-DOPA as substrates. The IC_{50} of the leaf and bark extracts were 51.0 μg/mL and 40.0 μg/mL, respectively. Mapunya *et al*. [69] also evaluated the effect of ethanol bark and leaf extracts on melanin biosynthesis by mouse melanocytes. The bark extract showed 26% reduction in melanin content of melanocyte cells at a concentration of 6.25 μg/mL [69].

Hypoglycaemic and Hypotensive Activities

Ojewole [70] evaluated hypoglycaemic and hypotensive activities of stem bark aqueous extracts of

H. caffrum using normal and diabetic rats in a streptozotocin (STZ)-induced diabetes mellitus model with chlorpropamide (250 mg/kg po) as a reference drug. Acute oral administrations of the extract at 50 mg/kg po to 800 mg/kg po caused dose-dependent hypoglycaemia in normal and STZ-treated diabetic rats. Acute intravenous administrations of the extract at 25 mg/kg iv to 400 mg/kg iv caused dose-dependent reductions in systemic arterial blood pressures and heart rates of the hypertensive, Dahl salt-sensitive rats [70].

Hepatoprotective Activities

Shabana *et al*. [21] evaluated the hepatoprotective activities of leaf ethanol extracts of *H. caffrum* by administering a daily dose of 50 mg/kg, 75 mg/kg and 100 mg/kg body weight of adult male albino rats for one month before induction of liver damage and administration of the tested solution was continued after liver damage for another one month. The authors measured the aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) enzymes serum levels. Hepatic protection was evidenced by the ability of the extracts to normalize the high enzyme parameters in a dose-dependent manner by 100% for AST, 64% for ALT and 50% [21].

Cytotoxicity Activities

Nawwar *et al*. [51] evaluated the cytotoxicity activities of aqueous methanol leaf extracts and the compound kaempferol 3-O-β-(2″-sulphatogalactopyranoside) isolated from *H. caffrum* by assessing the effect of the extract on the UV induced production of the proinflammatory cytokin IL-6 and of IL-8 by HaCaT (human adult low calcium high temperature) keratinocyte cells. The extract was found to diminish UV phototoxic reaction of keratinocytes but the compound kaempferol 3-O-β-(2″-sulphatogalactopyranoside) did not interact with UVB triggered IL-6 production of HaCaT keratinocytes [51]. Shabana *et al*. [21] evaluated cytotoxicity activities of leaf ethanol extracts of *H. caffrum* against human tumor cell lines: liver carcinoma (HEPG2), colon carcinoma (HCT116) and larynx carcinoma (HEP2) cell lines using the sulforhodamine B stain (SRB) assay with doxorubicin as a positive control. The extracts exhibited activities with IC_{50} values ranging from 1.2 μg/ml to 3.6 μg/ml while the positive control exhibited IC_{50} values ranging from 0.4 μg/ml to 0.7 μg/ml [21]. Mapunya *et al*. [69] evaluated the cytotoxicity activities of ethanol bark and leaf extracts of H. caffrum on the mouse melanocytes (B16-F10) cells using the 2,3-Bis-(2-methoxy-4-nitro-5-sulfophenyl]-2Htetrazolium-5-carboxyanilide salt (XTT) cytotoxicity assay. Bark extracts showed low toxicity effect on melanocyte cells at all concentrations tested with cell viability above 80%, however, leaf extracts showed toxicity to melanocytes cells at a concentration of 100 μg/mL [69]. Twilley *et al*. [67] evaluated cytotoxicity activities of ethanol leaf extracts of H. caffrum against human melanoma (A375), epidermoid carcinoma (A431), cervical epithelial carcinoma (HeLa) and human embryonic kidney cells (HEK-293) using the XTT assay with actinomycin D as a positive control. The extract exhibited low toxicity with IC_{50} values ranging from 62.5 μg/ml to 135.0 μg/ml [67]. Mongalo *et al*. [55] evaluated cytotoxicity activities of methanol: dichloromethane (1:1) against the Bovine dermis and Vero cells using the tetrazolium-based colorimetric (MTT) assay. The extracts exhibited median lethal dose (LD_{50}) values of 0.2 mg/mL and 0.3 mg/mL against Bovine dermis and Vero cell lines, respectively and the selectivity index (SI) ranged from 0.2 to 2.9 [55].

CONCLUSION

Harpephyllum caffrum is a well-known fruit and medicinal plant species in Southern Africa. It is also an important component of indigenous and traditional pharmacopeia in Southern Africa and folk medicine is regarded as an important part of indigenous culture in the region. In many cases, different plant parts such as bark, fruits and roots are used to manage and treat several human diseases. Detailed phytochemical evaluations of these are lacking although cardanols, fatty acid esters, flavonoids, phenolics and triterpenoids have been identified from the fruits, leaves and stem bark of H. caffrum. The studies focusing on biological activities of *H. caffrum* crude extracts and compounds isolated from the species have been conducted in *in vitro* and *in vivo*. *Harpephyllum caffrum* should be subjected to a detailed phytochemical, pharmacological and toxicological evaluations aimed at correlating its medicinal uses with its phytochemistry and pharmacological activities of the species.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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