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A REVIEW OF THE MEDICINAL PROPERTIES AND APPLICATIONS OF *Pycnanthus angolensis* (WELW) WARB

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Abstract

Pycnanthus angolensis (also known as African/false nutmeg) is native to the forest zones of West Central Africa. Its use in folklore for the cure of diseases is well documented. Data collected from several references from various research groups in the literature confirm its wide spread use in folk medicine. Among the ailments purported to be cured or controlled by extracts of the plant include diabetes, cognitive disorders, cancer, osteoarthritis, to assuage inflammation, fight microbial infection and for wound healing. Extensive investigative work conducted on the plant exposing its rich phytochemical profile probably provides clue to its value as an important medicinal plant. Over 50 phytochemicals have been isolated from the plant some of which are potential new drug leads. The current review presents the ethnobotanical uses of *Pycnanthus angolensis* through some evaluated biological activities of various extracts on different models to the numerous chemical compounds isolated from the plant. It concludes by succinctly touching on the current and future perspectives of the plant.

Keywords: *Pycnanthus angolensis*, medicinal plant, folklore, biological activities, phytochemical profile

Introduction

The Magnonliflorae super-order to which *Pycnanthus angolensis* (Myristicaceae) belong comprises 19 genera of trees and shrubs and 380 species of lowland rainforest trees distributed in Asia (four genera), Africa and Madagascar (nine genera) and America (six genera). Morphologically, the *Myristicaceae* which are easily recognizable on the fields by their straight trunks, characteristic blood-like sap exudates, few leaves and nutmeg-like fruits are considered one of the most primitive of the Angiosperms. They have simple alternate stipules, habitually dark green and leathery leaves with tiny male or female petalless flowers on different trees [1]. Male flowers have 2 to 20 united stamens while female flowers have a single ovary with one ovule (potential seed). A fleshy covering, known as an aril, surrounds the fluted seed. The fruits are yellowish-red, ovoid, drupes, with laciniate seed almost obovoid-globose to base embedded in a fleshy aril. An evergreen tree, *P. angolensis* may attain a height of 40 m and girth of 150 cm. It flowers in October and November, at the same time as the previous year's fruits are ripening. The fruits remain on the tree until about February. Dehiscence takes place on the tree, but many of the fruit clusters fall unopened [2]. *P. angolensis* is native to the forest zones of tropical Africa with a geographical distribution stretching across western Africa from Guinea to Cameroon, including the countries of Sierra Leone, Liberia, Cote D'Ivoire, Ghana, Togo, Benin, Nigeria, Equatorial Guinea, Angola and Uganda.

Folkloric uses

The medical importance of the plant has long been recognized and at present scientific research is rife on its therapeutic utility because traditional healers and ethnobotanists have ascribed numerous health benefits to the use of the plant. Literature is replete with numerous health benefits linked to the use of different parts of *P. angolensis* including but not limited its role in fighting hyperglycaemia, sterility in women, as an antimicrobial agent, analgesic, anthelmintic, antidote for poisoning, anti-bleeding agent, anti-inflammatory and pain soothing agent. At least there exists substantial anecdotal evidence supporting the health benefits of the various preparations of the plant either alone or in combination with other agents some of which have been summarized in table 1. Indeed numerous scientific studies seem to suggest that some of these claims may be accurate.

Major chemical constituents

In order to evaluate the potential of *P. angolensis* as a source of additional bioactive compounds, various parts of the plant have been investigated and important compounds with high therapeutic potentials reported some of which have been discussed below and summarised in table 2.

Flavonoids

P. *angolensis* is known to elaborate a number of flavonoid compounds including the flavonones genkwainin [3,4], 8-hydroxykanzakiflavone-2 [4], liguiritigentin [5] (–)-epicatechin and (+)-catechin [6]. Isoflavonoids established to be present in *P. angolensis* are biocchanin A [3,5,7,8], formononetin [4,5,7,9-11], 7, 4'-dimethoxy-2'-hydroxyisoflavone [5,10], prunetin [3,5], calycosin [3], irilone [5,8], tectorigenine, genistein, and 2'-hydroxybiochanin A [5]. Mansoor et al, 2011, studied the cytotoxic effects of some nine flavonoid compounds isolated from *P. angolensis* against hepatoma HuH-7 cells (at a concentration 20μM) and reported that genetisin exhibited the highest cytotoxicity of 50% when compared with the control compound used. Furthermore, when screened against a panel human hepatoma HuH-7 cells for apoptosis induction, most of these isoflavonoids exhibited higher potency than acclaimed control compounds used [5]. Other useful bioactivities of some of these flavonoids and isoflavonoids have been reported elsewhere [8].

Flavonoids are polyphenolic compounds possessing 15 carbon atoms; two benzene rings joined by a

linear three carbon chain. The six major subgroups of flavonoids include: chalcones, flavones, flavonols, flavanones, anthocyanins and isoflavonones. Flavonoids are widely valued as nutraceutical and cosmeceutical phytonutrients, which are based on their antioxidant activity. Flavonoids have long been known to exhibit several pharmacological properties; acting as anti-allergenic, anti-inflammatory, antiviral, antiproliferative, anti-cancer, antibacterial, vasodilatory, and antioxidative properties [12,13]. Flavonoids have also been proven to be good photo-protective shields against UV and ionizing radiations [14]. Circumstantial evidence exist supporting the relationships between the intake of flavonoids and reduced risk of coronary heart disease [15], neurodegenerative disorders [16] lung cancer [17,18], stomach and other forms of cancer [18]. In particular, isoflavonoids have been identified as chemopreventive against various types of cancer and cardiovascular diseases [19,20]. We have previously demonstrated that the structure of flavonoids extracted from citrus and other plants is related to their antioxidant, anti-proliferative and anti-metastatic properties [21-23]. Furthermore, our team have shown the antiproliferative action of several phenolic and ploy hydroxylated flavonoids on metastatic melanoma B16F10 and melan-a melanocyte cell lines [24-27]

Fatty acids

Some fatty acids are common plant and animal constituents and usually exist *in vivo* as esters. Some of these fatty acids are known to have diverse and potent biological activities. The fatty acid constituents of *P. angolensis* have been studied in detail. In addition to medically important myristoleic acid (9-tetradecenoic acid), lauric, oleic, palmitic acids and myristic acid (tetradecanoic acid) have been characterized from the seeds of *P. angolensis* [9,28].

Leonard and Simonton, 2010 demonstrated the effectiveness of cetyl myristoleate (CMO), a derivative of myristeoleic acid, in the treatment of osteoarthritis, joint inflammatory diseases of musculoskeletal system and other stress related traumas in animals preferably in equines. In a randomised controlled double-blind study, myristeoleic acid formulated to CMO was compared with phenylbutazone in subjects with rheumatoid arthritis. CMO was found to significantly improve morning stiffness, walking time and joint swelling, however, its effects were less than that elicited by phenylbutazone. A substantial drop in knee pain and disability due to osteoarthritis was observed during a randomised, double-blind placebo, controlled crossover study of 42 patients [28,29].

Myristoleic acid, identified as a cytotoxic component in *Serenoa repens* extracts has been found to induce apoptosis and necrosis in human prostate cancer LNCaP cells. Treating LNCaP cells with 130 mg/ml *S. repens* extract or 100 mg/ml myristoleic acid for 24 hr produced a proportion of 16.5 and 8.8%, apoptotic cells and 46.8 and 81.8% necrotic cells respectively. Thus, the extract from *S. repens* and myristoleic acid seems to induce both apoptosis and necrosis in LNCaP cells at the same time. When another prostatic cell line (PC-3 cells) was used in place of LNCaP cells, apoptotic/necrotic cell death was also observed after treatment with the extract [30,31]. Furthermore, myristeoleic acid a by-product of cheese has been shown to be one of three by-products effective at inhibiting *in vivo Candida albicans* germination with a minimum inhibitory concentration (MIC) of 9µM [32]. Moreover, a massive body of overriding evidence has been presented to show CMO can reduce disability related to migraine headaches, psoriasis broad-spectrum anti-inflammatory and analgesic applications [29].

P. angolensis presents a very important vegetable source of myristoleic acid which was formally largely obtained from ovine and porcine sources. The presence of myristoleic acid in commercially viable amounts in the seed fats of *P. angolensis* is significant in the sense that it satisfies all classes of users; animal sources raises debut in the minds of some users as to whether the product meets kosher and/or halal requirements. Besides, fatty acids sourced from land animal or marine animal origins

are non-vegetarian and when sourced from beef tallow run the risk, although slight, of inducing bovine spongiform encephalitis (mad-cow disease) [28].

Terpenes and Sesquiterepene

Terpenes represent a large group of compounds responsible for the fragrance of plants and comprise the so called essential oil fraction. They differ structurally from fatty acids in that they are branched and cyclized. When additional elements, such as oxygen, are added they are called *terpenoids*. Terpenes particularly triterpenes are known to display a wide spectrum of biological activities including anitumour, antiviral, bactericidal, fungicidal, analgesic, anti-inflammatory spermicidal and cytotoxic activities [33]. Simic et al, (2006) analysed the volatile oils from the stem bark of *P. angolensis* and isolated a number of compounds with the major constituents being; α-bergamotene (25.1%), terpinen-4-ol (16.6%), α-terpineol (15.6%), trans β-bergamotene (12.9%), α--curcumene (6%), piperitone (4.5%) and β-farnesene (4%). Other constituents include borneol (2.8%), bornyl acetate (1.6%), β-santalene (0.6%), acoradene (0.3%), β-bisabolene (3%), δ-cadinene (2.3%), germacrene B (1.0%), cembrene A (1.0%) and farnesyl acetone (2.0%). During screening of the leaf oils, only two compounds, spathulenol (82%) a sesquiterepene alcohol and caryophyllene oxide (14%) a sesquiterepene were detected. The authors further demonstrated the antimicrobial effects of these volatile oils against a panel of bacterial and fungal species. Even though the MICs were not reported, the authors found that the leaf essential oils were in general

see Table 1.

more potent against the bacterial than fungal strains used. On the other hand, the fungal species seemed to succumb more to the essential oils obtained from the plant bark. Further purification of the dicholoromethane extracts of the stem bark afforded the labdane-type diterpene ozic acid ($C_{20}H_{30}O_2$) which demonstrated moderate antiplasmodial activity against Dd2-chloroquine resistant *P. falciparum* strain [34].

Steroids

Chemical investigation into the stem, and roots resulted in the isolation of stigmast-4-en-6β-ol-3-one, stigmasterol [34], β-sitosterol [7,34] and other known non-steroidal compounds. These steroids showed partial *in vitro* suppression of the growth of *Plasmodium falciparum* parasites upon evaluation of their antimalarial activity [34]. Stigmast-4-en-6β-ol-3-one has been found elsewhere to possess potent antitumor-promoting activity [35], while ß-sitosterol has also been implicated in the mitigation of cardiovascular diseases through cholesterol reduction [36].

Cerebrosides (pycnangloside)

A biologically uncharacterised novel molecule, pycnangloside (Fig 1) ($C_{44}H_{85}NO_{10}$), has been structurally elucidated from the bark of *Pycnanthus angolensis* using comprehensive analyses of its 1D and 2D NMR spectroscopic, and ESI mass spectrometric data [7]. The fact that its biological activities remain relatively unknown is ostensibly because it has only recently been reported.

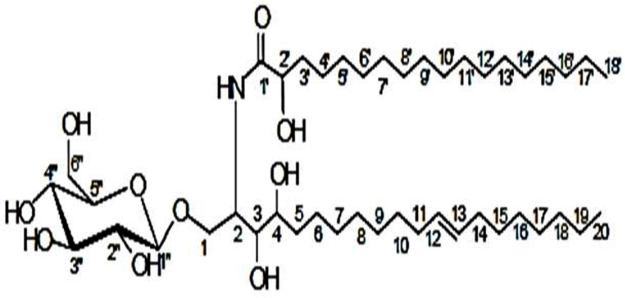

Fig 1: Structure of pycnangloside from Pycnanthus angolensis (adapted from Tsaassi et al, 2010)

Cerebrosides are a family of pharmacologically active and important glycosphingolipids, present in a wide variety of tissues and organs in biological systems. The cerebrosides are currently receiving

attention because of their therapeutic potential including antitumor/cytotoxic and anti-HIV-1 moderating potentials amongst others [37]. Cerebrosides are involved in a very wide range of biological activities such as cell agglutination, intracellular communication, cellular development, and antitumor/cytotoxic effects.

Allantoin

Allantoin ($C_4H_6N_4O_3$) a diuredide of glyoxylic acid has been reported to be present in the bark of *P. angolensis* [10,38,39]. Allantoin is well known for its healing, moisturizing, soothing and anti-irritating, keratolytic and non-toxic effect in dermatological, cosmetic and veterinary preparations. In cosmetology, allantoin is used for sunscreen and skin-care products. It has shown clinical potentials for the treatment of skin ulcers, wounds, scalds, (sun) burns, carbuncles, acne, skin eruptions, fissures, impetigo, eczema and psoriasis. It has also been used in various oral hygiene preparations such as toothpaste and mouthwash as well as in eye drops to treat watering eyes and in ear drops to clean the ear canal. It is effective at quite low concentrations, 0.1% up to 2%.

Lignans

P. angolensis is known to produce lignans in its stems, roots leaves and seed including 3,4-dimethoxy-3',4'-methylenedioxy-7,7'-epoxylignan [3] 4,5-dimethoxy-3',4'-methylenedioxy-2,7'-ycloligna-7,7'-diene, 4'-methoxy-4,5-methylenedioxy-2,7-cyclolign-7-ene4,5-dimethoxy-2,7'-cyclolign-7-en-4'-ol (pycnanthulignene A), [3,4], 2,7-dimethoxy-3,6 dimethylnaphthalene, 4,5-dimethoxy-3',4'-methylenedioxy-2,7'-cyclolign-7-ene (pycnanthulignene B) 3,6-dimethoxy-4,5-methylenedioxy-2,7'-cycloligna-7,7'-dien-4'-ol (pycnanthulignene D), 4'-methoxy-4,5-methylenedioxy-2,7'-cyclolign-7-ene [4], Calopiptin, (12 S, 13 S)-12, 13-dihydroxylabda-8, 14-dien-18-oic acid, (12 R,13 S)-12,13-dihydroxylabda-8 (17),14-dien-18-oic acid, [8], threo-4,4'-dihydroxy-3-methoxylignan (pycnantolol) [34], (–)-dihydroguaiaretic acid, heliobuphthalmin, talaumidin and hinokinin [9,34,40].

Dihydroguaiaretic acid showed non-selective cytotoxicity to a panel of cancer cell lines with an ED_{50} of 1.63 – 3.10 µg/ml [40] and prevented harmful effects of UV [41] which facilitates skin aging. Furthermore, dihydroguaiaretic acid is important for the treatment of shock, neoplasms [42], sepsis, melanoma, and lymphoma [43] and is a promising candidate for the treatment of Alzheimer's disease [44,45]. Working on a different plant Moon *et al*, (2008) isolated meso-dihydroguaiaretic acid from *Saururus chinensis* and showed that it inhibited the cyclooxygenase-2 (COX-2)-dependent phase of prostaglandin D generation in bone marrow-derived mast cells with an IC_{50} of 9.8 µM. However, it did not inhibit COX-2 protein expression in these cells at concentrations up to 30µM, suggesting that the lignan directly inhibits COX-2 activity. In addition, meso-dihydroguaiaretic steadily abrogated the production of leukotriene with an IC_{50} of 1.3 µM demonstrating that it inhibits both COX-2 and 5-lipoxygenase. Furthermore meso-dihydroguaiaretic was found to strongly inhibit the degranulation reaction in bone marrow-derived mast cells with an IC_{50} of 11.4µM providing strong basis for novel anti-inflammatory drug development [46]. Again meso-dihydroguaiaretic acid from the stem bark of *Machilus thunbergii* showed significant matrix metalloproteinase MMP-9 inhibition in human keratinocyte cells caused by ultraviolet irradiation. Moon *et al*, (2005) demonstrated that *meso*-dihydroguaiaretic acid can prevent the harmful effects of UV that lead to skin aging. The authors suggests that *meso*-dihydroguaiaretic acid should be viewed as a potential therapeutic agent for preventing and/or treating premature skin aging [41]. Li *et al.*, (2004) using bioassay-guided fractionation isolated a number of diaryldimethylbutane lignans, of which meso-dihydroguaiaretic acid, inhibited the *in vitro* enzymatic activity of topoisomerase I and II by 93.6 and 82.1% respectively at a concentration of 100 mM [47,48]. Wiart (2006a) notes that the *Myristicaceae* abounds in lignans with

biological activities against topoisomerases and advocates the search for lignans with potent topoisomerase inhibitory activities from amongst the Laurales–Magnoliales plant group. Nono *et al*, 2010, demonstrated that

see Table 2.

pycnanthulignenes A and C possess antibacterial activity against a panel of drug-resistant bacterial and pathogenic fungal strains using gentamicin and nystatin as references for antibacterial and antifungal tests respectively. The MIC values for pycnanthulignenes A varied from 28.7 µM (against S. aureus) to 230.9 µM (against K. pneumoniae and P. aeruginosa) while lowest MIC values of 63.8 µM observed with pycnanthulignenes A were against *S. aureus, E. coli,* and *C. albicans*.

Terpene-type quinones: the Pycnathuquinones

Quinones constitute a structurally diverse class of phenolic compounds with a wide range of pharmacological properties. Terepinoid quinones have frequently been isolated from microorganisms and plants to exploit their antimicrobial, antiviral and anticancer properties. Recently attention has been drawn to their anti-mycobacterial properties. *P. angolensis* is known to elaborate a series of unusual 6, 6, 5-tricyclic geranyltoluquinone terpene-like quinones called pycnanthuquinones (fig 2). A search for physiologically active compounds against diabetes using *in vitro* bioassay-guided fractionations of alcohol extracts of the root and leaves of *P. angolensis* (Warb.) against ob/ob and db/db mice models for type 2 diabetes led to the discovery of two terepene-type quinones, pycnanthuquinones A and B [38,49,50]. Further screening of the stem bark afforded another novel compound; pycnanthuquinones C [8] which was demonstrated to possess antifungal properties using *Trichophyton soudanense* as an experimental model. Recently too, Liard and Co-workers have reported the presence of pycnanthuquinone C in the Western Australian brown alga *Cystophora harveyi* [51] however, in both cases the authors have been silent about the anti-hyperglycemic property of the pycnanthuquinone C. Total synthesis of pycnanthuquinone C has since been achieved in the laboratory via the Diels-Alder type synthesis [52] however, the absolute configuration of the pycnanthuquinones still remain to be established. During the past decade and a half, Fort *et al.*, (2000) have convinced the scientific community that the pycnanthuquinones represent a new class of anti-diabetic compounds which is structurally distinct from the currently available oral type 2 diabetes remedies namely sulfonylureas, biguanides, disaccharidase inhibitors, and thiazolidinediones. Short of clinical data, this could well be the heralding of a new class of drugs for type -2 antidiabetic therapies and a classic case of a modern drug with an origin from ethnopharmacology and traditional medicine; undeniably, numerous drugs have entered the international pharmacopoeia via the study of ethnopharmacology and traditional medicine [53]. Remarkable advances into the study and discovery of these novel class of antidiabetic principles from *P. angolensis* has been extensively expounded elsewhere [38,49,50].

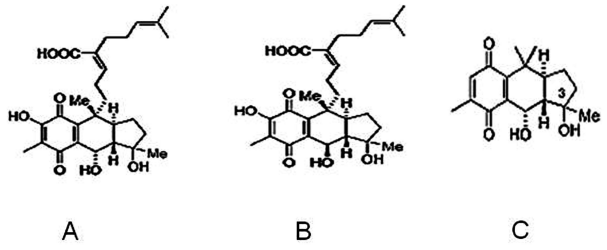

Fig 2: Pycnanthuquinones (A, B and C)

Plastoquinones and Ubiquinones

Fractionation of the crude ethanol extracts of the seed of *P. angolensis* yielded a series of medicinally relevant plastoquinones namely kombic acid, sargahydroquinoic and sargaquinoic acids and sargachromenol (an ubiquinone) [9,54]. The anti-inflammatory, antiproliferative, anti-aging, UV-protecting and anti-oxidative activities of these compounds has been established [55-58]. Further *in vitro* and *in vivo* studies have revealed other bioactivities inherent in them including cholesterol lowe-

ring effects, reduction of elevated plasma levels of Low Density Lipoproteins (LDL) cholesterol, inhibition of inducible nitric oxide synthase (iNOS) and Cyclooxygenase-2 (COX-2) protein expression, inhibition of LPS-induced iNOS and COX-2 mRNA expression.

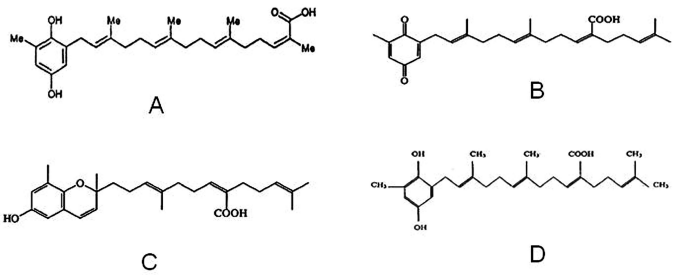

Fig 3: Kombic acid (A), Sargaquinoic acid (B), Sargachromenol (C), Sargahydroqunoic acid (D)

Activity-guided purification of *Sargassum micracanthum* obtained from the Coast of East Sea in Korea led Park et al., (2008) has yielded to a vasodilatatiory constituent sargahydroquinoic acid. The compound induced vasodilatation in the basilar and carotid arteries of rabbits in a concentration-dependent manner. The EC_{50} values for the basilar and carotid arteries were 11.8 ± 0.28 and 140 ± 0.6μM respectively. It selectively dilated the basilar artery more than 10-fold over the carotid artery without lowering systemic blood pressure. This implies that treatment with sargahydroquinoic acid may accelerate cerebral blood flow through dilatation of the basilar artery without influencing systemic blood pressure. The authors suggests that compounds that share a similar core structure with sargahydroquinoic acid, such as plastquinones and hydroquinones may be novel lead compounds for selective pharmacological agents for the human vascular system [59].

The acetylcholinesterase (AChE) and butylcholinesterase (BuChE) inhibitory activities of plastoquinones have been amply demonstrated [60] both sargaquinoic acid and sargachromenol isolated from *Sargassum sagamianum* showed AChE inhibitory activity at micromolar concentrations with IC_{50} 23.2 and 32.7 μM respectively. However, sargaquinoic acid demonstrated higher inhibitory activity on BuChE than on AChE; the observed IC_{50} of 26 nM was 1000-fold greater than the corresponding IC_{50} value for AChE inhibition. BuChE is a new drug target for the treatment of Alzheimer's disease. The authors remark that sargaquinoic acid represents an effective and selective inhibitor of BuChE with potency similar to or greater than the anticholinesterases in current clinical use, making it an interesting potential drug candidate for AD [60]. These results corroborate the findings of Elufioye *et al.*, (2010) following their attempt to find a scientific rationale for the use of extracts of *P. angolensis* for the treatment of cognitive problems in Nigerian folklore.

Only recently, Tchinda *et al.*, (2008) demonstrated the promising anti-diabetic potentials of sargaquinoic acid and sargachromenol sourced from the seeds of *P. angolensis*. While these compounds furnished IC_{50} values of 3 ± 0.123 and 4.6 ± 0.123μM respectively reputed α-glucosidase inhibitors deoxynojirimycin and acarbose had IC_{50} values of 425 ± 8.14μM and 780 ± 28μM.

Glyceryl-1, 3-ditetradecanoate

Tcinida *et al.*, (2008) examined in detail the fruits of *P. angolensis* and reported for the first time, the presence of a diglyceride; glyceryl-1, 3-ditetradecanoate together with two known plastoquinones. The authors further demonstrated the α-glucosidase inhibitory tendencies of these compounds with glycerol-1, 3-ditetradecanoate registering an IC_{50} of 522.0μM. This IC_{50} value compared favourably with deoxynojirimycin a potent α-glucosidase inhibitor which had an IC_{50} of 425 ± 8.14μM, and acarbose a popular drug used for type-2 diabetes therapy which had an IC_{50} of 780 ± 28μM. As indicated above, the plastoquinones proved to be better glycosidase inhibitors compared with the glycerol derivative. These findings led the authors to propose the use of extracts from the fruits of *P. angolensis* for the management of type-2 diabetes and related diseases. In our literature search, the mention of glycerol-1, 3-ditetradecanoate as a potential α-glycosidase (protease) inhibitor was

rare and this could well be one of the pioneering works involving this compound and the moderation type-2 diabetes. Apha-glucosidases are key enzymes catalyzing the final step in the digestive process of carbohydrates. Therefore, α-glucosidase inhibitors can retard the liberation of D-glucose from dietary complex carbohydrates and delay glucose absorption, resulting in reduced postprandial plasma glucose levels and suppression of postprandial hyperglycemia. An effective way to manage non-insulin-dependent diabetes mellitus (NIDDM) then is by inhibiting or reducing the activity of these enzymes (e.g. α-glucosidase and α-amylase) in the digestive organs there by retarding absorption of glucose and decreasing postprandial hyperglycemia. Presently, there is renewed interest in plant-based medicines and functional foods modulating physiological effects in the prevention and cure of diabetes and obesity. The plant kingdom is a wide field to search for natural effective oral hypoglycaemic agents that have slight or no side effects. Therefore, natural alpha-glucosidase and alpha-amylase inhibitors from plant sources offer an attractive strategy for the control of hyperglycaemia [61,62].

Some biological activities of crude extracts from *P. angolensis*

Most investigations regarding the bioactivities of medicinal plants is limited to examination of crude aqueous or organic solvent extracts and in most cases, the investigators have sought to validate the traditional medicinal use of the plant. Various workers using different types of extracts in a bid to assign a scientific rationale for the use of different parts of *P. angolensis* in folklore have demonstrated different important biological activities of the extracts thereby adding confidence to the prescriptions of local herbalist as well as paving the path for the effective screening for therapeutically relevant lead molecules. It is noteworthy to stress that crude plant extracts could be biologically active against a test model(s); however, the observed activity may be significantly reduced or virtually abolished when the compounds are isolated as pure substances as experienced by Abrantes *et al.*, (2008). In this light it seems logical to suggest that it may not always be essential to seek pure compounds to develop a therapeutic agent that requires a synergistic action of some of the natural components of the plant. As a matter of course the biologically active extracts need to be evaluated for general toxicity, since there may be unacceptably low distinctions between toxicity towards the test model and that shown towards the host. Table 2 highlights some biological activities of *P. angolensis* extracts reported in literature which are discussed in more details in the following sections.

Antimicrobial activity

The antimicrobial properties of different crude solvent extracts of *P. angolensis* have been investigated and reported by a number of researchers. Reasonable to significant anti-microbial, antifungal and anti- mycobacterial activities have been reported on these phyto-preparations (crude or fractionated extracts and sometimes individual compounds) under laboratory conditions. The antimicrobial activity of crude ethanol leaf extracts of *P. angolensis* on clinical strains of bacteria and fungi were investigated by Onocha and Otunla, (2010) using the disc diffusion method. The authors demonstrated that the leaves possessed the ability to inhibit the growth of two bacterial and three fungal strains. The mean zones of inhibition produced by the crude ethanol extracts of the leaf at 75 mg/ml was found to be around 15 mm for the bacterial species and 10-20 mm for the fungai while the reference drugs ampicillin and tioconazole at a concentration of 12.5 µg/ml yielded zones of inhibition of 19 mm and 12-16 mm respectively. Similarly Atindehou *et al.*, 2002 have shown that ethanol extracts of the roots of *P. angolensis* do possess some bactericidal properties against gram positive strains of bacteria. With regards to the antimicrobial activity, Oladimeji *et al.*, (2006) showed that leaf extracts and fractions of *P. angolensis* abrogated the *in vitro* survival of *Bacillus subtilis*,

and *Staphylococcus aureus*, were inactive against *Escherichia coli*, *Salmonella typhi* and *Klebsiella pneumonia*; and exhibited activity against the fungal isolates *Aspergilus niger* and *Candida albicans* although the potency in these assays may not have been clinically significant. Purified essential oils from the stem-bark and leaves have proven to have measurable antimicrobial activities against various fungal and bacterial strains [63,64]. The fact that most crude extracts of the plant demonstrated antimicrobial activity probably supports its use by traditional healers for the treatment of microbial infestations.

Antiprotozoal

Several vector-borne tropical diseases are protozoal infections, caused by protozoan parasites which replicate and multiply rapidly inside the host, invade the blood stream and lymphatic vessels or tissues. Some of these diseases, including leishmaniasis, trypansosomias, and malaria, persist without effective treatment. Although many drugs are available, some have become ineffective due to the development drug resistant strains. By far the most important vector-borne protozoal infection is malaria caused by *Plasmodium* parasites which are transmitted through the bite of some species of *Anopheles* mosquitoes.

Traditional remedies are continually being investigated as plant derived antimalarial drugs become more sought after. The anti-plasmodial activities of different extracts of *P. angolensis* have been investigated with promising outcomes. The chloroform and ethanol extracts of its stem-back showed activity against chloroquine-sensitive Plasmodium falciparum strain D6 and the chloroquine-resistant strain W2 with both extracts giving an IC_{50} of less than 25µg/ml [65]. Similarly, Abrantes *et al.*, 2008 showed that the dichloromethane, methanol and aqueous ethanol extracts of the stem bark afforded *in vitro* anti-plasmodial activity against 3D7 *P. falciparum* strain. While crude CH_2Cl_2 extracts produced remarkable activity with an IC_{50} of 1.6 µg/ml, the purified fractions lacked anti-plasmodial activity. Zirihi *et al.* 2005 confirmed that the ethanol extracts of the stem back of this plant possess moderate activity against chloroquine-resistant FcB1/Colombia strain of *Plasmodium falciparum*. In a related study, Do Céu de Madureira *et al.*, (2002) previously demonstrated that crude ethanol extracts of the stem bark of *P. angolensis* cleared female balb/C mice of parasitemia due to *P. berghei* ANKA infection thereby validating the traditional use of pytopreparations from *P. angolensis* against malaria fever.

P. angolensis extracts have shown promising anthelmintic properties. For instance, the crude chloroformic and methanolic extracts of the leaves and methanolic extracts of the stems were found to exhibit *in vitro* anthelmintic activities using *Fasciola gigantica*, *Taenia solium* and *Pheritima pasthuma* as experimental models consistent with the folkloric use of the plant as an anthelminthic [66]. Again, measurable activity was recorded when ethanolic extracts of the roots were evaluated for potential anthelminthic activities against the larvae of *Haemonchus contort* [67]. Similarly methanolic and chloroformic extracts of stem bark exhibited anthelmintic activity when tested *in vitro* against *Eudrilus eugeniae* with the methanolic extract registering a higher potency [68]. *In vitro* anti-leishmanial assay using methanolic extracts of the stem against promastigotes of *L. major* exhibited a leishmanicidal action with an IC_{50} of 70.59µg/ml. On the other hand, the methanolic extracts of the root was not leishmanicidal but cytotoxic while same solvent extracts of the leaves showed neither leishmanicidal nor cytotoxic activity [39]. When the nematicidially active crude fractions of *P. angolensis* (against *C. elegans*) were further fractionated, the lignan dihydroguaiaretic acid, with an LD_{50} of 10µg/ml was obtained [40].

Anticancer/antitumor activity

Cancer is a disease recognised by seven hallmarks: unlimited growth of abnormal cells, self-sufficiency in growth signals, insensitivity to growth inhibitors, evasion of apotosis, sustained angioge-

nesis, inflammatory microenvironment and eventually tissue invasion and metastasis [69,70]. It is estimated that without effective measurement, around 84 million people are likely to die of cancer between 2005 and 2015. Furthermore, in most developed countries, cancer is the second leading cause of death, falling only behind cardiovascular diseases [71] therefore it is important to address this ever-increasing burden. Extracts of *P. angolensis* have demonstrated some antitumor activities in several cancer cell lines. *In vitro* assay for anticancer activity of methanol extracts from the mature stem bark of *P. angolensis* have exhibited cytotoxicity and anti-proliferative effects on various cancer cell lines [72,73]. When nine flavonoids isolated from the ethyl acetate extracts of the plant were screened for apoptosis induction in human hepatoma HCH-7 cancer cell lines, the compounds tested showed higher apoptosis induction profiles compared with the control. The apoptosis inducing activity of these flavonoids was confirmed by caspase activity assays [5]. Pure compounds other than flavonoids and belonging to the hydroquinones such as kombic acid, sargahydroquinoic acid, sargachromeol, and hydroquinoic acid isolated from the seeds of *P. angolensis* and related compounds have been shown to be efficient at preventing and/or retarding the development of cancer [56-58,74]. Results of these studies may be a first step in the verification of the anecdotal claims of the folkloric use of *Pycnanthus angolensis* as an anticancer agent.

Cognitive disorders

Available records point to a progressive rise in the number of individuals afflicted with neurological disorders including Alzheimer's disease (AD), senile dementia, ataxia and myasthenia gravis. Special attention is required for researchers to develop better treatment for victims of these ailments. While butycholinesterase (BuChE) activity is thought to increase progressively in patients with AD, acetylcholinesterase (AChE) activity remains unchanged or declines. Both enzymes therefore represent legitimate therapeutic targets for ameliorating the cholinergic deficit considered to be responsible for the declines in cognitive, behavioural and global functioning characteristic of AD [75]. AChE and BuChE inhibitors are considered promising therapeutic agents for the treatment of AD to help maintain or elevate the levels of acetylcholine in the brain [76,77]. Only few synthetic medicines exist for treatment of cognitive dysfunction and memory loss associated with these diseases however, they have significant adverse effects. Hence, developing potential AChE inhibitors from botanicals could be helpful. Quiet recently, the *Amaryllidaceae* alkaloid, galanthamine was approved in a number of European countries for the treatment of Alzheimer's disease [78]. Following leads from folklore, Elufioye et al, 2010 screened methanolic extracts of *P. angolensis* (leaves, root bark and stem bark) for both AChE and BuChE inhibitory activities. They demonstrated that the crude stem-bark extracts exhibited the highest *in vitro* AChE and BuChE inhibitory of 66.52 ± 5.02% and 86.05±8.32% respectively while the leaf extracts gave nearly equal inhibitory activity of 43.96 ±3.04 and 43.59± 1.77% in that order. The root bark showed 15.51% inhibition towards AChE but could not inhibit the activity of BuChE. Barclay et al, (2010) recognised the pro-cognitive properties of extracts from the seeds of *P. angolensis* and traced it to the presence of hydroquinones specifically sargahydroquinoic acid. The authors suggest the use of these compounds in Alzheimer disease to enhance cognitive function, myasthenia gravis, glaucoma, learning and memory. Earlier studies by Choi *et al.*, 2007, demonstrated the effectiveness of sargaquinoic acid and sargachromenol derived from a marine plant towards the inhibition of BuChE and AChE activities which is in consonance with the findings of Barclay and others [58]. Substantial amounts of these compounds are present in the seed fat of *P. angolensis* may be confirming one of the folkloric uses of *Pycnanthus angolensis*.

Pain and Anti-inflammatory Activity

Excessive production of some prostaglandins

(PG) is known to provoke pain and inflammation and enhance blood clotting action. Cyclooxygenase has been implicated in the regulation of prostaglandin synthesis and two isoforms of this enzyme (COX-1 and COX-2) have been reported. COX-I is a constitutive isoform that exists in most tissues and is responsible for the production of prostanoids involved in homeostasis whilst the inducible isoform (COX-2) is responsible for the production of prostanoids involved in inflammation [79]. Enhanced levels of COX-2 have been found in humans during the course of numerous inflammatory conditions including rheumatoid arthritis, osteoarthritis and acute or chronic inflammatory disease. Conventional Non-Steroidal Anti-inflammatory drugs (NSAIDs) non-selectively inhibit both COX isoforms. As the induction of COX-2 is responsible for the production of PGs at the site of inflammation, this enzyme represents a possible therapeutic target. Currently researchers are keenly interested in finding NSAIDs which selectively inhibit COX-2 with little or no interference to COX-1. Compounds that selectively inhibit COX-2 are highly promising new agents for the treatment of pain and inflammation, and for the prevention of cancer [79,80].

Herbal therapies present an attractive approach for the treatment of various inflammatory disorders. The important value of extracts and compounds from *P. angolensis* as anti-inflammatory remedies and treatment of adverse health conditions associated with inflammation and/or the presence of free radicals, joint diseases, arthritis, and allergies have been documented. Products from the seed of *P. angolensis* are believed to be useful for the prevention and treatment of conditions linked to inflammation.

Simon *et al*., (2010) determined that agents in the fruits of *P. angolensis* possess anti-inflammatory activities based on *in vitro* experiments utilizing lipopolysachharide induced murine (RAW 264.7) macrophage cells. iNOS a pro-inflammatory, enzyme responsible for the generation of NO, has been implicated in the pathogenesis of inflammatory diseases. The authors examined the effect of extractives derived from the seeds of *P. angolensis* namely *kombo* butter, *kombo* butter acid extract, sargaquinoic acid, sargachromenol, and sargahydroquinoic acid on levels NO production, iNOS activity, COX-2 proteins and mRNA expression in these cells. All test substances suppressed NO production, iNOS protein and mRNA expression, and COX-2 protein and mRNA expression in murine macrophages. On substance basis kombo butter was found to inhibit LPS-induced iNOS mRNA expression by approximately 43% at 5µg/ml and 80% at 10µg/ml while sargahydroquinoic acid inhibited iNOS mRNA expression by 31% at 25µM and 74% at 50µM, these values correlated well with the inhibition of iNOS protein expression by *kombo* butter and sargahydroquinoic acid. Even though *kombo* butter acid extract inhibited iNOS mRNA expression it was not dose dependent; inhibiting at approximately 50% at both 5 and 10µg/ml. Furthermore, sargaquinoic acid and sargachromenol both exhibited inhibitory activity at a concentration of 50µM. The inhibitory activity of compounds from *P. angolensis* was in many instances comparable to and in some cases exceeded that of the control compounds (vitamin E and indomethacin). Similarly, the investigation of the extractives from *P. angolensis* on COX-2 mRNA expression in LPS-induced RAW 264.7 mouse macrophage cells revealed the inhibitory activities of plant extractives. In particular, kombo butter inhibited LPS-induced COX-2 mRNA expression by nearly 25% at 10µg/ml, while sargachromenol inhibited COX-2 mRNA expression by 16% at a concentration of 50µM. Interestingly, sargahydroquinoic acid inhibited COX-2 mRNA expression by nearly 12% at a concentration of 25µM and by almost 19% at 50µM. As with the experiment regarding iNOS mRNA expression, vitamin E and indomethacin were included as comparative controls, however, neither of these compounds effected any inhibition of COX-2 mRNA expressions within the concentration ranges assayed. Each of the agents demonstrated activity at reducing NO production, iNOS protein and mRNA expression, and COX-2 protein and mRNA expression. Thus these agents from *P. angolensis* have been adjudged to possess beneficial inhibitory activities on the inflammatory response in

cells, both *in vitro* and *in vivo*. In a related study, Perez-Castorena *et al.*, (2002) evaluated the anti-inflammatory and antioxidant activities of sargahydroquinoic acid and sargachromenol isolated from *Roldana barba-johannis*, alongside their mixtures and methyl esters and showed their potency as antioxidants and anti-inflammatory compounds. For a more elaborate exposition of the anti-inflammatory potentials of extracts and compounds of *P. angolensis* as well as related compounds the reader is referred to [58,74].

Antioxidant Action

Phytochemical antioxidants are touted as free radical sinks, effectively neutralizing free radicals, active atoms or molecules that can damage DNA and corrode cell membranes. Free radicals are known to play a key role in the development of a number of adverse health conditions, including cancer, cardiovascular disease, and cataracts, and have also been implicated in both initiation and acceleration of the aging process. Given the wide range and gravity of the adverse health conditions associated with free radicals and other inflammatory factors, there is a critical need for agents capable of exerting antioxidant and anti-inflammatory effects to ameliorate the pharmacological treatment of conditions such as cancer, cardiovascular disease, cataracts, rheumatic diseases, fibromyalgia, Alzheimer's disease and numerous other neurodegenerative conditions. In this regard, phyto-preparations could come in handy. Studies have shown that extracts of *P. angolensis* do possess important liposoluble antioxidant activities comparable to or even better than well-known antioxidants like Vitamin E [55,57,58]. Simon *et al.*, (2010) studied the antioxidant properties of extractives (*kombo* butter, *kombo* butter acid extract, and purified sargaquinoic acid, sargachromenol, and sargahydroquinoic acid) from the seeds of *P. angolensis* and found them to be strong antioxidants using both 2,2'-diphenylpicrylydrazyl (DPPH) and 2,2'-azinobis- (3-thylbenzothiazoline-6-sulfonic acid (ABTS) free radical scavenging assays with trolox as standard. Against DPPH, the respective IC_{50} values of 17.3 and 9µg/ml for purified sargachromenol and sargahydroquinoic acid was ample proof that the compounds are good free radical scavengers. Also, kombo butter acid extract, with an IC_{50} of 25.2µg/ml, was found to be a much better DPPH free radical scavenger than kombo butter. Results of the ABTS free radical scavenging assays corroborated the outcomes of the DPPH assay. The antioxidant components have also been proposed as topical applications in different cosmetic and herbal formulations. In consonance with these reports, Tchnida *et al*., 2008 demonstrated in nitric oxide scavenging assay that crude CH_2Cl_2-MeOH extracts of the fruits of *P. angolensis* possess 99.0 % compared with 90.3 % Radical Scavenging Activity elicited by n-propyl gallate standard.

Anti-atherosclerotic effect (Cholesterol lowering)

Hypercholesterolemia remains to be one of the major risk factors of coronary heart disease, the leading cause of death in the world. Atherosclerosis is a complex multi-cellular process involving oxidation of cholesterol and the intracellular accumulation of oxidized cholesterol. Currently available hypolipidemic drugs like gemfibrozil, bezafibrate, lovastatin, and nicotinic acid are not totally safe particularly when used for prolonged periods [36]. Several plant species are known to possess anti-hypercholesterolemic action and may afford a suitable alternative to current day cholesterol lowering medicaments. Extractives of *P. angolensis* have been shown to be efficient at reducing elevated plasma levels of total and LDL cholesterol as well as plasma apolipoprotein B (ApoB) concentrations in humans. ApoB is the dominant protein constituent of low-density lipoprotein (LDL) thought to stabilize lipid emulsions, serve as a cofactor and modulator of enzymatic reactions, manage export of lipids out of cells and direct lipids to target organs. ApoB levels are positively correlated with the risk of coronary disease. Studying the effects of extractives from *P. angolensis* on ApoB

concentration, Leonard (2004) exposed confluent HepG2 cells (which have the capacity to secrete and catabolize lipoproteins similar to LDL) to kombic acid and its derivatives. The cells were incubated in serum-free medium, which inhibits cell proliferation but stimulates biosynthesis of LDL-like lipoproteins in the presence or absence of kombic acid or its derivatives at the range of nontoxic concentrations (determined by MTT cell viability assay). Changes in medium concentration of ApoB were evaluated by ELISA and compared with changes induced in the absence of kombic acid or its derivatives. Kombic acid and its derivatives caused a dose dependent reduction of medium ApoB proving to be useful cholesterol-lowering agents [56].

Wound healing

Over the years, different herbal products have been used in the management and treatment of wounds particularly in folklore. In Nigerian traditional herbal practice, a mixture with ratio 1:1:2 of exudates of *Anchomones difformis*: *Cyrtosperma senegalense* and *Pycnanthus angolensis* respectively, is used for treatment of corneal ulcers. Similarly [81] there are reports that decoctions of the stem bark and leaves of *P. angolensis* are employed to stem haemorrhoids, stomach ulcer and chronic wounds in Ghana. Following these folkloric leads Agyare *et al.*, using human keratinocytes and dermal fibroblasts have confirmed the *in vitro* wound healing capability of ethanol and aqueous extracts of the stem bark of *P. angolensis*. Moreover, [82] the exudates of *P. angolensis* exhibited antibacterial activity, and healed *in vivo* corneal ulcers induced in rabbits even in the absence of prescribed exudates of *A. difformis* and *C. senegalensis*. Even though further confirmations and clinical studies are warranted, these initial findings points to bioactive principles present in both the exudates and stem bark of *P. angolensis* that are capable of stimulating wound healing and may thus justify its traditional use to heal wounds. Therefore, an interesting development from these reports would be a systematic investigation of compounds responsible for these wound healing properties of *P. angolensis*. Besides, the plant is known to elaborate allantoin along with other known antimicrobial agents which together might have some level of wound healing activity. Allantoin is known to have supportive effects on the primary and secondary wound healing process and is known to have bactericidal and anti-inflammatory effects [83-85].

Current & future perspectives

From the above review, *P. angolensis* appears to be a rich source of phytochemicals that can be used to design and develop potentially useful therapeutic agents. Some extracts and compounds isolated from *P. angolensis* have been found to have antitumor (cytotoxic), cholesterol lowering, possess significant antioxidant and anti-inflammatory activities, and iNO inhibitory, anti-ulcerogenic, antimicrobial and anti-hyperglycaemic. Indeed, some of these promising results are worthy of further investigation. For example, meso-dihydroguaiaretic acid has been ascertained to inhibit the enzymatic activity of DNA topoisomerase I and II. The topoisomerases have recently been identified as molecular targets of a variety of pharmaceutical agents. Some of the drugs that target the topoisomerases are anticancer drugs. Thus further investigation into the structure-activity relationship could lead to a better understanding of the mechanism of action of these anticancer principles. The AchE and BuChE inhibitory activities observed could be the action of different bioactives expressed in different parts of the plants as crude extracts of the stem bark and pure sargaquinoic acid (from the seed) both exhibited inhibitory activities. Moreover, mention of a new class of anti-diabetic compounds in pycnanthuquinones A and B elaborated by *P. angolensis* is crucial to say the least. It will be particularly encouraging to see results of the clinical trials on the pycnanthuquinones as well as studies on their safety and efficacies either alone or in combination with conventional therapies. This will go a long way to help control and reduce the overall burden of diabetes. *P. angolensis* also ex-

presses the α-glycosidase inhibitors, glyceryl-1, 3-ditetradecanoate, sargaquinoic acid and sargachromenol. It seems likely that more than one anti-diabetic therapy could be derived from the plant. As noted earlier the butter extracted from the seeds of *Pycnanthus angolensis* could become the much-needed vegetable substitute for animal-fat based cetyl myristoleate employed in arthritis management.

Most of the characterized compounds are only poorly understood biologically since many reports are limited to isolation and structure elucidation for unascribed reasons. Howbeit, many of these compounds are found in low concentrations in the plant as part of complex mixtures which makes their isolation and purification highly expensive. Nonetheless, these could serve as important templates for future synthesis.

The current paradigm is to evaluate antioxidants from flora (for obvious reasons) for their radioprotective potential in order to exploit them for the development of countermeasure agents for radiation exposure [86]. The *in vitro* and *in vivo* antioxidant potential of *P. angolensis* has been amply demonstrated. In particular the plastoquinones/ubiquinones kombic acid, sargahydroquinoic acid, sargachromenol and sargahydroquinone and the flavonoid compounds if evaluated could lead to promising radioprotective compounds. Literature search for the radioprotective evaluation of these compounds or other phytochemicals elaborated by *P. angolensis* did not yield results probably due to the fact that there is no place in folklore for radioprotection to offer research leads in this direction. It will be interesting to investigate this property of the plant extracts and if confirmed, this might increase the economic potential and prospects for the plant. Further work on this topic should be encouraged, and one can reasonably expect interesting results to radioprotective leads. Again, through the literature search, it has been noted that the potential genotoxic effects that may follow usage of the preparations from *P. angolensis* have not been investigated even though there is extensive coverage on cytotoxicity. In our view this constitutes a very vital aspect of the genetic safety evaluation of herbal extracts in a bid to uncover lead molecules with therapeutic utility. Previous pharmacological screening and toxicology assays on plants used medically showed that several plants used for medicinal purposes cause damage to the genetic material and, therefore, should be used with caution [87].

Plants over exploitation have become a global concern, but even so, most developing countries are still involved in plant over-exploitation and the trend is anticipated to continue if adequate control measures are not put in place. Notable examples of over exploited plants are *Okoubaka aubrevillei*, *Garcinia afzelii*, *G. epunctata*, and *G. kola* in Ghana, Côte d'Ivoire and Nigeria. What is highly significant from a resource management viewpoint is that so far, most of the items of commerce in *P. angolensis* seem to be elaborated in the seed (i.e myristeoleic acid, sargahydroquinoic acid, kombic acid, sargachromenol and sargahydroquinone) and the leaves (the pycnanthuquinones), thus unsustainably high levels of exploitation may not pose too much challenge since these parts are renewable. The fact that the stem bark and roots also contain constituents with important biologic activities like flavonoids but also lower levels (compared with the leaves) of pycnanthuquinones could lead to destructive harvesting when demand for these compounds are triggered. At any rate, local threat of over-exploitation of *P. angolensis* is more likely to arise due to demand for its timber than the herbal medicine trade. [Amanor, 1997] notes that in Ghana, *P. angolensis* is one of the forest trees that is popularly preserved by farmers and recognized as having favourable interactions with crops, however, in recent years, with growing shortage of timber in off-reserve areas it has been increasingly exploited by timber contractors. According to the author, in the past *P. angolensis* was hardly exploited and considered an inferior timber species. In 1994, with increasing shortages of prime timber species *P. angolensis* together with three other previously less exploited species accounted for 80% of export volume. Probably in bid to maintain sustainability

and for continual generation of income for indigenes who ply their trade in this plant, Mapongmetsem, (2007) recommends that new opportunities for exploiting the oil and medicinal properties should be investigated.

In conclusion, the phytochemistry of *P. angolensis* reported in current literature is probably not quiet exhaustive. Most of the phytochemical investigations have centred on the above phytochemicals; however, the Myristeacea may have become important due to their ability to elaborate therapeutically relevant compounds like indole alkaloids (with potential for anti-depression), phenylacylphenols and phenylpropanoids [1]. No report about these compounds exists for *P. angolensis*. It is quite obvious that *P. angolensis* requires thorough phytochemical and pharmacological investigations to unearth more useful phytochemicals.

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Conflict of interest statement

The authors certify that there is no conflict of interest concerning the contents of the study.

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Figures

Tables

Part Used	Place	Documented Use	Type of Extract	Method	Ref.
Leaves	Ghana	Haemorrhoids, stomach ulcer, chronic wounds	Decoction		[89]
		Dropsy	Decoction	enema	[2]
	Nigeria, Ghana	Toothache, chronic fungal infection			[2], [10]
	Ghana	enema to treat ascites	Decoction		[9,90]
		Oral thrush in children	Leaf-juice		[90]
Stem-bark	Ghana	Haemorrhoids, stomach ulcer, chronic wounds	Decoction		[38,89]
	Ghana, Cote d'Ivoire, São Tomé, Cameron	Malaria, anaemia, prevent abortion, scabies	Decoction /infusion		[9,65,81,91-95]
	Cameroon	Intestinal helminthic infection, constipation, vomiting, vaginal toilet	Not described		[38,96]
		Jaundice	Macerate	Not described	[97]
	Guinea, Côte d'Ivoire. Guinea-Bissau	Purgative, leprosy, female sterility, purify breast milk	Hot water decoction,	Oral	[4,7,9,38,39,54]
	Nigeria	Tuberculosis, cancer, coated tongue	Maceration, poultice, Mix with other plants	Oral	[4,72,98,99]
	Ghana, Nigeria	Analgesic (headache, body aches, chest pain)	Made into paste with *Piper guineense* and water	Topical application	[7,9,38,66,95,100]
	Congo	Gynaecological problems, infertility, gonorrhoea	Not described		[9]
Bark (root/ stem)	Guinea, Ghana	Emeto-purgative, antidote for poisoning, leprosy, stomach-ache, anthelminthic	Decoction		[2,7,10,68,90,100]
	Ghana	Oral thrush in children	Bark exudate		[7,38,49]
	Ghana, Nigeria	Appetizer and for the treatment of stomach-ache vesiculopustular skin lesions caused by Onchocerca toothache, poison antidote	Pounded bark, bark infusion or latex		[49,90,100]
	Cameroon	Toothache, lactation failure	Decoction	Brush teeth; oral	[101]
Root- Bark	Ghana, Nigeria	Anthelminthic	Hot water infusion	Oral	[2,67,68]
	Cote d'Ivoire	Schistosomiasis	macerate		[9]
Twigs/wood	Nigeria, other parts of West Africa	Toothache, skin disease, stomachache, oral thrush, shingles	Pulverize		[7,10,38,102]
Sap/Latex	Ghana, Nigeria	Arrest bleeding (syptic)	Neat Sap	Apply topically	[2,49,68,90,100]
		Eye troubles, e.g. cataract, filarial in eye, schistosomiasis	Latex	Not described	[66,100]

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	Cameroon, Ghana	cure thrush, skin and fungal infections (antimicrobial)	Fat as mouthwash and topical application	[2,7,8,38,103]
Seeds/fruits	Nigeria	Anti-inflammatory, pneumonia infections, craw-craw, analgesic		[66,68]
		Rhinitis, cough and sore throat		[4,38,104]
		Rheumatism and hemorrhoids		[7,38,104]
shoot, bark, leaves	Cameroon	Dysentery, anaemia	Not described	[94]
Unnamed part	Ghana	Blood tonic, constipation, menstrual pains, unstable pregnancy, stomach ulcer	Not described	[105]

Plant Part	Activity Tested	Type Extract	Test Model	Results	Ref
leaves, roots and stem	Antimicrobial, Antibacterial, antifungal, Anthelmintic	Chloroform and methanol	*S.typhii, ,Ps. aeruginosa, A. niger, Candida albicans, Dermatophyte. sp,Fasciola gigantica,T. solium, Pheritima pasthuma.*	Methanol extract of leave active against 2 bacterial test models and 3 fungal models used. Methanol extracts of leaf and stem possesses anthelmintic activity	[100]
	Antileishmaniasis,cytotoxicity	Methanol	*Lemna. Major, Artemia salina* (brine shrimps)	Stem extract was leishmanicidal with IC_{50} of 70.59µg/ ml but wasn't cytotoxic. Root extract cytotoxic with an D_{50} 727.70 µg/ ml but was not leishmanicidal; Leave extract was inactive.	[39]
Leaves and Bark	Antimicrobial	Steam (fractionated into pure products)	*K. pneumoniae, E. coli, S. enteritidis, . S. aureus, Aspergillus niger,Candida albicans, Ps aeruginosa*	Leave oil more potent on *P. aeruginosa, E. coli S. enteritidis and S. aureus* than bark oil. But bark oil more potent on *C. albicans*, *A. niger* and *K. pneumonia* than leave extracts	[63,64]
Stem bark	Antiplasmodial	Chloroform and methanol	chloroquine-sensitive strain *Plasm falciparum* strain D6 and chloroquine-resistant (strain W2)	IC_{50} = < 25µg/ml: IC_{50} chloroquine = 0.055µg/ml	[65]
	Antiplasmodial	dichloromethane, methanol and aqueous ethanol	3D7 *Plasmfalciparum* strain Dd2 P. falciparum strains	Crude CH_2Cl_2 extract was most active with an IC_{50} of 1.6 µg/mL; pure isolates gave weaker anti-plasmodial activity	[34]
	Anti-cancer	Methanol	MCF-7, COR-L23 and SVK-14 cell lines	IC50 < 50µg/ml	[72]
Stem bark	Anti-cancer	Ethyl acetate fractionated to pure compounds	HuH-7 cell lines	Nine flavonoid compounds isolated. Testing at 20 µM for each compound genetisin gave highest cytotoxicity of 50% compared with the control. For apoptosis induction compounds exhibited higher potency than well-known control compounds	[5]
	anti-diabetic (antihyperglycemic)	Ethanol (fractionation to pycnanthuquinone A and B)	db/db mouse model for Type 2 diabetes	Significant blood glucose lowering effects observed for pycnanthuquinones A and B when administrated orally at 100 and 250 mg/kg. Effects observed for pycnanthuquinone A on days 1 and 2, and for pycnanthuquinone B on day 2, at 100 and 250 mg/kg dose, respectively.	[38]
	Anthelminthic	Methanolic and chloroform	*Eudrilus eugeniae*	Methanol extracts more active than chloroform extract significant effects shown at tested concentrations (10–20mg/ml).	[68]
	Anticancer/, cytotoxicity	methanol	MiaPaCa-2, CCRF-CEM, CEM/ADR5000 (MDR sub-line) and (HUVEC normal cell lines).	Active against CCRF-CEM at 20µg/ml, but no activity noted for MiaPaCa-2 and CEM/ADR5000 at same concentration.	[73]
Stem bark	Antimalarial	Ethanol	Chloroquine-resistant FcB1/Colombia strain of *Plasmodium falciparum*	Active against test model IC_{50} = 18.2±2.7 µg/ml	[91]
Roots	Anti-microbial	CH2Cl2-CH3OH (1:1) further fractionated to pure compounds	Drug-resistant microorganisms; *S. aureus, E.Coli, Shigella dysenteriae, K. pneumonia, P. aeruginosa, S. typhi* and *Citrobacter freundii* and two pathogenic fungi used were *Candida albicans and Microsporum audouinii.*	Significant antimicrobial activities. Ten compounds isolated, pycnanthulignenes A and C assessed foe antimicrobial activity. Significant activity against all organisms (S. aureus most sensitive). MIC for A varied from 28.7-230.9 µM. C exhibited inhibition against eight of the nine tested microorganisms. The lowest MIC value was 63.8 µM. Both compounds less activ than the reference antibiotics	[4]
Roots	Anti-bacterial and antifungal	Ethanol	*E. coli, P. aeruginosa, S. aureus, E. faecalis C. albicans and C. cucumerinum*	Bactericidal against gram positive strains but no report on antifungal activity	[106]
	anthelminthic activities	Ethanol	Haemonchus contortus	Active MIC 1.7mg/ml	[67]

Stem and root barks	Memory enhancement	Methanol	In vitro: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE)	Inhibited AchE and BuChE activities L: C 43.96±3.04%; B= 43.59 ± 1.77% Rb: C= 15.51 ±0.64%; B = 0% Sb: C = 66.52 ±5.02%; B = 86.05±8.32%	[107]
Seed/fruits	Anti-diabetic	CH_2Cl_2-MeOH	α-glycosidase	Demonstrated α-glycosidase inhibitory activity IC_{50} = 522.0 µM. Deoxynojirimycin IC_{50} = 425 ± 8.14 (a potent α-glycosidase inhibitor) Acarbose IC_{50} = 780 ± 28 µM clinically used drug for type-2 diabetes	[103]
Seed	anticancer cholesterollowering	Alcohol or supercritical CO_2	Rat liver microsome, Human low density lipoproteins, tumour bearing mice, MDAMB- 435 cells, MCF-7 estrogen receptor-positive human breast cancer cells	Extracts showed stronger antioxidant activity than vitamin E, inhibited proliferation of MDAMB- 435 and MCF-7 cancer cells synergistically with tamoxifen. IC_{50} comparable with the tocotrienols but gave lower IC_{50} in combination with tamoxifen than either of the compounds alone. Reduced elevated plasma levels of total and LDL cholesterol as well as plasma apolipoprotein B concentrations in humans.	[56]
Seed	Osteoporosis and osteoarthritis rheumatoid arthritis musculoskeletal conditions	Cetyl myristoleate (a cetyl alcohol ester of myristoleic acid acid).	Horse , human subjects	Restored swollen and stiff knees, arthritis and pain in horses. 92% of human subjects showed marked reduction of pain and inflammation when treated with cetyl myristoleate.	[28,29]
	Cognitive disorders,cancer, cell proliferation inhibition	Aq NaOH followed by acidification and purification	Rat liver microsomes, Human low density lipoproteins, cancer cells e.g. human breast cancer cells MCF-7, clooxygenase-2	Effective at inhibiting cell proliferation. Inhibits cyclooxygenase 2 activity	[57]