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Medicinal uses, phytochemistry and pharmacology of *Picralima nitida* (Apocynaceae) in tropical diseases: A review

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ABSTRACT

Picralima nitida Durand and Hook, (fam. Apocynaceae) is a West African plant with varied applications in African folk medicine. Various parts of the plant have been employed ethnomedicinally as remedy for fever, hypertension, jaundice, dysmenorrheal, gastrointestinal disorders and malaria. In order to reveal its full pharmacological and therapeutic potentials, the present review focuses on the current medicinal uses, phytochemistry, pharmacological and toxicological activities of this species. Literature survey on scientific journals, books as well as electronic sources have shown the isolation of alkaloids, tannins, polyphenols and steroids from different parts of the plant, pharmacological studies revealed that the extract or isolated compounds from this species posses analgesic, anti-inflammatory, hypoglyceamic, hypotensive, antiplasmodial, antimicrobial, antiulcer and antitumorigenic activities. Results from various scientific investigations to date have revealed the potential of the extract from the plant or isolated compounds for use in the treatment and prevention of various kinds of human diseases. However, further studies on the extracts and pure compounds from this species is required to completely assess its phytochemical, pharmacological and toxicological profile as well as the mechanism of action behind these pharmacological activities exhibited by the compounds isolated from this species.

1. Introduction

Picralima nitida (*P. nitida*) (Stapf.) T.A. Durand & H. Durand is the only species of the genus *Picralima* and it is related to *Hunteria and Pleiocarpa*. *P. nitida* (Syn. *Picralima klaineana* Pierre) is commonly called Picralima, Akuamma or Pile plant, it belongs to the hunterieae tribe of the apocynaceae family. The plant is widely distributed in high deciduous forest of West-Central Africa from Ivory Coast to West Cameroons, and extending across the Congo basin and Uganda[1-4]. *P. nitida* is an understorey tree which reaches up to 4-35 m in height, crown dense, trunk 5-60 m diameter; cylindrical, the wood is pale yellow, hard, elastic, fine-grained and taking a high polish. *P. nitida* bears white flowers (about 3 cm long) with ovoid fruits which at maturity are yellowish in colour. The leaves are broad (3-10 cm) and oblong (6-20 cm long) with tough tiny lateral nerves of about 14 to 24 pairs[2]. *P. nitida* has widely varied applications in West Africa folk medicine. Various parts of the plant; the leaves, seeds, stem bark and roots are used by herbalists for the treatment of fever, hypertension, jaundice, gastro-intestinal disorders and for malaria[2,5-9]. The extract from different parts of the plant have been found to exhibit a broad range of pharmacological activities which lends credence to its ethnomedicinal uses. Indole alkaloids isolated from the seeds of *P. nitida* such as akuammine, akuammidine, akuammicine, akuammigine and pseudoakuammigine are interesting compounds with opoiod analgesic activity. The pharmacological potential of these alkaloids have only partially been investigated, therefore more research is required to completely explore their pharmacologic and therapeutic potentials. The current review aims at giving a critical appraisal to the best of our knowledge the phytochemical, pharmacological and

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toxicological studies of this specie and hence creates a room for future research.

2. Etnomedicinal uses

Preparations from different parts of the plant are employed as crude drug or crude herbal extract as remedy for various kinds of human diseases.

Seeds: The seeds are widely used in West Africa especially in Nigeria, Cote d'ivoire and Ghana as antipyretic, aphrodisiac, for the treatment of malarial, pneumonia and other chest-conditions[7,9,10-14]. In Gabon the seeds are applied externally for the treatment of abscesses. In Ghana, the seed-decoction is given as an enema while the crushed seed is taken by mouth for chest-complaints, pneumonia, and for gastrointestinal disorders[15].

Fruits: The fruit is used in West Africa for the treatment of gastrointestinal disorder and dysmenorrhoea[3,16]. In Ghana, the fruit shell is filled with palm-wine which is drunk after it has absorb the bitter principle present as a remedy for fever[5].

Leaves: The leaves are used as a vermifuge and the leaf-sap is dripped into the ears for otitis[6].

Bark: The bark is used as laxatives and purgative, anthelmintic, treatment of venereal diseases, as febrifuges and also to treat hernia[5,17]. In Ivory Coast, a decoction of the bark is drunk in draught for jaundice and 'yellow fever'[2,18].

Root: The root is used as vermifuge, aphrodisiac, for fevers, malaria, pneumonia and gastrointestinal disorder[9-11,13].

3. Phytochemistry

Phytochemical screening of *P. nitida* has revealed the presence of alkaloids, tannins, saponins, flavonoids, terpenoids, steroids and glycosides in the plant[14,19-22]. Phytochemical investigation has led to the isolation of a number of alkaloids which are a major compounds from the seeds of *P. nitida*. Other phytochemicals that have been isolated from *P. nitida* are the polyphenols.

3.1. Alkaloids

Alkaloids are the major class of phytochemicals isolated from *P. nitida*. The first set of alkaloids isolated from *P. nitida* are the indole alkaloids; akuammine, pseudoakuammine, akuammidine, akuammicine, akuammigine, pseudoakuammigine, akuammiline and akuammenine[23]. The names were derived from the indigenous name of the plant in Ghana 'Akuamma'. After these, a number of alkaloids have been isolated and re-isolated from the plant. Among the alkaloid isolated are picraphylline, picracine, picraline, picralicine, picratidine, picranitine, burnamine, pericalline and pericine[24-29]. Most of these alkaloids have been reported to be present in the seeds of the plant but could also be found in the leaves, bark and roots. The chemical structures of these alkaloids are shown in Figure 1.

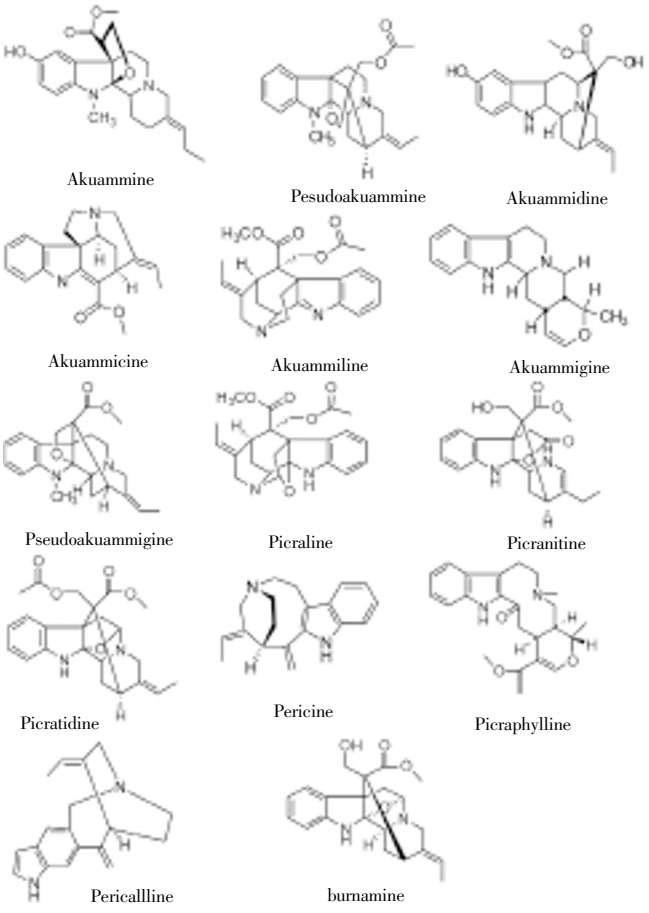

Figure 1. Chemical structures of alkaloids isolated from *P. nitida*.

3.2. Polyphenols

Three coumestan glycosides namely; 3-hydroxy-9-methoxy-2-[2′(*E*)-3′-methyl-4′-*O*- β -D- 3′-methyl-4′-*O*- β -D-glucopyranosylbutenyl]-8-[2″(*E*)-3″-methyl-4″-oxobutenyl]coumestan (Figure 2-structure 2) and 3-hydroxy-9-methoxy-4-[2′(*E*)-3′-methyl-4′-*O*- β -Dglucopyranosylbutenyl]-8-[2″(*E*)-3″-methyl4″oxobutenyl] coumestan (Figure 2- structure 3) were isolated from the roots of *P. nitida* by Kouam *et al*. These coumestan glycosides afforded three coumastan derivatives 3-hydroxy-9-methoxy-2-[2′(*E*)-4′-hydroxy-3′-methylbutenyl]-8-isoprenylcoumestan (Figure 2-

Table 1
Pharmacological activities of *P. nitida*.

Extract of plant part/compound	Pharmacological activity	References
Seed	Antimalarial, antileishmanial, larvicidal, analgesic, anti-inflammatory, antimicrobial, antiulcer, hypoglycaemic, antioxidant, cytotoxic	[14, 28,31,34,35,37,38,40,41,46,48-53]
Fruit	Antimalarial, antipyretic, anti-inflammatory, antidiarrhoea, hypoglycaemic	[22,31-33,50]
Leaf	Larvicidal, antimicrobial, hypoglycaemic, antioxidant	[21,38,44]
Stem bark	Antimalarial, trypanocidal, antimicrobial, antioxidant	[14,31,32,36,42-44]
Root	Antimalarial, antimicrobial, antioxidant, cytotoxic	[14,33,54,55]
Akuammidine	Analgesic	[28]
Akuammine	Analgesic	[28]
Akuammicine	Analgesic, antidiabetic	[28,45]
Pseudoakuammigine	Analgesic, anti-inflammatory	[28,39]
Coumestan derivatives	Antimicrobial	[30]

structure 4), 3-hydroxy-9-methoxy-2-[2′(*E*)-4′-hydroxy-3′-methylbutenyl]-8-[2″(*E*)-3″-methyl-4″-oxobutenyl] coumestan (Figure 2- structure 5) and 3-hydroxy-9-methoxy-4-[2′(*E*)-4′-hydroxy-3′-methylbutenyl]-8-[2″(*E*)-3″-methyl-4″-oxobutenyl]coumestan (Figure 2-structure 6) respectively following acid hydrolysis[30].

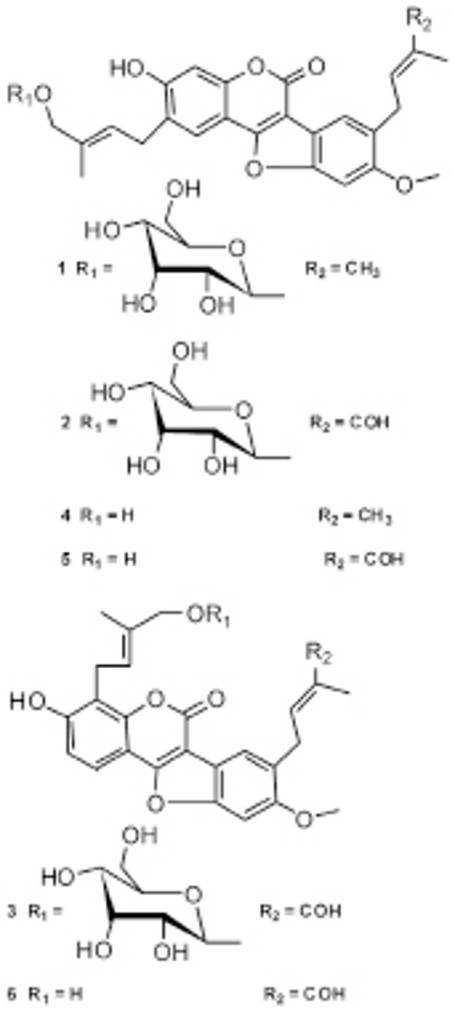

Figure 2. Coumestans and coumestan glycosides isolated from the roots of *P. nitida*.

4. Pharmacology

Based on the claimed ethnomedicinal uses, scientists have investigated a number of pharmacological parameters such as antimalarial, anti-inflammatory, analgesic, antidiabetic, antimicrobial, antioxidant, antiulcer, cytotoxic and toxicological profile of extracts as well as isolated compounds from *P. nitida*. Table 1 summarizes the pharmacological activities of *P. nitida*.

4.1. Antimalarial activity

The *in vitro* antimalarial activity of *P. nitida* extracts has been investigated. The seed, fruit rind and stem bark extracts showed remarkable inhibitory activity against drug resistant clones of *Plasmodium falciparum* at doses of 1.23-32 μg/mL[31]. Significant inhibitory activity of the methanol fruit extract was obtained on multi-drug resistant human *Plasmodium falciparium* with IC_{50} value of 1.75 μg/mL[32]. The root, stem bark and fruit rind extracts displayed significant inhibitory activities against asexual erythrocytic form of *Plasmodium falciparum* with IC_{50} values of 0.188, 0.545 and 1.581 μg/mL respectively[33]. The methanol seed extract of *P. nitida* demonstrated significant activity against the chloroquine-resistant *Plasmodium falciparum* W2 strain with IC_{50} value of (10.9±1.1) μg/mL[34]. The *in vivo* antiplasmodial activity of the ethanol seed extract of *P. nitida* was evaluated in chloroquine-sensitive *Plasmodium berghei berghei* infected mice. The result of this study showed that the ethanol seed extract of *P. nitida* exhibited a significant *in vivo* antiplasmodial activity in both early (4-Day chemosuppressive test) and established infections (Curative test). Ethanolic seed extract of *P. nitida* produced a dose dependent chemosuppressive effect of 65.5%, 70.4% and 73.0% respectively for 35, 70 and 115 mg/kg/day doses[35].

4.2. Trypanocidal activity

Wosu and Ibe investigated the effect of a boiling water extract of *P. nitida* bark against *Trypanosoma brucei* in rats. They found out that the extract (8 mg/kg) had trypanocidal effect which was statistically comparable to that of diminazene aceturate[36].

4.3. Antileishmanial activity

Chloroform extract of the seed of *P. nitida* was evaluated for possible antileishmanial activity using a radiorespirometric microtest technique and the result of the study confirmed activity against *Leishmania donovani* at 50 μg/mL[37].

4.4. Larvicidal activity

The larvicidal activity of ethanolic and aqueous extracts of the leaf of *P. nitida* was evaluated in static bioassay, on fourth instar larvae of *Anopheles gambiae*. The results obtained from the study showed a concentration and time dependent increase in larvicidal activity with 72 h LC_{50} values of 0.660% and 1.057% w/v for ethanol and aqueous leaf extracts respectively[21]. According to Dibua *et al*, the aqueous and methanol extracts of the leaf and seed of *P. nitida* also have a concentration and time dependent larvicidal activity in third and early fourth instar larvae of *Anopheles gambiae* with 72 h LC_{50} values of 0.164, 0.333 and 0.150 mg/mL for aqueous leaf extract, methanol leaf extract and methanol seed extract respectively[38].

4.5. Antipyretic activity

The antipyretic activity of *P. nitida* fruit has been demonstrated. The result of the study showed that the methanol fruit extract at a dose of 50 mg/kg produced a mean percentage antipyrexia of 38.7% on lipopolysaccharide-induced pyrexia in rabbits, which was comparable to aspirin (29.0% at 200 mg/kg)[32].

4.6. Analgesic activity

Menzies *et al* reported the opioid analgesic activity of five alkaloids *viz* akuammidine, akuammine, akuammicine, akuammigine and pseudoakuammigine extracted from the seeds of *P. nitida*. The result of the study revealed that four of the alkaloids *viz* akuammidine, akuammine, akuammicine and pseudoakuammigine competitively bound to opioid sites in homogenates of guinea pig brain[28]. In another study, pseudo-akuammigine was found also to exhibit analgesic effect *in vivo*. The ED_{50} value for this test was 10 mM which was 3.5 and 1.6 times less potent than morphine and indomethacin respectively. In this study, naloxone inhibited the analgesic effect of pseudo-akuammigine suggesting that the analgesic actions are mediated via interaction with opioid receptors[39]. The analgesic effect of the ethanol seed extract of *P. nitida* was reported by Ofori Kate Asantewaa, in her study, the extract increased the mean pain threshold of rats in a dose-dependent manner and also significantly ($P<0.05$) suppressed bradykinin-induced hyperalgesia in rats[40].

4.7. Anti-inflammatory activity

Pseudo-akuammigine was investigated for anti-inflammatory activity by the carrageenan-induced rat paw oedema. The alkaloid significantly ($P<0.05$) reduced the mean maximal and total paw swelling over a 6 h period when administered orally 1 h before induction of oedema in a dose-dependent manner. When administered after induction of oedema, pseudo-akuammigine (5.0 mg/kg) significantly ($P<0.05$) reduced established rat paw swelling to (82.89±4.60)% of the control response after 5 h[39]. In an earlier study conducted by Ezeamuzie *et al*, the methanol fruit extract of *P. nitida* showed potent and dose-dependent anti-inflammatory activity. The extract when administered intraperitoneally inhibited carrageenan-induced rat paw oedema with IC_{50} value of 102 mg/kg, and with the highest dose tested (300 mg/kg) producing 72.2% inhibition[32]. In a study conducted on the ethanol extract of *P. nitida* seeds, the extract at 1.5 and 3.0 g/kg *p.o.* suppressed the maximal carrageenan-induced rat paw oedema attained during 6 h by (28.8±1.5)% and (55.0±1.4)%, respectively[40]. Similarly, the total alkaloidal extract from the seeds of *P. nitida* at doses of 75-300 mg/kg *p.o.* significantly ($P<0.05$) and dose-dependently inhibited the maximal and total carrageenan-induced paw oedema and also reduced the adjuvant-induced tibio-tarsal joint swelling in rats over the 6 h period when administered 1 h prior to induction of oedema. In established inflammation, the alkaloidal extract (300 mg/kg *p.o.*) reduced the time course of carrageenan-induced paw oedema as well as the adjuvant-induced knee arthritis in rats[41].

4.8. Antidiarrhoeal activities

The antimicrobial activity of the methanol extract of *P. nitida* fruit-rinds against 15 pathogenic strains of enteric bacteria and 2 yeast strains implicated in infective diarrhoea was investigated *in vitro*, and the antidiarrhoeal effect of the

extract against *Shigella dysenteriae* type 1 (sd1)-induced diarrhea was determined *in vivo*[22]. The result of this study showed that the extract was effective against *Escherichia coli* (*E. coli*), *Staphylococcus aureus (S. aureus)*, *Shigella dysenteriae*, *Proteus vulgaris (P. vulgaris)*, *Enterobacter cloacae*, *Streptococcus feacalis*, *Pseudomonas aeruginosa (P. aeruginosa)*, *Proteus mirabilis, Salmonella typhi, Bacillus cereus* and *Candida albicans (C. albicans)* with *P. vulgaris* being the most sensitive. The *in vivo* anti-shigellosis activity revealed that *P. nitida* fruit-rind extract effectively and significantly reduced sd1 density, the frequency and mass of diarrhoea stool after day-3 in diarrheic rats[22].

4.9. Antimicrobial activity

Ethanol, benzene, chloroform and aqueous (cold and hot) extracts of *P. nitida* (seed, stem bark and root) were tested against five bacterial strains: *E. coli*, *P. aeruginosa*, *Bacillus subtilis (B. subtilis)*, *S. aureus* and *Salmonella kintambo (S. kintambo)*. All tested organisms were sensitive to the ethanol extracts of the root and stem bark with the highest activity against *S. kintambo* [mean zone of inhibition was (25.00±2.65) mm]. The cold water extract of the seed was active against the bacterial strains except *S. kintambo*, with the highest activity against *B. subtilis* [mean zone of inhibition (14.0±1.0) mm]. The hot water seed extract had activity only against *S. aureus* and *B. subtilis*. The benzene and chloroform extracts showed no activity against the test bacterial strains[14,42]. The basic fraction of the methanol extract of the stem bark of *P. nitida* was shown to exhibited significant antimicrobial activity against a wide range of Gram-positive bacteria and fungi, but limited activity against Gram-negative bacteria[43]. The antifungal activities of ethanol and aqueous leaf extracts of *P. nitida* were evaluated in three fungal species: *Aspergillus flavus*, *C. albicans* and *Microsporum canis*. Results obtained revealed that both the aqueous and ethanol leaf extracts exerted antifungal effect on *Aspergillus flavus* and *C. albicans* in a dose-dependent manner, but no antifungal effect was exhibited against *Microsporum canis*[21]. The antimicrobial activities of six coumestan derivatives (Figure 2) isolated from the roots of *P. nitida* gainst *E. coli, S. aureus,* and *P. vulgaris* has been demonstrated[30].

4.10. Antiulcer activity

The antiulcer activity of the methanol extract, chloroform and methanol fractions of *P. nitida* seeds were evaluated using the aspirin-pylorus-ligation method in rats. The study revealed that the extract and fractions of *P. nitida* seeds produced significant (P<0.05) reduction of ulcer index, total acidity, pepsin activity and increase in mucoprotective parameter such as phenol red content. The study indicates potent antiulcer activity of *P. nitida* with percentage ulcer inhibition of 56.36%, 40.00% and 56.36% for the methanol extract, chloroform and methanol fraction respectively compared to the control (Normal saline)[19].

4.11. Hypoglycaemic activity

Teugwa *et al* investigated the antidiabetic potential of methanol and hydroethanol extracts of the stem bark and leaves of *P. nitida* in streptozotocin-induced diabetes in mice. The result of the study showed that the methanol leaf extract of *P. nitida* at 300 mg/kg exhibited significant antidiabetic activity with 38.48% glycaemia reduction[44]. The hypoglycaemic activity of six indole alkaloids (akuammicine, 10-deoxyakuammine, akuammine, akuammidine, burnamine and picraline) isolated from the chloroform extract of the seeds of *P. nitida* were investigated using glucose uptake in fully differentiated 3T3-L1 adipocytes. The result of the experiment showed that akuammicine had a concentration dependent stimulation of glucose uptake (P<0.01) after 24 h in fully differentiated 3T3-L1 adipocytes[45]. Ethanol and butanol extracts of *P. nitida* seed were evaluated for their hypoglyceamic effects in streptozotocin-induced diabetes in Pregnant rats, result indicated that butanol seed extract of *P. nitida* significantly decreased glycemia in diabetic pregnant rats from day 16 until delivery on day 21[46]. Contrarily, the ethanol seed extract of *P. nitida* has been shown to increase glucose level in alloxan-induced diabetic rats[47]. The discrepancy in the results may be as a result of the differences in constituents of the extract due to the solvent used for the extraction. The seed oil of *P. nitida* (2.0 mL/kg *p.o.* and 0.125 mL/kg *i.p.*) has been demonstrated to cause a steady reduction in blood glucose in rats whereas when administered at 1.0 mL/kg and 0.25 mL/kg *i.p.* there was an initial hyperglyceamic effect followed by sustained hypoglycaemic effect lasting over 6 h[48]. The effect of alkaloids and glycosides extracts of the seeds of *P. nitida* on mean fasting blood sugar in alloxanized diabetic rats were evaluated by Okonta and Aguwa. Their findings showed that the glycosides extract have more potent hypoglycaemic effect than the alkaloids extract[49]. The hypoglycaemic effect of the methanol extracts of the seed, pulp and fruit rind of *P. nitida* were investigated by Inya-Agha *et al* the result showed a significant (P<0.01) hypoglycaemic effect of all extracts at 300 and 900 mg/kg in alloxan-induced diabetes in rats[50]. Aguwa *et al* confirmed the hypoglycaemic effect of the aqueous seed extract of *P. nitida* in alloxan-induced diabetic rabbits[51]. The blood

glucose lowering effect of the coconut water extract of *P. nitida* seeds in alloxan-induced diabetic rats and rabbits has been demonstrated[52,53].

4.12. Antioxidant activity

The *in vitro* antioxidant activities of methanol and hydroethanol extracts of the stem bark and leaves of *P. nitida* were evaluated by the 1, 1-Diphenyl-2-picrylhydrazyl (DPPH) free radical-scavenging method and the effect of extracts treatment on selected oxidative stress markers: Malondialdehyde, hydrogen peroxides and catalase were also evaluated in mice. The extracts exhibited good free radical scavenging activity and extracts treatment resulted in a significant reduction in malondialdehyde and hydrogen peroxide levels as well as a marked increase in catalase activity[43]. The antioxidant capacity of ethanol, ether, ethyl acetate, butanol and aqueous extracts of *P. nitida* seeds were determined using free radical induced heamolysis in red blood cells. In the study, it was noted that *P. nitida* seed extract have good antioxidant capacity with the buthanol extract exhibiting the highest activity[45]. Similarly, the antioxidant activity of methanol root bark extract of *P. nitida* has been investigated in vitro using the DPPH free radical scavenging method. The study revealed that the extract exhibited appreciable percentage radical scavenging activities with IC_{50} value of 5 μg/mL[54].

4.13. Cytotoxic activity

The antiproliferative and apoptotic effects of the crude methanol extract and fractions of *P. nitida* root bark were investigated *in-vitro* using human breast cancer cell line (MCF-7). The result indicated a marked reduction in cell proliferation and increase apoptosis in MCF-7 cells after extract treatment, these effects were highly significant (P<0.001) in the chloroform fraction of the extract[55]. *P. nitida* ethanol seed extract was shown to significantly (P<0.05) inhibits human T cell (Jurkat) proliferation activated by anti-CD3 antibody in a concentration-dependent manner[45].

4.14. Toxicity

The acute toxicological profile of the methanol fruit rind of *P. nitida* in rats revealed signs of toxic effect on the liver, kidneys and the lungs after prolonged exposure at high doses (1.5-6 g/kg) with LD_{50} values of 14.5 and 12.5 g/kg for male and female rats respectively. These effects were characterized by marked elevation in serum aspartate amino-transferase (AST), alanine amino-transferase (ALT), glucose, creatinine, total cholesterol and protein[19]. Acute intraperitoneal toxicity tests of the basic alkaloidal fraction of *P. nitida* stem bark showed a dose-dependent toxicity characterised by inflammation and necrosis of the hepatocytes accompanied by reduction in neutrophilic count and a corresponding increase in lymphocytic count. Conjuctiva application showed no sign of reddening or irritation and dermal tests also showed no sensitization, inflammation or death in the animal models used[56]. The acute and sub-chronic toxicity studies of the hydroethanol extract of *P. nitida* leaves (1-5 g/kg *p.o.* in mice) was carried out by Ilodigwe *et al*, the result of the study showed that *P. nitida* leaf extract caused no physical sign of toxicity within 24 h. after prolonged administration, assessment of haematological parameters showed that there was no significant elevation of hemoglobin concentration, packed cell volume and red blood cell count at lower doses. While at higher doses, there was a significant (P<0.05) elevation of white blood cell count and biochemical studies revealed a dose- and time-dependent elevation of serum AST, ALT, and serum alkaline phosphatase and a concomitant degeneration and rupture of the hepatocytes[57]. Acute toxicity of the methanol pulp, seed and fruit rind extract of *P. nitida* on rats revealed a mild toxic effect with LD_{50} values of 7 071.06, 948.68 and 1 364.91 mg/kg, respectively[49].

5. Conclusion

P. nitida a West African plant has great usefulness in African traditional medicine especially in the rainforest regions of Nigeria, Ghana, Cote d'Ivoire, Gabon and Cameroon. Various parts of the plant including the seeds, fruits, fruit pulp, fruit rind, leaves, stems and roots are employed ethnomedicinally as remedy for a variety of human diseases such as malaria, diabetes, hypertention, fever, infections, pain and various inflammatory conditions.

The present review gave a critical appraisal of the ethnomedicine, phytochemistry and pharmacology of *P. nitida*, phytochemical investigation of various parts of the plants revealed the presence of alkaloids, tannins, saponins, glycosides, sterols and various phenolic compounds. Isolation and characterization of chemical compounds from the plant especially from the seeds revealed that alkaloids (the indole alkaloids) are a major component of *P. nitida*. Extracts and pure compounds from *P. nitida* have exhibited numerous pharmacological activities ranging from antimicrobial, antiprotozoal, analgesic, antipyretic, anti-inflammatory, antidiabetic, antioxidant and cytotoxic

activities. These findings justified the applications of the plant in African folklore and also provide a platform for further investigations to completely explore the pharmacologic and therapeutic potentials of the plant.

Conflict of interest statement

We declare that we have no conflict of interest.

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