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***Terminalia avicennioides* as a Potential Candidate for Pharmaceutical Industry: A Review.**

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ABSTRACT

Terminalia avicennioides is an important medicinal plant used to manage many pathological conditions among most inhabitants of rural communities in Nigeria and many other African countries. It belongs to family Combretaceae and found commonly growing in the savannah region of West Africa. The parts of the plant mostly used for medicinal purpose are root and stem barks extracts, which are rich sources of phytochemicals such as anthraquinone, saponins, steroids, tannins and terpenes among others. In folk medicine, there are claims that the plant has been used to cure various diseases such as dental caries, skin infections, sore and ulcer, syphilis, bloody sputum, ringworm infection, gastrointestinal helminthes and several others. In this review, we have tried to provide bases for most of these claims at the instance of the results of modern investigations on the biological activities of the plant extract. The possibility of employing the plant extract in the field of green chemistry for probable application in biomedical industries was also discussed.

Keywords: *Terminalia avicennioides*, uses, phytochemicals, biological activities, nanoparticles

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INTRODUCTION

Plants have been employed for many decades as remedies to many diseases afflicting humans. Despite the various advances in modern medicine, larger proportion of the world's population (about 90%) still relies completely on raw herbs and unrefined extracts as medicines [1]. According to Cox and Balick [2], plants have been a rich source of medicines because they produce a host of bioactive molecules, most of which probably evolved as chemical defenses against predation or infection. Modern health care services is gradually getting out of reach of most of the world's population largely because of high cost and as such, people turn to rely on traditional medicine and medicinal plants to meet their primary health care needs. Today in most parts of the world especially in Asia and Africa, there are expanding markets for medicinal plants as herbal components of health foods and preventative medicines have become integrated into people's dietary plans. There are many popular medicinal plants in the world of which *Terminalia avicennioides* is one. This review is designed to examine the botany of this plant, various medicinal potentials attributed to its extracts, safety of the extracts, possible areas for future research endeavours and suggestion for its utilization and adoption in the medical delivery system.

Taxonomy and Description

Terminalia avicennioides Guill and Perr. Is a tree plant widely distributed and commonly growing in the Savannah region of West Africa [3]. The genus *Terminalia* belongs to family Combretaceae consisting of about 514 species of which only 54 are accepted and recognized [4]. Of these 54 species, 11 species are well represented in West Africa and have been used for various medicinal purposes. Some of these other species aside *Terminalia avicennioides* include; *Terminalia glaucescens*, *Terminalia ivorensis*, *Terminalia macroptera*, *Terminalia laxiflora*, *Terminalia albida*, *T. mantaly*, *T. mollis*, and in particular, *T. scutifera* among others. Species such as *Terminalia chebula* Retz., *Terminalia superb*, *Terminalia catappa*, *Terminalia arjuna*, *Terminalia ferdinandiana* are found in Asian countries, especially India, Indochina, Burma, Cambodia, Thailand, Laos, Vietnam and Malaysia. *Terminalia avicennioides* is locally referred to as "baushe" among the Hausa [5], 'Kpace" in Nupe, "Kpayi" in Gwari [6], "Idi" among the Yoruba. It grows as shrub or small tree with short bole to 10m high, sometimes bushy and branching from the base. It is a tree with yellowish brown, hard and durable wood.

Phytochemical constituents

Several bioactive hydro-lysable tannin compounds including ellagic acid, punicalagin, flavogallonic acid and terchebulin [7] have been isolated from this plant, and none of them have been shown to have antimycobacterial activity at low concentrations. The root bark of *T. avicennioides* contains anthraquinone, saponins, steroids, tannins and terpenes [8]. A chemical compound called friedelin was also isolated from the root bark of this plant [9] with significant activity against *Bacillus Calmette Guerin* (BCG) at 4.9µg/ml. Friedelin had earlier been reported to exhibit antifeedant and anti-inflammatory activities [10] without cytotoxicity. Friedelin had also been found to show significant hepatoprotective activity [11]. A new triterpenoid named glaucescic acid was recently isolated from another species of the plant called *Terminalia glaucescens* [12], which suggest the richness of member of genera in various phytochemicals of medicinal values. An extensive array of triterpenes has been reported to exhibit antimycobacterial activity [13], in which oleanane series were discovered to exhibit significant antimycobacterial activity.

Plant parts and application in folk medicine

Its roots are used as chewing sticks in Ibadan area of Nigeria and have been claimed to cure dental carries and skin infections [14]. The root bark decoction is used in Ivory Coast for draught and enema for severe jaundice [15], in Senegal for sores and ulcer [16], while in Nigeria for gastrointestinal disorders [17] as well as for syphilis by the Jukuns [18]. The seeds, fruits, roots and rinds are used in the treatment of bloody sputum in the human and cough by the Nupes in North Central Nigeria [19]. This plant is traditionally used to treat ringworm infections and other skin diseases [20]. In addition, dried, powdered roots of the plant mixed with roasted bulbs of *Crinum* spp. and made into an ointment with fresh cow butter is used for the treatment of rheumatic pains and joint swellings [3]. The Fulanis (the major cattle rearing people in Nigeria) use a decoction from the root of *T. avicennioides* to treat gastrointestinal helminth parasites [21].

The survey of Atawodi *et al.* [22] revealed that the aqueous extract of its stem bark is traditionally employed to treat sleeping sickness and it was later discovered to be active against trypanosomes [23], diarrhoea [17], *Candida albicans* [24] and malaria parasite [25]. Some studies also showed that the stem bark extract of *T. avicennioides* exhibited both vibriocidal and typhoidal activities against *Vibrio cholera* and *Salmonella* spp (both *Salmonella typhi* and *Salmonella paratyphi*) respectively [26,27,28], while significant antimicrobial activities against *Staphylococcus aureus* was also reported [29]. Various extracts of *T. avicennioides* are used in Nigeria to treat ailments such as helminthiasis [30], while the efficacy of these extracts on healing of ulcer (gastric and peptic ulcers) and wounds has also been evaluated [31,32].

Biological activities of its extracts

Antioxidant activity

Plant chemical substances such as flavonoids, tannins, have been shown to scavenge free radicals and therefore are viewed as promising therapeutic drugs for free radicals pathologies [33,34]. *T. avicennioides* stem bark extract contain phytochemicals such as glycosides, phenols, tannins, saponins, flavonoids, and ellagic acid [29], which have profound antioxidant effects. According to Akanbi [35], *T. avicennioides* has tendency to boost antioxidant level in organism because of the potential of its methanolic stem bark extract to elicit significant increase in serum and liver catalase (CAT) and superoxide dismutase (SOD) levels in laboratory rats. Furthermore, antioxidant effect of methanolic extract of this plant in treated infected mice was also reported by Omonkhua *et al.* [36]. The effects observed were listed to include an increase in antioxidant enzymes SOD and CAT activities, and a decrease in malondialdehyde (MDA) concentration.

Antibacterial activity

The crude extract of the *T. avicennioides* root bark was already observed to exhibit broad growth inhibition against microbes causing infectious diseases [29,37,38] and it was especially found to significantly inhibit activities of *M. tuberculosis* and BCG at 78 and 200 μ g/ml respectively [39,40]. In addition, the crude methanolic extract of the plant was also found to be active against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Bacillus subtilis*, *Salmonella typhi*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Neisseria gonorrhoea* and *Candida albicans* with minimum inhibitory concentration (MIC) of 0.3mg/mL for *S. pyogenes* and *B. subtilis* while MIC of 0.4mg/mL for others [8]. However, it was reported to be inactive against *Corynebacterium ulcerans* and *Klebsiella pneumoniae*.

Terpenoidal fractions of *Terminalia avicennioides* was prepared using combination of chromatographic techniques (Flash column chromatography and Tin-layer Chromatography) and were found to be active against some bacteria implicated in human infections such as *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* with MICs of 0.425, 0.425 and 0.213 μ /ml respectively [38]. Some respiratory infections are caused by *Pseudomonas* species while *E coli* have been implicated in some gastrointestinal diseases and lung infections especially in immunodeficient patients. In another study, Triterpenoid Friedelin isolated from the root bark of *T. avicennioides* revealed significant antimycobacterial activity against BCG at MIC of 4.9 μ g/mL [9]. These results probably provide bases for the use of this plant extract in the treatment of bloody sputum and cough by the Nupes of North Central Nigeria [6].

Furthermore, aqueous extracts of *T. avicennioides* stem bark, either singly or in combination with *Ocimum gratissimum* (leaf extract) were investigated and discovered to manifest marked shigellicidal activity that is comparable to antibacterial effects of ofloxacin [41]. The extracts were shown to inhibit strains of Shigella such as *S. dysenteriae*, *S. flexneri*, *S. sonnei* and *S. boydii* with MIC of 243.8-431.3 μ g/mL. This study provides additional information regarding the wide range of Gram-negative coverage of *T. avicennioides* thus lending credence to their therapeutic use in herbal preparations among people in the rural communities.

Antifungal Activity

Chloroform, ethanolic, methanolic, ethyl acetate and aqueous root extracts of *Terminalia avicennioides* were reported to show *in vitro* antifungal activities against *Aspergillus niger*, *Aspergillus fumigatus*, *Penicillium* species, *Microsporum audouinii* and *Trichophyton rubrum* [37]. Of the five root bark extracts, Ethanolic extracts of the plant roots were most effective with MIC range between 0.03 μ g/ml and

0.05 μ g/ml while the minimum fungicidal concentration ranged between 0.04 μ g/ml and 0.05 μ g/ml. It was observed that the antifungal substances contained in the extracts were fungistatic at lower concentrations while turning fungicidal at higher concentrations of the extracts, which is similar to the report of Banso and Adeyemo [42] on some other plant extracts.

Antihelminthic effect

In a study carried out to assess the antihelminthic effects of four extracts of *Terminalia avicennioides* (i.e. extracts obtained using butanol, methanol, chloroform and petroleum ether as solvents) on Laboratory rats purposely infected orally with *Nippostrongylus brasiliensis*, only butanolic extract produced a consistently high and significant ($P < 0.05$) antihelminthic effect [30]. The choice of this strain of hookworm was based on the understanding that *N. brasiliensis* is more resistant to antihelminthics than most other gastrointestinal helminth parasites [43,44]. The extract was noted to produce dose dependent deparasitization in the infected rats.

Antitrypanosomal effect

A comparative investigation was conducted by Alayande et al. [45] to assess the efficacy of aqueous extract of *T. avicennioides* singly and in combination with diminazene aceturate (Berenil) in rats infected with *Trypanosoma brucei brucei*. It was discovered that, aqueous extract treated rats manifested reduction in the parasitaemia and significant increase in the average survival time, but were not cured. However, those infected rats treated with Berenil alone and combination of its half therapeutic dose with the plant extract were completely cured. This study highlighted trypanocidal effect of *T. avicennioides* bark extract, even though it could not eliminate the parasite completely, but it reduces the level of parasitaemia and improved the status of anaemia.

In a related study, aqueous and methanolic extracts of the roots, leaves and stem bark of *Terminalia avicennioides* were tested in vitro and in vivo against *Trypanosoma brucei brucei* [5]. It was observed that the root and stem bark extracts completely immobilized trypanosomes within 30 minutes of incubation at 20 mg/ml concentration, with the aqueous root extract displaying the highest activity, and the methanol extract of the leaf, the least. Anti trypanosomal effects of the root and stem bark extract compared favourably with that of the standard drug diminazine aceturate. Both crude extracts and bioassay-guided fractions were observed to significantly suppress parasitemia, alleviate anemia and prolonged life span in a dose dependent manner. The ethylacetate: methanolic portion of the bioassay-guided fractions was noted to show the greatest anti-trypanosomal activity with saponin as the major phytochemical constituent, which probably suggests its dominant role in the observed effect.

Antimalarial effect

Methanolic extract of *T. avicennioides* have been reported by several authors to show antimalarial effects comparable to that of artesunate which is a standard drug [35,36]. For instance, the extract administered to *Plasmodium berghei* infected rat at 100 and 200mg/Kg was observed to suppress parasitemia after 1day by 18 and 11% respectively, while the suppression level was raised after 5days to 82 and 84%. The hemoglobin, red blood cell, and lymphocyte counts that were decreased and neutrophil count that was increased by the infection were all restored to normalcy. The serum and liver superoxide dismutase activities were significantly increased with simultaneous reduction in serum malondialdehyde concentration compared to untreated infected mice. In addition to this, high density lipid was also reported to be significantly higher while triglyceride was significantly lower in the plant extract treated rat than control [35]. It was inferred from the study that *T. avicennioides* may provide better protection against the malaria severity and complications.

Gastroprotective effect

Gastroprotective effects of different doses of methanolic extract of *T. avicennioides* on acute mucosal damage induced by 0.6 M HCl and on mucus production in the stomach of rats were demonstrated by Suleiman et al. [31]. In this investigation, animal treated with methanolic extract of the plant at a dose of 350mg/kg were observed to show a significant reduction of gastric lesion produced by HCl while those treated at doses of 500 and 900mg/kg revealed a highly significant reduction in gastric damage compared to normal

saline (untreated) control rats. Administered doses of the extracts (350, 500 and 900mg/kg) were also observed to elicit a significant increase in mucus production compared to normal saline (untreated) and cimetidine (treated) control rats. The effect of the extract on both gastric damage and mucus production were shown to be dose-dependent. This finding further explains the claim that the extracts of the plant has ulcer-healing effect, which was attributed partly to its antibacterial action, particularly against *H. pylori*.

Wound Healing Activity

Wound healing activity of ethanolic extract of *T. avicennioides* root bark was investigated in two wound models (excision and incision) using standard procedure [32]. It was shown that the extract produced wound healing effects comparable to that of penicillin ointment in term of wound contracting ability, closure, decreased in surface area, tissue regeneration and reduced days of healing. The wounds closed completely at 18th and 19th days for penicillin ointment and ethanolic root bark extract treated rat groups respectively while the wounds in those groups treated with simple ointment still remained opened. It was deduced that tannins and anthraquinones which are the major phytoconstituents of the root bark extract of *T. avicennioides* [19] might have been responsible for the healing activities observed. This probably justify the rationale for the traditional use of this plant in wound management.

Toxicity

There is very little information on toxicity studies carried out on the plant. The one conducted so far was on in vitro cytotoxicity using brine shrimps and it was observed that, only petroleum ether extract of the plant root bark exhibited remarkable toxicity on brine shrimps larvae at ED₅₀ of 63.2µg/ml [46]. Ethylacetate extract produced moderate toxicity at ED₅₀ of 297µg/ml while ethanolic extract was nontoxic (ED₅₀ >1000µ). Bulus et al. [47] investigated acute toxicity effect of aqueous extract of stem bark of *T. avicennioides* on white albino rats and reported LD50 >5000mg/kg body weight. There was no significant weight decrease among dosed groups up to 1000mg/kg body weight, however liver congestion was observed with 100mg/kg body weight dose group. Nevertheless, the organ-body weight ratio for kidney, liver and heart were not significantly different from the control group. Liver congestion was the only major pathology associated with treatment of rat with aqueous extract of *T. avicennioides*, which necessitate the need to determine to what extent ingestion of extracts from the plant will be toxic and the therapeutic dosage for clinical applications. In addition, a particular study conducted on anticancer activity of the aqueous extracts of *T. avicennioides* revealed that it significantly decreased *in vitro* cancer cell viability with increasing dose and time, indicating cytotoxicity against EAC cell lines [48]. This lends support to the possibility of the plant extract to serve as potent anticancer agent. In vivo toxicity study carried out with the ethanolic extract of a member of the same genera (*T. paniculata*) revealed very healthy and protective results [49]. Furthermore, other members of the genera such as *T. belerica*, *T. mollis*, *T. chebula*, and *T. arjuna* [50,51,52,53] were reported to show related activities. However, extract of *T. avicennioides* appeared to be safer in traditional medicine compared with aqueous extract of *T. mollis* [51].

Application in nanotechnology

Extracts of members of genera *Terminalia* have also been found useful in green chemistry for possible application in the field of biomedicine and other areas. For instance, *T. catappa* leaf extract was found very efficient in fast reduction of chloroaurate ions leading to the formation of highly stable gold nanoparticles in solution [54]. Also, aqueous leaf extract of *T. arjuna* was also discovered to be very active in bioreduction of gold ions to gold nanoparticles with potential to induce mitotic cell division in *Allium cepa* roots and pollen viability in *Gloriosa superba* without toxicity [55]. Kumar et al. [56] reported green synthesis of silver nanoparticles using extract of *T. chebula* fruit. The synthesized silver nanoparticles were observed to show good antimicrobial activities towards both Gram-positive bacteria (*S. aureus* ATCC 25923) and Gram-negative bacteria (*E. coli* ATCC 25922). Despite the great medicinal potential of *T. avicennioides*, it was discovered that it has not been explored in the field of nanotechnology. It is worthy to note that effort to explore extracts of *T. avicennioides* in the synthesis of metal nanoparticles and evaluation of its toxicity using plant model is presently being pursued and at advance stage. This study when completed will further enhance our understanding of the potential of *T. avicennioides* with the possibility of its exploitation in drug delivery.

CONCLUSION

T. avicennioides usage in folk medicine to remediate many pathological conditions has been validated by numerous research findings which point to the possibility of its adoption in modern medical delivery. The major parts of the plant that are used in pharmacological preparations either singly or in combination are root and stem barks. The fact that its phytochemical extracts are virtually nontoxic in vivo in test organisms suggests the suitability of this plant for incorporation into modern health care system. In addition, the nontoxic nature of the plant extract will further enhance its acceptability over most of the synthetic drugs with high level of toxicity and greater side effects, which further debilitate human systems after curing the targeted ailments. Furthermore, it is possible that this medicinal plant will find useful application in the field of nanomedicine because of nontoxic nature of its extract on the biological system. However, there is need for further investigation to validate the non or less toxic reports as claimed by earlier findings.

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