Chapter

Analgesic and Anti-Inflammatory Effect of Ghanaian Medicinal Plants

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Abstract

Medicinal plants continue to be used in various cultures of the world as safe therapeutic agents against various issues including pain and inflammation which underlie almost every disease process. In Ghanaian traditional medicine, various parts of several plants have been used alone or in combination of therapies for the treatment of various painful inflammatory conditions. In this chapter, the anti-inflammatory and analgesic (antinociceptive) properties of selected medicinal plants from Ghana are reviewed. Evidence of pharmacological activities of crude extracts and fractions in *in-vitro* and *in-vivo* models, bioactive anti-inflammatory and antinociceptive compounds isolated as well as possible mechanisms of anti-inflammatory and antinociceptive action are discussed.

Keywords: inflammation, nociception, analgesia, herbal medicine, Ghana

1. Introduction

Inflammation is a complex defensive and protective response of living tissues to injury, irritation or infection which is accompanied by typical symptoms of pain, swelling, redness and fever. It is a mechanism by which the body identifies and neutralises noxious stimuli by increasing the blood flow to the site of tissue injured. Inflammation is a defensive mechanism but the complexity of events as well as the mediators released often result in the induction or aggravation of several disease conditions [1, 2]. Painful conditions such as rheumatoid arthritis, osteoarthritis, asthma, inflammatory bowel disease, colitis and hepatitis as well as other chronic diseases including cardiovascular and neurodegenerative diseases are all conditions whose pathophysiology involves inflammation [3]. These diseases impose a huge social and economic burden on individual victims, their families, and societies as a whole. Moreover, they can cause disability, impairing the social function of people, reducing their quality of life and sometimes resulting in death [2]. Millions of people suffering from different types of painful inflammatory conditions wish to find effective interventions with fewer or no side effects [4].

1.1 Current drugs for the treatment of inflammation and pain and their major side effects

The range of anti-inflammatory and analgesic agents currently available all work to relieve pain, reduce inflammation, and slow down or stop tissue damage. These include non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs), opioids and corticosteroids. Some antidepressants and anti-convulsants have also been shown to increase patients' threshold to pain [5].

NSAIDS such as diclofenac, ibuprofen and aspirin act by blocking certain stages of the arachidonic acid pathway, specifically by inhibiting lipoxygenase (LOX) and cyclooxygenase enzymes (COX-1 and COX-2) responsible for converting arachidonic acid to prostaglandins (PGs). Though effective, NSAIDS are associated with major adverse effects such as gastrointestinal ulceration, intestinal perforation, cardiovascular risks, hepatotoxicity and renal failure after long term use [6].

DMARDs such as methotrexate, sulfasalazine, gold compounds and penicillamine slow the progression of joint destruction in chronic inflammatory conditions like arthritis but are reported to cause kidney failure, skin reactions, liver problems and gastrointestinal side effects [7].

Corticosteroids such as prednisone, cortisone and methylprednisolone act by inhibiting the action of phospholipase A_2 which subsequently blocks the biosynthesis of inflammatory mediators such as prostaglandins and leukotrienes. Adverse effects such as delayed wound healing, hypertension, fluid retention, weight gain and osteoporosis are reported [8].

Opioids such as morphine, codeine and pethidine are very effective centrally working analgesics which increase the threshold of pain at the spinal level. These are associated with unwanted behavioural tendencies such as physical dependence, development of tolerance and respiratory depression [9].

1.2 Anti-inflammatory and analgesic agents extracted from medicinal plants

The adverse effects of most currently used orthodox drugs for the management of painful inflammatory conditions give a strong motivation for researchers to search for other appropriate and effective treatment [10]. Through this search, drugs of plant origin have attracted much attention due to their wide acceptance, availability, reported effectiveness and safety. The discovery of the anti-inflammatory agent salicin and subsequently, aspirin from *Salix fragilis* was a significant evidence to affirm the ability of plants to produce anti-inflammatory compounds [11]. Other plant products such as capsaicin (*Capsicum annum*), curcumin (*Curcuma longa*) and frankincense (*Boswellia serrata*) have been effectively utilised as adjuncts in the treatment of inflammatory conditions and pain [12–14]. Apart from being potent, these products have an added advantage of causing no significant adverse effect or toxicity to liver and kidney cells like other synthetic agents. Medicinal plants are therefore considered as sources of anti-inflammatory and analgesic agents and as practicable alternatives to conventional medicines [15].

1.3 Experimental methods used for screening anti-inflammatory and antinociceptive activities of herbal extracts

Based on the symptoms of inflammation, several *in-vivo* and *in-vitro* screening methods have been employed to evaluate the anti-inflammatory activity of plant extracts and natural compounds.

To investigate the anti-inflammatory activity of plant extracts against acute and chronic inflammation *in-vivo*, oedema, granuloma and arthritis models

have been used. To induce inflammation, phlogistic substances or irritants such as carrageenan, mustard, dextran, egg-white, yeast, zymosan-LOX, serotonin, histamine, kaolin, etc. are employed. Some applicable methods described in literature are the carrageenan-induced paw oedema in rats or chicks, croton-oil or oxazolone-induced ear oedema in mice, UV erythema in guinea pigs, granuloma pouch technique and pleurisy in mice [16]. Adjuvant-induced and collagen-induced arthritis models are also efficient in chronic inflammation studies. *In-vitro* methods have mainly focused on the inhibition of the activation of local inflammatory mediators such as leukotrienes [tumour necrosis factor alpha (TNF-α), interleukins (IL-6, IL-1β)], prostaglandins (PGE_2), prostacyclin, thromboxane A2, interferon-λ (IFN-λ), inducible nitric oxide synthase (iNOS) and reactive oxygen species. The level of these mediators at the inflamed site is measured and compared to control groups [17, 18]. Other *in-vitro* methods include human red blood cell stabilisation and protein denaturation assays.

To determine the antinociceptive effects of herbal extracts, chemically-induced (formalin and acetic acid-induced writhing test) and thermal-induced pain models (hot plate, tail immersion, tail flick, Hargreaves paw withdrawal methods) in experimental animals are commonly used [19].

1.4 Use of herbal medicine in Ghana

Like other developing countries, Ghana continues to search for more effective and appropriate ways of providing the health needs of its developing populace. Generally, the high cost of Western therapeutic medications and additionally their unavailability to the rural communities has prompted a high interest for herbal medicines [20]. In this regard, intensive efforts are being made to explore plants that might be of therapeutic significance to the Ghanaian community. Several reports cutting across the boundaries of botany, medicine and pharmacy have highlighted the use of different plants alone or in combination therapies for the treatment diseases [21–23].

Considering the evolving interest in studying traditional systems of healthcare and exploiting the potential of natural products for future drug development, this communication presents a compilation of data on plants with promising anti-inflammatory and analgesic activity with special emphasis on plants found in Ghana. Their pharmacological action, anti-inflammatory or analgesic constituents and possible mechanisms of actions are hereby discussed. It is envisioned that this information will be helpful to the indigenes for their primary healthcare and for researchers, to further identify the active chemical constituents and mechanisms responsible for the analgesic and anti-inflammatory potential of these plants [24].

1.5 Methods used for identifying herbal materials with anti-inflammatory and analgesic activities

Electronic databases including PubMed, SciFinder and Google Scholar were employed in the search for medicinal plants with reported anti-inflammatory and analgesic activities collected from various parts of Ghana. The inclusion criteria were that (i) plant should be used in Ghanaian traditional medicine for treatment of inflammatory condition or pain; (ii) validated *in-vitro* and *in-vivo* models for screening anti-inflammatory and antinociceptive activity were employed; (iii) the right botanical names, plant parts used, types of extracts prepared, active constituents and mechanisms of action if identified were mentioned. Consideration was also given to plants with significant activity differences with reference to control groups.

2. Plants with anti-inflammatory and analgesic activities from Ghana

2.1 *Albizia zygia* (DC.) J.F. Macbr. (*Leguminosae-Mimosoideae*)

Albizia zygia is a medium-sized ornamental shade tree widely distributed in secondary forest and semi-deciduous forest zones of West and East Africa. It grows up to about 30 m tall, has a branchless cylindrical bole with a greenish-grey smooth outer bark and an orange-brown fibrous inner bark. It has alternate bipinnately compound leaves and bears oblong flat pods. It is commonly known as the West African walnut and locally called '*okuro*' in Ghana (Akan). The leaf infusion is used for the treatment of lumbago, fever, waist pain and sexually transmitted infection. The bark decoction is administered to treat respiratory tract disease, malaria fever, constipation and worm infestation. The crushed bark is applied topically to treat yaws, heal wounds and toothache [25].

In previous studies, the leaves and roots were evaluated for their analgesic properties in animal models. Oral administration of the 70% ethanolic leaf extract in rats caused a significant reduction in both neurogenic and inflammatory phases of formalin-induced paw licking with maximal inhibition of 67.81 ± 8.73% and 72.85 ± 12.74% respectively [26]. The hydro-alcoholic root extract also caused a significant diminishing of acetic acid-induced visceral pain, formalin-induced paw pain, thermal and carrageenan-induced mechanical hyperalgesia in animals *via* opioidergic, adenosinergic and muscarinic cholinergic mechanisms [27].

To validate its anti-inflammatory effects, the hydro-alcoholic root extract was evaluated in carrageenan-induced paw oedema and caused a significant reduction of paw oedema in cockerels. The extract was found to increase the expression of endogenous antioxidants such as superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) as well as reduced the action of myeloperoxidase (MPO) and malondialdehyde (MDA) levels at the inflamed site [26].

2.2 *Anopyxis klaineana* (Pierre) Engl. (*Rhizophoraceae*)

A. klaineana is a medium sized to large tree found in the evergreen and semi-deciduous forest of tropical Africa. It grows up to about 50 m tall, has a branchless, cylindrical bole with longitudinally fissured greyish-brown outer bark and a thick pale orange inner bark. It has simple leathery, glabrous leaves which occur in whorls of 3–4 and bears greenish-white hairy flowers. *A. klaineana* is locally traded as '*kokoti(e)*' in Ghana and '*bodioa*' in Cote d'Ivoire. The stem bark decoction is used to treat joint pain, gonorrhoea, skin and respiratory tract infection, pneumonia, bronchitis and malaria. Its leaves are also applied as a poultice to heal wounds [28].

The anti-inflammatory activity of the stem bark of *A. klaineana* was evaluated in previous studies. Various solvent extracts including the petroleum ether, ethyl acetate and methanol extracts showed anti-inflammatory activity in a time and dose-dependent manner, by suppressing carrageenan-induced foot pad swelling in chicks. A tetranortriterpenoid called methyl angolensate was isolated as the major constituent of the stem bark and showed anti-inflammatory activity by significantly suppressing foot pad oedema in chicks with an ED_{50} of 4.05 ± 0.0034 [29]. In another study, a tirucallane triterpenoid isolated from the stem bark namely 3,23-dioxotirucalla-7,24-dien-21-oic acid, exhibited remarkable anti-inflammatory activity in a PGE_2 competitive inhibition immunoassay with an IC_{50} value of 3.63 μM which was comparable to the positive control, cortisone (IC_{50} = 2.59 μM). Methyl angolensate further demonstrated remarkable competitive inhibition of PGE_2 with an IC_{50} of 10.23 μM confirming its *in-vivo* anti-inflammatory effect [30].

2.3 *Calotropis procera* (Ait) f. (*Apocynaceae*)

C. procera is a medium-large sized bushy shrub which grows on coarse, sandy or alkaline soils of West and East Africa also found in the Indian Ocean islands and the north of South Africa. The plant can be identified by decussate, broadly ovate, leathery leaves and bears purple flowers with erect lobes [31]. It is locally called '*mpatu-asa*' (Akan) in Ghana. In traditional medicine, the bark decoction is used for the treatment of rheumatism, arthritis, headache and general body pain. The latex from leafy twigs and flowers is used for treating conjunctivitis, nasopharyngeal infection, tooth ache, wound healing, and vermifuge. The root bark decoction is used for treating cutaneous and subcutaneous skin infection and yaws [32, 33].

A study was conducted to determine the anti-inflammatory effect of the alcoholic extract of *C. procera* leaf in *in-vitro* models including the heat-induced haemolysis, hypotonic-induced haemolysis, albumin denaturation and the bovine serum albumin assay. The 70% alcoholic leaf extract at 1000 μg/mL significantly demonstrated anti-inflammatory effect by stabilising human red blood cells exposed to heat (69.24% inhibition) and hypotonic solution (85.09% inhibition). The extract prevented denaturation of protein (albumin) as well as bovine serum by 87.8% and 96.86% respectively. In *in-vivo* studies, the extract caused significant reduction of carrageenan-induced paw oedema in both acute and chronic inflammation [34].

2.4 *Capparis erythrocarpos* Isert (*Capparaceae*)

C. erythrocarpos is a climbing shrub distributed in the coastal scrubs and inlands of many African countries and commonly referred to as 'salt bush'. The plant is densely thorny and branched with re-curved hooks, growing up to about 6m in height. Its bears green elliptical leaves, which are alternately arranged [35]. The roots are used in traditional medicine for the management of rheumatism and arthritis. Other plant parts also find use in the treatment of eye and ear infection, fever, epilepsy and as aphrodisiac. The powdered root is used at the Center for Scientific Research in to Plant Medicine (CSRPM), Mampong, Ghana for the management of arthritis [21].

To validate the analgesic effect of *C. erythrocarpos*, the 70% ethanol extract of the root, stem bark and leaf were investigated in the formalin-induced nociception, hot plate and acetic acid-induced writhing assays in mice and rats. The root extract (100 mg/kg *p.o.*) was found to significantly and dose-dependently reduce pain in the early and late phases of formalin-induced pain by 47.54 ± 5.65% and 80.01 ± 3.77% respectively via interaction with adenosinergic receptors [36]. In other studies, the leaf extract at 200 mg/kg *p.o.* showed significant analgesic effects by reducing acetic acid writhing by 27.43% and increasing the pain threshold in the hot plate assay by 184.5% [37].

To validate its anti-inflammatory effect in both acute and chronic inflammation, the 70% alcoholic root extract was investigated in the carrageenan-induced paw oedema and Freund's adjuvant-induced arthritis models respectively. The extract at 30 mg/kg *p.o.* caused marked reduction in foot oedema by 48.86 ± 20.41% and significantly reduced knee joint swelling in arthritis by 34.19 ± 15.73%. The extract prevented systemic spread of inflammation from ipsilateral to contralateral limbs [38]. In another study, the leaves, stem bark and roots also demonstrated marked anti-arthritic activity by reducing rat paw volumes in the Complete Freund's adjuvant model with ED50 values (mg/kg) of 182.5, 181.5 and 36.4 respectively [39].

2.5 *Cassia sieberiana* D.C. (*Caesalpinaceae*)

C. sieberiana is a tropical woody shrub found growing in the bushy savannahs and coastal shrubs of many African countries. The plant grows up to about 20 m tall, has a short twisted bole, with a greyish-brown fissured bark. It has spirally arranged paripinnately compound leaves which bear bright yellow flowers and dehiscent pods as fruits. The entire plant is purgative and diuretic. The root decoction and leaf infusions are used as pain reliever in rheumatism and arthritis, for treatment of ear infection, skin disease, malaria fever, gastrointestinal infection, oedema, sexually transmitted infection, as laxative and vermifuge. The boiled and squeezed fresh leaves are applied topically to heal wounds, pleurisy and boils [25, 40].

A study conducted to investigate the analgesic effects of the aqueous and ethyl acetate root extracts indicated that in the hot plate assay, the aqueous extract attenuated hyperalgesia in a dose-dependent manner with an ED_{50} of 9.7 ± 3.9 mg/kg. The ethyl acetate fraction also showed antinociceptive activity in the formalin-induced nociception, yeast induced hyperalgesia, hot plate and acetic acid writhing tests. The analgesic effect was significantly blocked by Naloxone, atropine and theophylline indicating interactions with the opioidergic, muscarinic cholinergic or adenosinergic pathways [41, 42].

In-vivo study detected that the ethyl acetate extract of *C. sieberiana* root exhibits anti-inflammatory activity by reducing carrageenan-induced foot oedema in chicks [42]. Furthermore, the 70% ethanolic root extracts dose-dependently attenuated *Mycobacterium tuberculosis*-carrageenan-induced inflammation in the rats. Serum levels of IL-1α, IL-6 and TNF-α were reduced with increasing levels of IL-10 suggesting that the anti-inflammatory activity of the root bark extract may be as a result of its immune-modulatory effects *via* interactions with these pro-inflammatory mediators [43].

2.6 *Commelina diffusa* Burm. f. (*Commelinaceae*)

C. diffusa is a perennial herb distributed in tropical African countries including Ghana, Nigeria, Ivory Coast, Gabon and Congo. The plant is a smooth and sparsely hairy herb with mucilaginous leaves and creeping stems which ascends above and roots at the nodes. It is commonly called 'climbing day flower'. The Akans in Ghana fancifully refer to it as '*Nyame bewu ansa na mawu*' meaning '*God will die before I die*' alluding to its tenacity to life. In Ghana and Nigeria, the pounded leaves are applied topically to boils and swollen glands and as a rubefacient to relief pain in rheumatism and arthritis. Other reported uses include for the treatment of skin abscess, wound, gonorrhoea, ear infection and for the relief of severe menstrual pain [44].

To evaluate its anti-inflammatory effect, the 70% ethanolic leaf extract was investigated in the carrageenan-induced foot pad oedema in chicks. The extract (30, 100 and 300 mg/kg *p.o.*) showed a dose-dependent inhibition of foot pad oedema with the maximum inhibition of 43.55% at 300 mg/kg confirming it anti-inflammatory effects [44].

2.7 *Erythrophleum ivoren*se (A Chev.) (*Fabaceae*)

E. ivorense is a large tree widely distributed in the evergreen primary and secondary forests of tropical Africa. It grows to about 40 m tall, with a cylindrical bole, sometimes fluted at the base. It is called by names like 'forest ordeal tree', 'red water tree' and 'sasswood tree' in West African countries. Among the Akan tribe in Ghana, *E. ivorense* is known as '*potrodum*'. The stem-bark and roots are usually

employed in the treatment of epilepsy, emesis, pain, oedema, constipation and worm infestation [45].

The carrageenan-induced foot pad oedema in chick was used to evaluate the anti-inflammatory activity of the roots of *E. ivorense*. The 70% alcoholic root extract suppressed foot pad oedema in a time and dose-dependent manner. Three constituents, a casein type diterpene namely erythroivorensin A, betulininc acid and the flavonoid, eriodictyol isolated from the roots exhibited significant reduction of carrageenan-induced foot pad oedema better than the standard drug diclofenac [46].

2.8 *Ficus exasperata* Vahl (*Moraceae*)

F. exasperata, commonly known as 'sand paper tree', is a deciduous, shrub growing up to about 30 m tall. It has a buttressed bole with a pale grey-green outer bark and creamy-white inner bark which exudes a clear, viscid sap when damaged. It has alternate simple pubescent leaves which are elliptical in shape. In Ghana, it is locally called '*onyankyerɛn*' (Akan), '*nyadɛlɛ*' (Nzema) or *nyadkese* (Ga). The plant is used in folk medicine for the treatment of sprain, arthritis, rheumatism, intestinal and stomach infection, high blood pressure, abscesses and respiratory tract disease [47].

The analgesic activity of the 70% alcoholic leaf extract was investigated in murine models. The extract elicited a dose-dependent significant antinociceptive effect in the formalin-induced nociception assay through interactions with adenosinergic and opioidergic pathways [48]. The leaf extract also caused significant reduction in acute carrageenan-kaolin-induced muscle hyperalgesia (ED_{50} = 31.23 ± 11.91). Significant attenuation of chronic muscle hyperalgesia in both ipsilateral and contralateral paws and total reversal of the chronic muscle hyperalgesia in rats was produced by the leaf extract [49].

The hydro-alcoholic stem bark and leaf extracts at 30–300 mg/kg, *p.o.* dose-dependently inhibited carrageenan-induced foot oedema with ED_{50}s of 50.65 ± 0.012 and 46.05 ± 12.3 respectively [50]. Moreover, the leaf extract significantly reduced the arthritic oedema in ipsilateral paws of rats with a maximal inhibition of 34.46 ± 11.42% and significantly prevented the systemic spread to the contralateral paws [51]. Furanocoumarins namely bergapten, oxypeucedanin hydrate and the sterolin, sitosterol-3-O-β-D-glucopyranoside isolated from the stem bark also exhibited anti-inflammatory activities [52].

2.9 *Glyphaea brevis* (Spreng) Monachino (*Tiliaceae*)

G. brevis is a medium sized spreading climber usually found growing in forest re-growths, rocky savannahs and swampy areas of tropical Africa. It possesses straggling sparsely stellate branchlets, which bear ovate-oblong leaves and lemon-yellow flowers. Its fruits are spindle-shaped and brown in colour with irregularly ellipsoid seeds. The leaves are used to treat dyspepsia, gastric ulcer, oedema, pain and worm infestation. The root decoction is used to treat male sexual impotence, constipation, chest pain and gastrointestinal infection [53].

The anti-inflammatory effects of the 70% ethanol extracts of the leaves and stem bark were investigated by the carrageenan induced foot pad oedema method. The extracts exhibited potent anti-inflammatory activity in doses of 30, 100 and 300 mg/kg *p.o.*, by reducing foot oedema with similar potencies at ED_{50}s ~ 21.00 mg/kg [54]. In another study, oral administration of the 70% ethanol extract of the stem bark exerted inhibitory effects on carrageenan-induced paw oedema, systemic anaphylaxis and chronic inflammation in the Freund's adjuvant-induced arthritis models. The effect was significant when the extract was given both prophylactically and therapeutically [55].

2.10 *Haematostaphis barteri* Hook. f. (*Anarcadiaceae*)

H. barteri is a woody plant typical of tropical Africa widely distributed in rocky savanna areas of Ghana, Upper Volta, Nigeria, Cameroon and Sudan. It reaches up to about 8 m high, about 65 cm in girth with a bark that contains a clear gum. It bears characteristic reddish-purple drupes which are edible with an acrid taste [33]. It is commonly called 'blood plum' and in the Upper West region of Ghana where it is locally referred to as '*zimbringa*' (Dagaari). In traditional medicine, the boiled leaves are used to treat malaria. The stem bark decoction is used for the treatment of hepatitis and sleeping sickness, while the roots are used in the treatment of oedema, pain and swelling [56].

The antinociceptive and anti-inflammatory effects of the plant were investigated in previous studies. The aqueous leaf extract significantly blocked the progression of the neurogenic and inflammatory phases of formalin-induced nociception in a dose-dependent manner. The study further revealed that *H. barteri* inhibits nociception in mice by modulating the opioidergic, adrenergic, muscarinic, ATP-sensitive K^+ channels and adenosinergic nociceptive pathways [57]. Moreover, the aqueous leaf extract inhibited carrageenan, histamine and serotonin-induced rat paw oedema significantly [58].

2.11 *Hilleria latifolia* (Lam.) H. Walt. (*Phytolaccaceae*)

H. latifolia is a woody perennial herb about 2 m tall, with weak spiky hairs on young branches. It has alternate, simple elliptical leaves, bears several whitish-green sepals and a lens-shaped fruit with a thin wrinkled pericarp. In Ghana it is locally called '*Avegboma*' (Ewe) and '*Anafranaku*' (Akan-Twi) and used for the treatment of arthritis, rheumatism, oedema, gout, worm infestation, parasitic and viral infection of the skin, respiratory and pulmonary disease including asthma [25, 59].

The ethanolic extract of the aerial plant parts of the plant was investigated for analgesic and anti-inflammatory effect *in-vivo*. The extract in doses of 30–300 mg/kg *p.o.* demonstrated remarkable antinociceptive activity in the chemical and thermal-induced pain models. It produced a dose-related analgesic effect and significantly suppressed the development of morphine tolerance after repeated co-administration with morphine [60]. Its analgesic effect is *via* alteration of adenosinergic, muscarinic cholinergic and opioid pathways [61].

The 70% ethanolic extract of the aerial parts also significantly inhibited acute inflammation in the carrageenan-induced foot oedema [61] and significantly reduced poly-arthritic oedema in the ipsilateral paw of rats but was unable to prevent systemic spread to contralateral limbs in the Freund's adjuvant-induced arthritis model [62].

2.12 *Jatropha curcas* L. (*Euphorbiaceae*)

J. curcas is a shrub or small tree about, 2–5 m tall, with a smooth bark and sparsely lenticellate branches. The leaves are broadly palmate and inflorescences greenish-yellow. At maturity it produces ellipsoidal capsules containing black seeds. The seed oil is used to treat eczema, skin disease and to soothe rheumatic pain. The root powder is topically applied as a paste to treat swelling and inflammatory condition such as gout [63].

In studies of its analgesic activity, the 70% ethanolic root extract (30–300 mg/kg, *p.o.*) significantly inhibited acute and chronic skeletal hyperalgesia induced by 3% kaolin-carrageenan mixture in both ipsilateral and contralateral limbs of rats [64].

2.13 *Lannea acida* A. Rich (*Anacadiaceae*)

The name of the genus, *Lannea*, originates from the Latin word '*lana*' which translates to 'wool' alluding to the densely hairy young plant parts or possibly to the wool on the roots of some *Lannea* species. The plant occurs in different habitats in Sub-Saharan Africa including Benin, Burkina Faso, Cameroon, Central African Republic, Côte d'Ivoire, Gambia, Ghana, Guinea, Mali, Niger, and Nigeria. It usually grows in wooded savannah, forest edges, bushed grassland, rocky outcrops, and near rivers on sandy soils. It bears berry-like fruits which occur in large clusters and are consumed either fresh or dried. The fruits have a slightly acidic but pleasant taste. In traditional medicine, *L. acida* is used for the treatment of inflammatory condition, pain, schistosomiasis, haemorrhoid and toothache [65].

The aqueous stem bark extract was evaluated for anti-inflammatory effect and caused a significant dose-dependent reduction of PGE_2-induced rat paw oedema with maximal oedema inhibition of 67.1%. The stem bark extract also inhibited writhing movement in the acetic acid-induced writhing test in mice models [66].

2.14 *Newbouldia laevis* Seem. (*Bignoniaceae*)

N. laevis is a shrubby small to medium sized ornamental tree with several vertically ascending stems usually found growing in the wooded savanna and deciduous forests across tropical Africa. The plant has shiny dark green leaves and bears large terminal purple flowers. *N. laevis* finds use in folk medicine for the treatment of epilepsy, elephantiasis, haemorrhoid, pelvic pain, peptic and skin ulcer, rheumatism and as antidote to snake bite [40].

The analgesic and anti-inflammatory activity of the leaves have been investigated in several models. At 300 mg/kg *p.o.*, the 70% ethanol leaf extract significantly increased the paw withdrawal latency of mice in a tail immersion (withdrawal) test by 88.45 ± 19.81% indicating decreased sensitivity to pain. The leaf extract further inhibited the neurogenic (54.47 ± 8.60%) and inflammatory phases (83.62 ± 6.03%) of formalin-induced nociception and blocked the effect of carrageenan-induced thermal hyperalgesia by 37.60 ± 7.26% [67]. In another study, the hydro-alcoholic stem bark extract significantly and dose-dependently decreased formalin-induced nociceptive behaviour in rats [68].

The ethanolic leaf extract significantly and dose-dependently, inhibited carrageenan-induced foot oedema with maximal inhibition of 64.41 ± 11.47% [67]. In another study, the ethanol stem bark extract inhibited the poly-arthritic phase limb swelling in rat adjuvant-induced arthritis by 28.11 ± 2.02% justifying the use of the stem bark in the management of arthritis [69].

2.15 *Palisota hirsuta* K. Schum (*Commelinaceae*)

P. hirsuta is one of the most commonly used species of Commelinaceae. It is a robust perennial herb with lax inflorescences, lateral branches, purplish flowers and black glossy fruits. It is usually found in lowland rain-forest of West Africa. In Ghana it is commonly called '*somenini*' or '*mpentemi*' in Akan, '*sumbe*' in Ewe and '*sombenyin*' in Fante languages. Various parts of the plant are used in traditional medicine for the treatment of general body pain, earache, pelvic pain, piles, tooth ache, swelling and wound [70].

The ethanolic leaf extract of *P. hirsuta* was investigated for its analgesic effect. The extract (30–300 mg/kg *p.o.*) caused a significant increase in tail withdrawal latency by 73.75 ± 14.99%; reversed carrageenan-induced hyperalgesia with a percentage maximum effect of 154.79 ± 15.84%; reduced the number of acetic acid

writhing with an ED_{50} of 80.20 ± 0.58 mg/kg and decreased formalin-induced nociception by 83.46 ± 6.67% and 94.56 ± 4.12% in the early and late phases respectively [71].

In other studies, oral administration of the leaf extract (30–300 mg/kg *p.o.*) resulted in a dose-dependent complete reversal of vincristine-induced neuropathic pain in rats [72]. An ecdysteroid called 20-hydroxyecdysone was isolated from the root and was found to inhibit formalin-induced nociception in rats by 71.39 ± 9.19% and 89.19 ± 3.81% respectively in the early and late phases [73].

The ethanolic root extract (50–400 mg/kg *p.o.*) demonstrated remarkable reduction of carrageenan-induced foot oedema in chicks in both curative (62.52 ± 4.73%) and prophylactic (58.90 ± 11.38%) treatment regimens [74]. Further, the ethanolic leaf extract caused significant reduction in arthritic oedema induced by Freund's adjuvant and prevented the systemic spread of arthritis from the ipsilateral to the contralateral limb [75].

2.16 *Picralima nitida* (Stapf) T. Durand & H. Durand (*Apocynaceae*)

P. nitida is a medium sized to large tree which reaches up to 35 m in height with a dense crown, a pale yellow, fine grained inner wood and a cylindrical trunk. The leaves are broadly oblong with hard tiny lateral nerves and bear white flowers with ovoid fruits which turn yellow at maturity. *P. nitida* is widely distributed in the deciduous forests of West and Central Africa. In Ghana, the seeds are locally known as '*akuama*' (Asante-Akan) or '*onwema*' (Fante) and are used for the treatment of pain of various aetiologies as well as fever. Other plant parts find use in folk medicine for the treatment of malaria, fever, worm infestation, venereal disease, respiratory tract infection, constipation and jaundice [76].

Investigation of the analgesic effects of seeds collected from Ghana established that the aqueous seed extract possessed significant antinociceptive effect in murine models tested by the hot plate assay. Indole alkaloids isolated from the seeds, namely akuammidine, akuammine, akuammicine, akuammigine and pseudoakuammigine also exhibited potent analgesic effects in an isolated tissue and radio-ligand binding assay, demonstrating varying degrees of agonist and antagonist activity at μ-, δ-, and κ-opioid receptors [77, 78].

In anti-inflammatory studies, the hydro-ethanolic extract of the seeds demonstrated a dose-dependent suppression of paw oedema in the carrageenan-induced paw oedema assay. The extract further showed inhibition of chronic inflammation in rat adjuvant-induced arthritis. The total alkaloidal extract at 75–300 mg/kg *p.o.* caused a significant dose-dependent inhibition of total oedema formation in carrageenan-induced paw oedema assay and reduced adjuvant-induced knee joint swelling in rats [79]. Pseudoakuammigine displayed significant dose-dependent suppression of total paw oedema by 82.8 ± 94.6% [78].

2.17 *Phyllanthus muellerianus* (Kuntze) Exell. (*Euphorbiaceae*)

P. muellerianus is a straggling shrub about 12 m tall with spreading branches and several short axillary shoots dispersed in the deciduous and secondary forests of tropical Africa. It has simple alternate glabrous leaves and clustered whitish-green flowers. The plant bears fleshy six-seeded smooth capsules which are green when young and black at maturity. The fresh twigs are chewed to prevent toothache and also used to treat dysmenorrhea, dropsy, wound, swelling, oedema, tumour, paralysis and epilepsy [80].

The aerial part of the plant was investigated for analgesic and anti-inflammatory effects in various models. Oral administration of the aqueous extract in doses

of 30, 100, 300 mg/kg, produced significant antinociceptive effect in the acetic acid-induced abdominal writhing and formalin-induced nociception models in rats [81]. The antinociceptive effect of its major constituent geraniin was demonstrated *via* interaction with opioidergic receptors. Geraniin was found to potentiate the antinociceptive effects of diclofenac and morphine when co-administered [82].

In the carrageenan-induced acute inflammation model, the 70% ethanolic extract of the whole plant and 10 mg/kg of its major constituent geraniin significantly reduced paw oedema by 46.75 ± 4.97% and 61.65 ± 6.70% respectively. The extract and geraniin further attenuated arthritis by reducing total limb swelling in the Freund's adjuvant-induced arthritis model. Histomorphological analysis revealed reduced bone damage in both extract and geraniin treated groups [83].

2.18 *Secamone afzelii* (Schult.) K. Schum (*Asclepiadaceae*)

S. afzelii is a slender creeping woody climber about 12 m long, with dark brown branches which contain whitish latex. Its leaves are pinnately compound with entire margins and exude an odourless white gummy substance with slightly acrid taste when cut. It bears numerous flowers and achene (cypsela) fruits. In West Africa, the leaves are used to treat constipation, pain in rheumatism and arthritis, gastrointestinal discomfort, urinary tract and sexually transmitted infection [84].

To evaluate the anti-inflammatory effect of the plant, the ethanolic leaf extract (30–300 mg/kg *p.o.*) was examined in the carrageenan-induced foot oedema in chicks and caused a dose-dependent inhibition foot oedema. The highest dose of the extract gave a 44.26% inhibition of oedema [85].

2.19 *Synedrella nodiflora* (Linn.) Gaertn. (*Asteraceae*)

S. nodiflora is a common weed usually found growing along the banks of rivers, streams and roadsides of tropical African countries. It is an erect branched annual herb with ascending woody stems branching dichotomously from the base. It leaves occur in opposite pairs, elliptic in shape with finely toothed margins and bear small crowded yellow flowers at nodes. The whole plant is boiled in water and drank for the treatment of convulsion, threatened miscarriage, constipation, arthritis and as haemostatic [86].

The analgesic effect of the whole plant was investigated in several animal models. The ethanolic extract of the whole plant (100–1000 mg/kg *p.o.*) significantly reduced the number of writhes in mice during an acetic acid-induced writhing assay (ED_{50} = 141.9 ± 37.16) and inhibited both neurogenic (ED_{50} = 25.98 ± 14.59) and inflammatory (ED_{50} = 30.24 ± 18.08) phases of the nociceptive pain produced by formalin *via* adenosinergic mechanisms [87]. In other studies, the hydroethanolic extract of the whole plant (100–1000 mg/kg *p.o.*) caused a significant decrease to pain perception in mechanical, tactile, cold water and thermal hyperalgesia in paclitaxel and vincristine-induced neuropathic pain [88, 89].

2.20 *Trichilia monadelpha* (Thonn) JJ De Wilde (*Meliaceae*)

T. monadelpha is an evergreen, small to medium-sized tree with a straight cylindrical bole, smooth greyish outer bark and a pale pink inner wood. Its leaves are alternate, imparipinnately compound. It bears greenish yellow flowers and an obovoid 6-seeded dehiscent capsule. It is commonly known as '*otanduru*' (Akan-Twi) in Ghana and found growing at the river banks near evergreen semi deciduous forests. Various parts of the plant find use in traditional medicine for the treatment of inflammatory condition and neurological disorder such as epilepsy and psychosis [90].

Various solvent extracts (pet-ether, ethyl acetate and methanol) of the stem bark were evaluated for analgesic and anti-inflammatory effect. A significant dose-dependent antinociceptive activity in the chemical, thermal and mechanical models of pain was elicited by interaction with opioidergic, muscarinic cholinergic and adenosinergic pathways [91].

The aqueous and pet-ether stem bark extracts suppressed carrageenan-induced foot oedema in chicks by 57.79 ± 3.92% and 63.83 ± 12.0% respectively. In a Complete Freund's Adjuvant-induced arthritis assay, the aqueous extract (100 mg/kg *p.o.*) caused a significant attenuation of chronic inflammation by reducing joint thickness by 64.41 ± 5.56% [92]. Moreover, the stem bark extract caused significant reduction in the high levels of TNF-α, IL-6, malonaldehyde and myeloperoxidase and increased the levels of superoxide dismutase [93] and improved arthritic score by reducing redness, swelling and joint stiffness in rats. Hyperplasia, formation of pannus and exudation of inflammatory cells into synovial spaces were also reduced [94].

2.21 *Vernonia amygdalina* Delile. (*Compositae*)

V. amygdalina is a widely grown shrub in many African countries including Ghana, Nigeria, Cameroon, Togo, Benin, Guinea and Sierra Leone. It reaches up to about 10 m tall and is severally branched with a greyish-brown smooth bark. Its leaves are ovate-elliptical in shape, simple and alternately arranged with minutely toothed margin. It bears a 10-ribbed achene pubescent dark brown to black fruit. Due to the bitterness of its leaves, the plant is called 'bitter leaf' in many countries. In Ghana, the Akans refer to it as '*awonwene*' (Twi) literally meaning 'bitterness'. The leaves, stem bark and roots are used to treat malaria, fever, worm infestation, skin and nasopharyngeal infection, diarrhoea, dysentery, diabetes and as pain reliever in arthritis and rheumatism [95].

In previous studies, the anti-inflammatory properties of the leaves were evaluated in various models. The ethanol extracts of the young and old leaves (200 mg/kg *p.o.*) caused a significant dose-dependent inhibition of carrageenan-induced cold allodynia, increased the tail withdrawal latency in the tail immersion test and reduced the paw licking time in formalin-induced nociception test in rats *via* opioidergic, nitric oxide cyclic GMP and the muscarinic cholinergic pathways [96].

The young leaf extract at 50, 100 and 200 mg/kg *p.o.* significantly and dose-dependently reduced carrageenan-induced foot pad oedema by 59.61%, 67.52% and 86.31% respectively. Similarly, the old leaf extract at same doses exhibited remarkable suppression of oedema formation by 56.11%, 63.37% and 67.41% respectively [96].

2.22 *Wissadula amplissima* var. rostrata (Schum. & Thonn.) (*Malvaceae*)

W. amplissima is an erect, shrubby herb which grows up to 2.5 m tall on rocky and loamy soils of grassland, bushes and forests in tropical Africa. The leaves have entire or slightly toothed margins, densely pubescent on the lower surface but with sparsely stellate hairs on the dark green upper surface. The leaves are used as a poultice to relief spider bite and sting by venomous insects [25, 97].

The anti-inflammatory activity of the pet ether, chloroform and methanol fractions was investigated in 7-day old chicks and showed significant dose-dependent reduction of carrageenan-induced foot oedema. Maximal oedema inhibition was recorded as 68.25 ± 2.03%, 77.83 ± 0.81% and 62.21 ± 2.61% for the three extracts respectively [98].

2.23 *Xylopia aethiopica* (Dunal) A. Rich. (*Annonaceae*)

X. aethiopica is a tall evergreen aromatic tree with a smooth greyish-brown bark, severally branched crown and a buttressed bole. Its leaves are coriaceous, green on the upper surface and greenish-brown to orange on the lower surface. It bears small dark brown, cylindrical twisted bean-like aromatic pods, with about 5–8 black seeds per pod. The tree is usually found in lowland rainforests, coastal brackish swamps and deciduous forests of tropical Africa. The fruit is the most important part of the plant and is commonly known as the 'African pepper'. In Ghana it is locally referred to as '*hwentia*' (Twi), '*tso*' (Ewe) and '*soo*' (Ga). It is used as a flavouring in the preparation of soups and for the treatment of inflammatory conditions such as arthritis, bronchitis, rheumatism, lumbago, headache, neuralgia and colic pain [25].

The ethanolic fruits extract and its major diterpene constituent, xylopic acid were investigated for analgesic effects in several pain models. The fruit extract (XAE, 30–300 mg/kg *p.o.*) and xylopic acid (XA, 10–100 mg/kg *p.o.*) inhibited acetic acid-induced visceral nociception, formalin-induced paw pain, thermally-induced as well as carrageenan-induced mechanical and thermal hyperalgesia [99]. XAE and XA also exhibited anti-hyperalgesic and anti-allodynic properties in vincristine and paclitaxel-induced neuropathic pain [100, 101]. Co-administration of XA and pregabalin synergistically reduced paclitaxel induced neuropathic pain without causing any toxicity [102]. XAE and XA dose-dependently reduced both acute and chronic carrageenan-induced musculoskeletal pain [103] *via* opioidergic, adenosinergic, adrenergic, bradykinin and prostaglandin nociceptive pathways [104].

In anti-inflammatory studies, the aqueous fruit extract (300 mg/kg *p.o.*) caused a significant reduction of carrageenan-induced paw oedema in mice through inhibition of histamine release from mast cells [105]. Histopathology revealed substantial reduction in mononuclear infiltration, formation of pannus and bone erosion [106]. XA also caused inhibition of inhibition of histamine, serotonin, bradykinin and prostaglandin E_2-induced inflammation [107].

2.24 *Ziziphus abyssinica* Hochst Ex A. Rich (*Rhamnaceae*)

Z. abyssinica is a thorny, semi-deciduous plant, varying in habit from an erect shrub, a climbing plant or a tree with sagging branches that form a heavy, rounded crown. It usually reaches up to about 12 m tall and has a straight bole. It is commonly known as 'Catch thorn' in English and '*larukluror*' among the Sissala people of Ghana. The root and leaves are useful in folk medicine for treatment of pneumonia, tonsillitis, burn wound, chest pain, migraine and as a general pain-killer [108].

The analgesic and anti-inflammatory effects of the roots were investigated. The hydro-ethanolic root bark extract (30–300 mg/kg, *p.o.*) dose-dependently inhibited acetic acid-, formalin- and glutamate-induced nociception with maximal inhibition of 86.29 ± 2.27%, 84.97 ± 5.35%, and 82.81 ± 5.97% respectively. The paw withdrawal latencies in both tail-immersion and carrageenan-induced hyperalgesia were also prolonged [109]. Moreover, the root extract reversed hyper-nociception induced by intra-plantar injection of TNF-α, IL-1β, bradykinin and prostaglandin E_2 *via* interactions with opioidergic, adenosinergic, ATP-sensitive potassium channels and nitric oxide cyclic GMP pathways [110].

In an *in-vitro* assay, the hydro-alcoholic root extract at 100 μg/mL inhibited heat and hypotonic-induced haemolysis of human red blood cells by 61.8% and 42.98% respectively. The extracts also inhibited protein (albumin) and bovine serum albumin denaturation. Significant reduction of carrageenan-induced paw oedema

and a decreased the level of neutrophils in the peritoneal cavity were observed after oral administration of the root extract [111].

3. Conclusion

The Ghanaian flora provides a potent promising source for new therapeutic interventions for local population. The anti-inflammatory and analgesic activities of the crude extracts and fractions of several medicinal plants employed in Ghanaian traditional medicine have been validated in several models. However, the specific bioactive constituents are not yet identified. Therefore further studies to isolate and verify these anti-inflammatory and analgesic compounds are highly recommended. Further evaluation of safety profiles and standardisation of most active plants will add substantial value to the reported bioactivities and make these plants attractive for adaptation to pharmaceutical companies for further development.

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Conflict of interest

Authors have no conflict of interest to declare.

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