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Tetrapleura tetraptera Taub- Ethnopharmacology, Chemistry, Medicinal and Nutritional Values- A Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SKA and EOI have contributed to the chemistry and pharmacology of this plant and have collaborated with author IIJ in all facets of the work- literature search, collection of data and information, referencing and have collectively made inputs to the lay-out and design, read through and approved the final manuscript for publication.

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Review Article

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ABSTRACT

Ethnopharmacological Relevance: *Tetrapleura tetraptera* Taub (Fabaceae-Mimosoideae) is a well-known tree growing widely in forest zones all over West Africa. It is used in wound-healing, diabetes mellitus, asthma, hypertension, epilepsy, convulsions, leprosy, mental illness, inflammation, arthritis and rheumatoid pain, schistosomiasis control, as a general tonic and as a flavourer/spice.
Aim of this Review: The present review article which is in three parts gives an update on the chemistry, nutritional and medicinal values of its fruit, extracts and isolated compounds. It gives the

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opportunity to highlight the various ethnopharmacological uses as well as the pharmacological findings on *T. tetraptera* and discuss them.
Findings: *T. tetraptera* was reported to contain various biologically-active compounds such as 7-Hydroxy-6-methoxy coumarin- an anticonvulsant and hypotensive, hentriacontane-an anti-inflammatory agent, N-acetylglycosides of oleanolic acid, echinocystic acid and 27-hydroxyolean-12(13)-en-28-oic acid-as molluscicidal saponins, echinocystic acid-3-O sodium sulphate, chalcones-butein and isoliquiritigenin and the flavanone-naringenin-strong antioxidants, fatty acids-with a high level of omega-3 and omega-6 acids, propanoids, amino acids-as bioactive and antioxidant constituents and structurally-related compounds. The extracts and some of the isolated compounds showed sedative, hypotensive, molluscicidal, CNS depressant, anti-inflammatory, antimicrobial, wound-healing, contraceptive, analgesic, hypoglycaemic, antioxidant, hypolipidaemic, antimalarial, muscle-relaxant, anticonvulsant, hypothermic and anxiolytic effects in experimental animals. Nutritional assessments and phytochemical analyses of the fruit revealed the composition of mineral content, composition of essential oil, fatty acid profile, tannin content, crude protein content and toxic constituents which showed the nutritional importance of the fruit.
Conclusion: It is now known that *T. tetraptera* remains a rich source of extracts and chemical compounds that can benefit man in medicine and food; this justifies its use to spice dishes and for medicinal purposes.

Keywords: Tetrapleura tetraptera; ethnopharmacology; chemical constituents; nutritional quality; medicinal values/ pharmacological properties; review.

1. INTRODUCTION

Plant Identity: *Tetrapleura tetraptera* (Schum et Thonn) Taubert (Fabaceae-Mimosoideae);

Synonyms: *Tetrapleura thonningii* Benth, *Adenanthera tetraptera* Schum et Thonn;

Common names; *Aidan* tree (English);

Vernacular names; *Aridan/Aidan* (Yoruba), *Uyayak* (Ibiobio), *Oshosho* (Igbo), *Ora ora* (Awka), *Ighimiakia (*Bini), *Imiminje* (Etsako), *Prekese* (Twi, Ghana), *Dawo* (Hausa) etc.

T. tetraptera is deciduous, grows on the fringe of the West and Central African rainforest zone (found in Uganda, Mali, Burkina Faso, Mauritania and countries from Gambia to Nigeria) and is at its best growing most luxuriantly in the rain forest, reaching 20-25 m in height, with a girth of about 1.2-3 m. It is found also throughout riverian forest, in the southern savannah woodland as well as in the forest outliners in the African plains. The stem bark is fairly smooth, greyish-brown and thin. Leaves are sessile, glabrous or minutely hairy with a common stalk some 15-30 cm long and slightly channeled on the upper phase. Fruit has been described as being persistent, hanging at the ends of branches on stout stalks 25 cm long. The fruit appears green when still tender but on maturity and ripening, it is shiny, glabrous, dark-purple-brown some 15-25 cm long by about 4-5 cm broad (depending on size), with four longitudinal, winglike ridges nearly 2.5-3.0 cm broad. Two of these wings are woody while the other two are soft and are used for food, drinks and medicine, The small, black, hard and flat seeds are hidden in the pods [1].

T. tetraptera growing in most parts of West Africa begins to flower by the middle and end of February till the early or mid-April when young tender green fruits begin to appear. The indehiscent fruits are ripe from September to December and may be collected from the trees when they drop. The fruits are supposed to contain oily, aromatic and sugary substances. When the fruits drop as red brown pods, their smell attracts insects, termites, animals and even humans who need them for food and other uses.

Fig. 1. *T. tetraptera* at fruiting stage

Fig. 2. *T. tetraptera* fruit

2. ETHNOPHARMACOLOGY

The soft fleshy ridges of the fruit of *T. tetraptera* are perhaps one of the commonest ingredients of many drug preparations for inflammation and rheumatic pains, febrile convulsions, infantile flatulence and stomach gripes in West Africa.

In an earlier communication, it was noted that an infusion of the whole fruit was usually taken for feverish conditions and constipation, and as an enema and emetic [2]. Preparations containing the extracts are often used to manage or control arthritis and inflammatory conditions, diabetes mellitus, epilepsy, jaundice, hypertension, schistosomiasis, asthma, fever, malaria, microbial infections and pain [1].

Herb-sellers and food vendors in West Africa and some parts of Europe have displayed this fruit for sale as an item for culinary use and a recuperative tonic, and have advertised products made from the leaves and fruits as '*exotic African food or spice'* (Dami Botanicals Ltd, West Midlands, UK.). In all the regions where it grows, the sweet smell or fragrance of the fruit is highly valued, it is used to spice dishes and its fruit and stem bark are used for medicinal purposes [3,4]. (The products are advertised to control cholesterol level, promote production of breast milk, enhance healing of reproductive wounds, control hypertension and for use as scent in perfumery industries (Ganapi Ghana Ltd, Kumasi, Ghana). The *Asante* of Ghana call *T. tetraptera* fruit *"Prekese the sweet scenter, whose odour is felt in all houses when it starts from the end of town*--" [3]. The pungent scent of its fruit also earned for it '*Prekese, the insuppressible, whose presence permeates houses as he touches at its outskirts*----'[4].

In the Eastern parts of Nigeria, *T. tetraptera* fruits are used to prepare soups for mothers from the first day of delivery to prevent postpartum contraction. It is also an important component of pot-herbs [5] and it is widely used in the preparation of pepper soup in Southern Nigeria.

The stem bark, root, leaves or fruit are usually added to palm wine in neighbouring countries to make for "more potent wine." The fruits are usually charred and the ash resulting from burnt fruits is collected and used in the making of black soaps traditionally formulated, in admixture with certain plant materials such as charred *Threobroma cacao* fruits and *Cola nitida* fruits, to wash off feverish conditions, skin rashes, treat ulcers or even drunk in very low doses for internal cleansing in herbal medicine.

3. PHYTOCHEMISTRY

The isolation and identification by spectral methods of L-γ- Ethylideneglutamic acid and L-γ-Methyleneglutamic acid in the seeds of *T. tetraptera* was reported by Gmelin and Larson [6]. The authors isolated their products using paper and ion exchange chromatography and identified them by spectral methods- IR, ORD and NMR.

Activity-directed fractionation of *T. tetraptera* fruit extracts for anticonvulsant agents yielded 7-Hydroxy-6-methoxy-2H-1-benzopyran-2-one (Scopoletin) **(1)**, phenolic acds, fatty acids and soluble amino acids characterized by their spectral data and chromatographic behavior [7,8]. Scopoletin was extracted from powdered fruits and its concentration in the fruit was determined by HPTLC-Spectroflourimetry and by polarography [9]. Further activity-directed analysis of the fruit gave 3-0-[ß-D-glucopyranosyl-2'-acetamido-2'- deoxy]-oleanolic acid (Aridanin*)* **(2)**. Isolated as a white powder, compound **(2)** was identified by its spectral characteristics- ^{1}H and ^{13}C NMR, FDMS, M.pt. and by the spectral characteristics of its per-acetylated derivative [10]. Other compounds isolated were hentriacontane $\{CH_3(CH_2)_{29}CH_3$, **(3)**}, carbohydrate residues, phenylpropanoids-ferulic acid **(4)**, caffeic acid **(5)** and p-coumaric acid **(6)**, identified by their chromatographic behavior (PC, TLC) and MS.

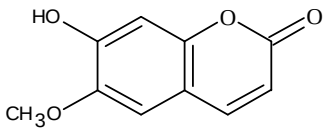
Activity-guided investigation of the fruit alcoholic extracts for molluscicidal properties afforded 3-[(2-acetamido-2-deoxy-ß-D-glucopyranosyl)oxy]-16α-hydroxyolean-12-en-28-oic acid **(7)**, 3-{[O-ß-

D-galactopyranosyl-(1→4)-(2-acetamido-2-deoxy-ß-D-glucopyranosyl)oxy]}olean-12-en-28-oic **(8)**, 3-{(O-ß-D-glucopyranosyl-(1→6)-(2-acetamido-2-deoxy-ß-D-glucopyranosyl)oxy}olean-12-en-28-oic **(9)**, a new glucoside of aridanin, and 3-{[O-ß-D-glucopyranosyl-(1→6)-ß-D-glucopyranosyl]-oxy}-27-hydroxyolean-12-en-28-oic acid **(10)** [11,12]. These saponins were identified by their spectral data (DCI-MS, ^{1}H and ^{13}C NMR) and information from chemical and enzymatic actions.

The presence of **(2), (7)** and **(9)** was confirmed also in the stem bark [13] as echinocystic acid -3-O-sodium sulphate **(11)** was reported as a new sulphated triterpene. Compound **(9)** was 100% lethal to *B. glabrata* at 20 ppm while **(11)** was not molluscicidal at the same concentration. All the isolated triterpenes isolated were investigated for anti-mutagenic properties.

The isolation of three flavonoid constituents was reported from the ethanolic extract of the mature fruit [14]: these were identified as 2', 4, 4'-trihydroxychalcone-*Isoliquiritigenin* **(12)**, 2', 3, 4, 4'-tetrahydroxychalcone-*Butein* **(13)** and 4', 5, 7-trihydroxyflavanone-*Naringenin* **(14).** The authors claimed a first report of the isolation of flavonoids in the genus *Tetrapleura.*

Motivated by the ethnopharmacological importance of *T. tetraptera* and the search for new bio-active saponins from Cameroonian medicinal plants, the stem bark and the roots of this plant were investigated [15]. Two new triterpene saponins acylated with monoterpene acid and ferulic acid resp. were isolated from the stem bark and four known oleanane-type saponins were isolated from the root. The two new saponins were identified as tetrapteroside A, 3-O-{6-O-[(2E,6S)-2,6-dimethyl-6-hydroxyocta-2,7-dienoyl]-ß-D-glupyranosyl-(1→2)-ß-D-glucopyranosyl-(1→3)-ß-D-glucopyranosyl-(1→4)-[ß-D-glucopyranosyl-(1→2)]-ß-D-glucopyranosyl}-3,27-dihydroxyoleanolic acid **(15)** and tetrapteroside B, 3-O-{ß-D-glucopyranosyl-(1→2)-6-O-(E)-feruloyl]-ß-D-glucopyranosyl-(1→3)-ß-D-glucopyranosyl-(1→4)-[ß-D-glucopyranosyl-(1→2)-ß-D-glucopyranosyl}-3,27-dihydroxyoleanolic acid) **(16).** The two tetrapterosides A and B were obtained through multiple chromatographic steps (VLC, FLASH, MPLC) and identified by spectral methods (MS, ^{1}H, ^{13}C NMR, and 2D NMR-COSY, NOESY, TOCSY, HMBC, HSQC) [15].



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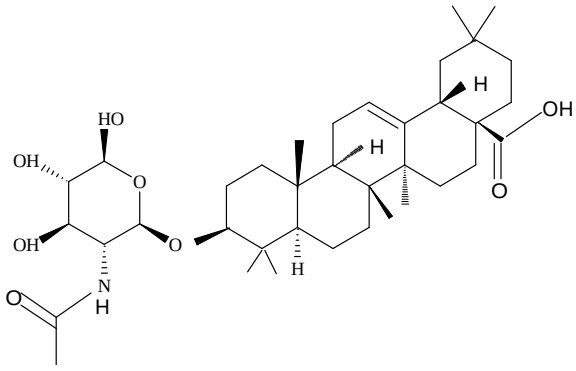

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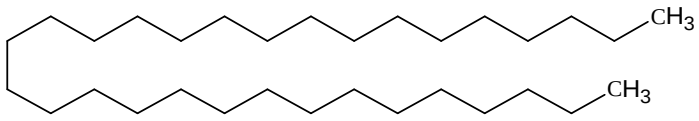

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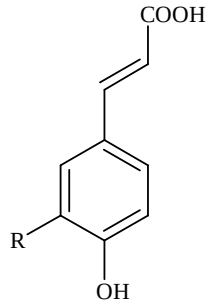
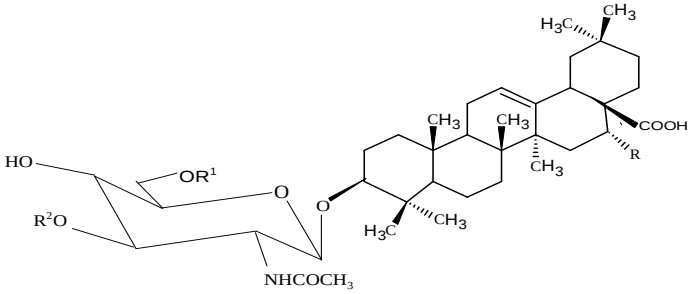
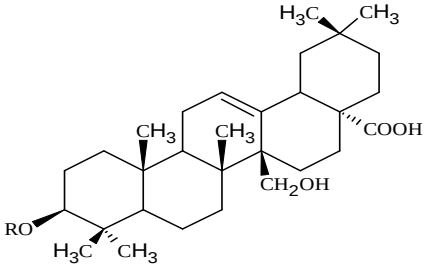


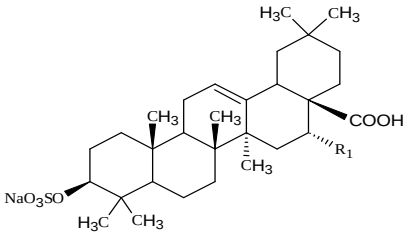
4; R = OMe, **5**; R = OH, **6**; R = H,



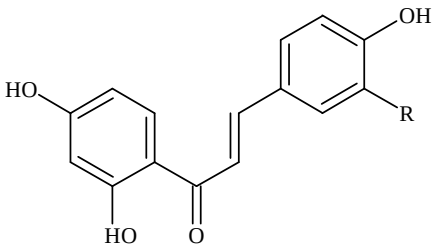
	R	R^1	R^2
7	α-OH	H	H
8	H	H	Gal
9	H	Glc	H



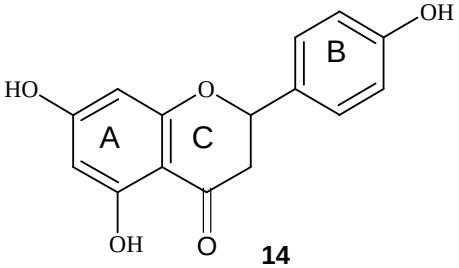
10; R = Glc^6- Glc



11; R_1 = α- OH



12; R = OH, **13**; R = H



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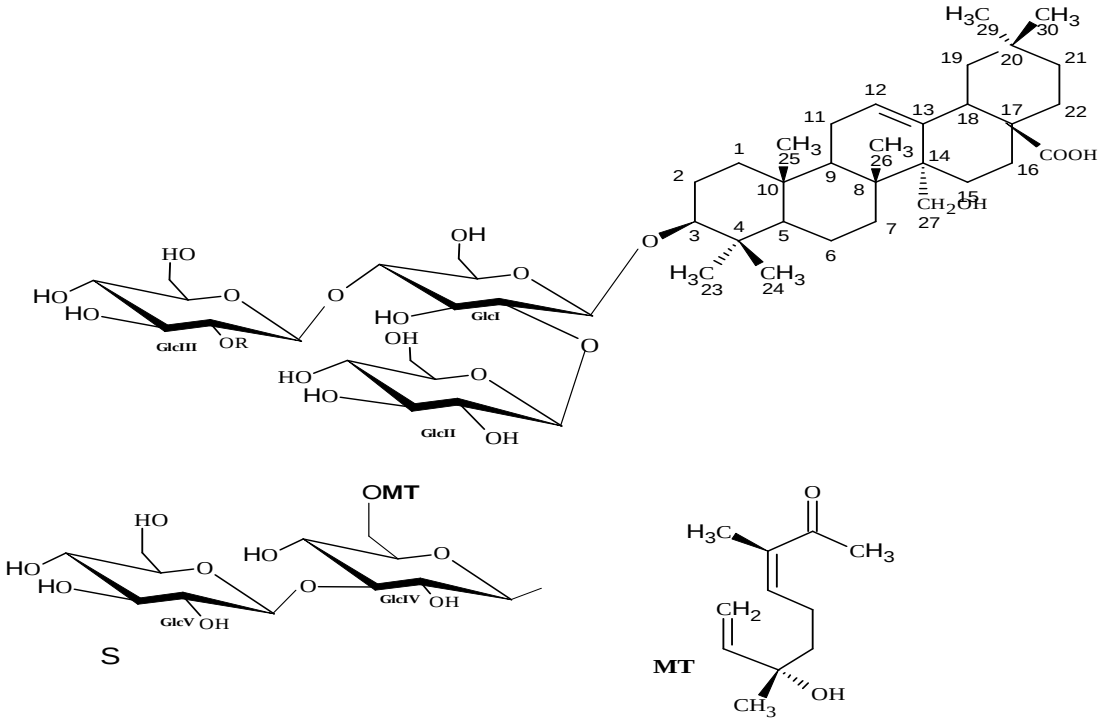

Where R = S

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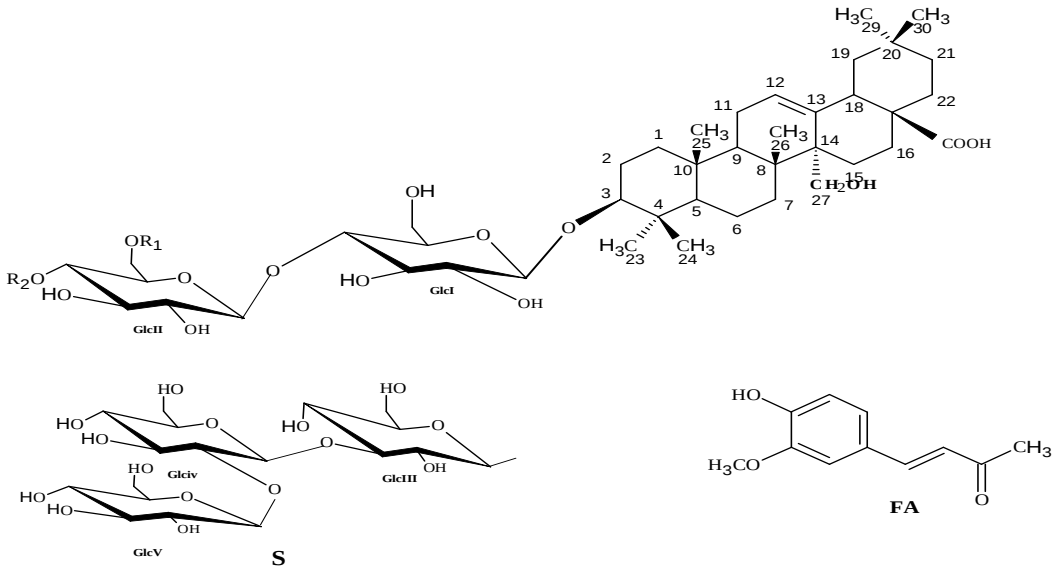

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4. ASSESSMENT OF NUTRITIONAL QUALITY

Some of the contributions of various laboratories to the determination of total phenolic content, flavonoids, mineral content, crude protein content, fatty acid profile, essential oil composition, crude fibre determination and phytochemical screening for plant metabolites in *T. tetraptera* have been summarized as they appear below;

The dry fruit shell, fruit pulp and seed of *T. tetraptera* were examined for nutritional quality by Essien et al. [16] and were found to contain varying amounts of nutrients- protein, lipids and mineral which were comparable in content or even higher in content than as found in more popular spices such as red pepper, onion, curry and ginger, The authors observed that the crude lipid fraction which indicated the location of the aroma of the spice enhanced the processing of the fruit and served to improve its use for commercial purposes. In another communication [17], the fruit was assayed for toxic constituents- hydrogen cyanide, phytates, oxalates, tannins and saponins. The authors found that the level of these toxicants compared with other sources as components in human diets.

The nutritional value of fresh mature fruits harvested in Southern Nigeria was analyzed by Dosunmu [18]; it was found that the crude protein content of the fruit was low (2.21%) in the fleshy mesocarp and even lower (0.51%) in the seeds. The author could not detect protein in the woody mesocarp. Whereas Sodium (Na) content was low, the fruit and seed were rich in Potassium (K), Iron (Fe), Magnesium (Mg) and Phosphorous (P). The fruit contained oxalate (8.14-16.6 mg/100 g), tannins (16.5-35.7 mg/100 g), hydrocyanic acid (98-100 mg/100 g) and ascorbic acid (68 mg/100 g). It was found that the oil had the properties of a drying oil and that carbohydrate residues- sucrose, glucose and fructose were found in the fruit.

Ngassoum et al. [19] analyzed t*he* aroma components of the fresh and dried fruit shell of *T. tetraptera,* and more than 40 compounds were identified. The dried and powdered sample was extracted with hexane at room temperature to give an oleo-resin sample which furnished three main components- 2-methyl-2-buteic acid (67.3%), 2-methylbutanoic acid (31.0%) and limonene (1.7%). The 0.2ml dichloromethane extract analyzed for the headspace sample and contained six major compounds- 2-methylbutanoic acid ethyl ester (41.3%), 2-methyl-2-butenoic acid ethyl ester (23.1%),

2-methylbutanol (17.1%), butanoic acid ethyl ester (9.6%), 2-methyl butanoic acid (7.1%) and 2-methyl-2-butenoic acid (1.7%). The third sample, derived from fresh and dried samples extracted using Solid Phase Microextraction (SPME) contained complex aroma systems and esters of lower acids and esters, ketones and alcohols, including acetic acid (48.2%/13.0%), 2-methylbutanoic acid (8.1%/14.5%), 2-methyl-2-butenoic acid (3.5%/ 5.4%) and butanoic acid (1.9% 9.5%). Esters identified were 2-methyl-2-butenoic acid ethyl ester (10.3%/0.9%) and 2-methylbutanoic acid ethyl ester (3.4%/1.4%), the ketones included 2-hydroxy-3-butanone (8.1%/ 31.6%) and 3-methylbutanone (0.3%/ 3.9%) and alcohols represented by 3-methylbutanol (6.1%/ 3.6%) and butanol (0.4%/ 4.6%). Some aroma-intense monoterpenes were found in the SPME samples and these were limonene (2.0%/ 2.4%), δ-3-carene (0.5%/ 0.7%), p-cymene (0.3%/ 0.3%), 1,8-cineole (0.3%/ 0.1%), p-myrcene (0.1%/ 0.1%), γ-terpinene (0.1%/ 0.1%) and α-terpinolene (0.1%/ 0.2%), all previously identified from *Citrus* peel and *Cymbopogon citratus.* The authors identified some of these components as being responsible for the odour impressions, smell and taste of *T. tetraptera* fruit.

Okwu [20] assessed the potential of the fruit as a spice and flavouring agent. It was reported that the fruit contained crude protein (7.44%-17.5%), crude lipid (4.98%-20.36%), crude fibre (17%-20.24%), carbohydrate (43.18%-49.06%) and food energy (234.42- 379.48 g/cal.). Ca, P, K, Zn and Fe constituted major minerals in the fruit.

Proximate analysis of the fruit gave ash (9%), fibre (45%), oil (4%), moisture (3%) and crude protein (5.6%) [21]. Mineral analysis was estimated (mg/100 g of fruit) as Ca (1.68%), Fe (12.02%), K (7.74%), Zn (10.59%), Na (4.74%), Mg (2.4%) and P (1.3%). The fruit contained alkaloids (1%), flavonoids (2.5%), saponins (20%) and tannins (0.12%).

The chemical composition of the fruit was evaluated by Akin-Idowu et al. [22]. It was reported that the fruit contained ash (3.17-3.48%), crude protein (5.13-8.65%), sugar (3.29-39.63%) and starch (7.56-29.10%). The mineral content (mg/kg) was Fe (29.69-65.06), Zn (5.35-25.16), Cu (4.00-12.54), Mg (392.35-2951.28), Mn (16.23-178.91), Na (119.48-2364.93), Ca (1348.63-13839.86), K (8631.09-14881.00) and B (1.14-6.23). The fruit also contained phytochemicals (mg/100 g dry weight of fruit); total polyphenol (38.05-2907.15), flavonoid (10.30-410.75), saponin (60.80-953.40), tannin (135.50-1097.50) and phytate (1021.00-5170.00).

T. tetraptera fruit was investigated for total chlorophyll, total carotenoids, β- carotene contents, fatty acid profiles and their associated health benefits to consumers [23]. The fatty acid profile of the seed revealed that the most predominant fatty acids were C18:2n6 (51%), C20:5n3 (13%), C18:ln9 (10.78%), C22:3n3 (5.55%) and C16:O (7.01%). The total unsaturated fatty acids content was found greater than the total saturated fatty acids and this made the authors to conclude that this could greatly contribute to fighting cancers, high cholesterol levels, obesity and cardiovascular-related diseases.

Darfour et al. [24] investigated the effect of gamma irradiation as a post-harvest processing technique on *T. tetraptera* fruit and the subsequent effect of the irradiation on some physicochemicals, free radical scavenging activity and physicochemical properties. The dried fruit powder was subjected to the irradiation. The total phenolic content, total flavonoid and DPPH free radical scavenging activity, p^H, lactic acid, vitamin C, moisture, carbohydrate, protein and trace element content of the samples were analyzed. The antioxidant potential of the *T. tetraptera* extract was enhanced in the solvent used for the extraction and it was found safe for human consumption as far as trace metal levels were concerned.

The composition of the essential oil and fatty acids of the dry fruits was analyzed (GC/MS) by Udourich et al. [25]. Of the 44 compounds characterized as essential oil constituents, the major constituents were acetic acid (34.59%), 2-hydroxy-3-butanone (18.25%), butanoic acd (8.35%), 2-methyl butanoic acid (7.58%), butanol (4.30%) and nerol (3.25%). Fifteen other compounds constituted the fatty acid composition and the major fatty acids identified were palmitic acid (49.44%), linoleic acid (26.81%), oleic acid (19.72%) and stearic acid (3.20%). The fatty acid composition was estimated to be 54% saturated while 46% was unsaturated with omega-6 and omega-3 fatty acids constituting 27% and 0.1% resp. and omega-9 fatty acid, 20%. Other components of the essential oil were citral (0.16%), geranial (0.18%), neral (0.23%), (6)-paradol (0.03%) and (6)-gingerol (0.14%) which occurred in trace or negligible amounts. The

characteristic fragrance of the fruit was attributed mostly to 2-methyl butanol (7.45%), butanol (4.3%) and nerol (3.25%); the fruity flavor to 2-methyl butenoic acid ethyl ester (2.70%) and 2-methyl butanoic acid ethyl ester (2.09%) and the pungent odour mostly to 2-hydroxy-3-butanone (18.25%) [26]. The proximate (%) nutrient contents of the fruit were estimated as ash (3.40%), protein (9.63%), carbohydrate (36.86%), fibre (44.81%), moisture (1.90%) and lipids (3.40%). The authors concluded that the essential oil was not a true essential oil because of its unusual high content of acetic acid.

The composition of the amino-acids and fatty acids of *T. tetraptera* fruit was evaluated along with those of nineteen other wild plants used as spices in Cameroon [27]. Total protein content (g/100g DM) for the fruit was 4.96±0.28 (N×6.25). The fruit was also shown to have a low level of essential amino acids (15.85%). Non-essential amino-acid composition (g/100 g protein) of the fruit was however given as Aspartate (14.47±0.04), Glutamine (19.46±0.03), Serine (7.64±0.04), Proline (0.24±0.04) and Glycine (42.34±0.04). These values are very significant. As expected, the fruit was also found to be rich in essential fatty acids; the total fat content (g/100g DM) of the fruit was put at 5.64±0.32. Essential fatty acids found in high amounts in *T. tetraptera* fruit were C18: 3n3, omega-3 fatty acid (33.64%±0.42), C22: 6n3, docohexaenoic acid, omega-3 acid, estimated at 11.9±0.28, and the C20:5 omega-3, eicosapentanoic acid estimated at 5.96±1.55. Palmitic acid, a saturated fatty acid, omega-9, C16: ln 9C was estimated at 22.77±0.85. All the other fatty acids were not detected.

The results of the various analyses of the fruit in different laboratories have been listed; this fruit was found to contain substantial and essential nutrients. Proteins are valuable as they constitute a major part of the body weight of humans and contain essential amino-acids which often act as bioactive substances or as antioxidants. Deficiency of essential amino-acids usually lead to a slow down and development of growth in children, allowing diseases and causing destruction of cells in adults.

Aspartic acid, measured as aspartate + asparagine, in the fruit [27] occurred as 14.47±0.04. It usually occurs as a physiological compound on mammalian pituitary and testis and has a role in the regulation of the release and synthesis of luteinizing hormone (LH) and testosterone [28]. Glutamine composition, estimated as glutamate+ glutamine, was also high in the fruit; it is recognized as the amino-acid in muscles, helping to build and maintain muscle tissue and working against muscle hypertrophy which usually appear after attacks of diseases [29]. Glutamic acid is a neurotransmitter for the CNS, the brain and the spinal cord. It acts as the fuel for the brain as it helps to correct physiological imbalances in the body. Serine composition was calculated as 7.64±0.04. Serine is an amino-acid necessary for the development of the muscles and the maintenance of the immune system, and so important in the formation of RNA and DNA from the cells. The content of glycine in the fruit (42.34±0.04) was high [27]. Glycine is known to retard muscle degeneration, improving glycogen storage and so releasing glucose for energy needs as appropriate [27]. Leucine (7.23±0.03 g/ 100 gm protein) functions in synergy with isoleucine and valine to promote muscle function, skin and bones.

Unsaturated fatty acids generally help to reduce risk of cardiovascular, psychiatric, neurological, dermatological and rheumatic diseases, development and maintenance of the human bodies especially the brain- development and functioning [30]. This is in agreement with the general notion that fatty acids regulate a variety of enzymatic processes and may control several chronic inflammatory diseases. The consumption of eicosapentaenoic acid: C20:5 omega-3 and acid docohexanoic: C22: 6 omega-3 found in the fruit is known to induce a decrease in triglycerides due to a reduction in the production of LDL, and sometimes, an increase of HDL [30]. Oils rich in linoleic acid are important for human health as they reduce atherosclerosis by interaction with HDL in blood [31]. Some polyunsaturated fatty acids such as linoleic acid and arachidonic acid known as vitamin F are required for growth and protection of the skin [32].

The ash content, the index of mineral content, revealed high levels of Mg, K, Ca, P, Fe and Zn in *T. tetraptera* fruit. Most of the minerals are present in concentrations higher than the required daily intake [22] for man and are essential in human nutrition. The high level of Fe suggests a good source of an important component of haemoglobin which plays the important role of taking oxygen from the heart to the cells. Zn provides protection against viruses causing respiratory tract infections [33], its

deficiency causes diarrhea and mental depression. The presence of Ca and Mg is beneficial in nutrition. Mg is important in Ca metabolism in bones and management of circulatory diseases and facilitates muscle relaxation [34]. It serves as a catalyst in energy-producing reactions within the cells. Ca and P are involved in bone and teeth formation, blood clotting and transmission of nerve muscles in chilly weather.

Epidemiological studies have continued to demonstrate that cardiovascular diseases such as hypertension (or elevated blood pressure) have become a major risk factor for coronary heart disease and stroke. Nutraceuticals and supplements that are of benefit in those with hypertension, for example, include antioxidants such as vitamins, the unsaturated fatty acids, flavonoids [35,36] and crude proteins as have been described in *T. tetraptera* fruit and these can explain the use of the fruit for managing cardiovascular diseases. These results show that edible fruits such as *T. tetraptera* fruit can contribute to the diets and well-being of indigenous people.

5. PHARMACOLOGICAL ACTIVITIES OF *Tetrapleura tetraptera* EXTRACTS/ *ISOLATED* COMPOUNDS

5.1 Anticonvulsant Activity

The search for anticonvulsants of plant origin led to the isolation and identification of scopoletin in *T. tetraptera* fruit [2]. Scopoletin (30-50mg/kg) produced quiecense and reduction of spontaneous locomotor activity in mice, it delayed the onset of seizures induced by leptazol (100 mg/kg) and protected about 70% of the animals used. The animals were all protected at higher doses. The cardiovascular and neuromuscular properties, and the mechanism of its hypotensive effects were investigated [37,38]. The properties associated with scopoletin are similar to those ascribed to its derivative, scoparone, which was isolated from *Artemisia scoparia* and which also showed strong anticonvulsant activities [39]. Many health benefits of scopoletin are now known; Scopoletin may have some benefits on people at risk of some types of cancer. It was reported that scopoletin inhibited proliferation of certain cancer cells by inducing apoptosis [40,41]. Scopoletin was found to inhibit hepatic lipid peroxidation and increased the activity of oxidants, superoxide dismutase and catalase. Other studies suggested that scopoletin might benefit those at risk of high triglyceride, cholesterol and glucose levels [42,43].

The fruit volatile oil was screened for anticonvulsant activity [44]. It was reported that the fresh fruit oil given intraperitonially in mice offered some protection against leptazol-induced convulsions, a dose of 0.4ml of the oil per mouse protected 78% of the experimental animals when administered 30 minutes prior to leptazol administration. It was also reported that 0.6ml of the oil, though prolonged the onset of convulsions and the average time of death did not completely protect the animals.

The anticonvulsant and analgesic properties of the fruit were investigated by Ojewole [45]. In this study, phenobarbitone (20 mg/kg i.p.) and diazepam (0.5 mg/kg i.p) were used as reference anticonvulsant agents for comparison. It was observed that like the standard anticonvulsant agents used as reference, *T. tetraptera* fruit aqueous extract (TTE, 50-800 mg/kg i.p) significantly ($p < 0.05$-0.001) delayed the onset of, and antagonized pentylenetetrazole (PTZ)-induced seizures. The aqueous extract of the fruit (TTE, 50-800 mg/kg i.p) also profoundly antagonized picrotoxin (PCT)- induced seizures, but only partially and weakly antagonized bicuculine (BCL)-induced seizures. These findings confirmed the earlier studies that the fruit aqueous extracts possessed anticonvulsant properties.

5.2 CNS-Depressant Properties of (2)-Aridanin

Studies were carried out to investigate the central nervous system depressant activities of **(2)** [46,47,48]. The authors investigated the effects of **(2)** on novelty-induced rearing, head dips, locomotor activity and on learning and memory. The authors reported that head dip reduction was noticed only with the highest dose (30 mg/kg, i.p.) while in Y-maze, a reduction in number of entrance (locomotion) with no change in percentage alternation on short tern working memory was obtained. It was observed that **(2)**, at various doses reduced novelty-induced rearing and locomotor activity in mice and also reversed the central excitatory effect of flumazenil. When the neuropharmacological effects of the compound was examined regarding stereotyped behaviours and hexobarbitone-induced sleeping time (HIST) in mice [46], the authors found out that **(2)** potentiated the hexobarbitone-induced

sleeping time, but did not change the stereotyped behavior induced by apomorphine. The authors reported that these effects of **(2)** suggested that it had a strong central depressant action which may be sedative in nature but lack psychopharmacological activities.

Compound **(2)** was also investigated for anticonvulsant, analgesic and hypothermic effects in mice [49]. It was reported that **(2)** protected mice used in pentylenetetrazole (PTZ)-induced seizures but not in strychnine and picrotoxin-induced convulsions.

These findings on the anticonvulsant, hypothermic and CNS depressant properties of the fruit extracts and isolates lend pharmacological support to the folkloric uses of the fruit for the management and/or control of epilepsy and childhood convulsions in the West African sub-region.

5.3 Analgesic Activity

The analgesic effects of *T. tetraptera* fruit aqueous extract (TTE) was investigated in mice, using morphine (MPN, 10mg/kg i.p.) and Diclofenac (DIC, 100 mg./kg i.p.) as reference agents for comparison. The fruit aqueous extract (TTE, 50-800 mg/kg i.p.) produced dose-dependent, significant ($p < 0.05$-0.001) analgesic effects against thermally and chemically- induced pain in mice. These results confirmed that the crude aqueous extracts of the fruit possessed analgesic and anti-inflammatory effects in experimental animals [45].

In their investigation of the analgesic and hypothermic effects of **(2),** [46], nociception was evaluated by using the hot plate method. Pain response latency on the hot plate (described as jump latency) was measured in seconds at 30 minutes interval for 1.5hr and compared to the control. Acetic acid-induced writhing test was carried out using mice as experimental animal. Analgesic and hypothermic actions were mediated through opiods and cholinergic, 5-HT receptors. The authors reported that **(2)** (15-30 mg/kg, i.p.) decreased rectal temperature and acetic acid-induced writhes in mice. The hypothermic action of **(2)** was reversed by pretreatment with cyproheptadine (0.1 mg/kg, i.p.), atropine (2 mg/kg, i.p.), naltrexone (0.25 mg/kg, i.p.) but not with haloperidol (0.1 mg/kg i.p.). The effect on acetic acid-induced writhing was completely blocked by naltrexone alone. The authors reported that **(2)** did not show any analgesic activity using the hot plate test but significantly reduced acetic acid-induced writhing in mice, with **(2)** (30 mg/kg i. p.) completely suppressing the writhes; and concluded that the compound showed both analgesic and hypothermic activities.

5.4 Anxiolytic Activity of (2)-Aridanin

The anxiolytic activity of **(2)** was *investigated* [49] in mice using Elevated Plus Maze (EPM) with diazepam as a standard drug. The authors reported that **(2)** (5-10 mg/kg i.p.) administered 30 min prior induced anxiolytic effect expressed by increase in number of entries in and time spent in the open arms and percentage of open arm entries and decrease in number of entries and time spent in the closed arms. The treatment of mice with flumazenil (2.0 mg/kg, i. p.) 15 min before the administration of **(2)** (10 mg/kg, i.p.) blocked the **(2)-** induced anxiolytic effect. It was found that this compound induced a dose-dependent anxiolytic effect in mice and that the effect is similar to the one observed with diazepam, a typical benzodiazepine drug. The treatment with flumazenil and the resultant blockade of the **(2)**-induced anxiolytic effect led the authors to conclude that the effect was exerted through interaction with the GABA-benzodiazepine receptor complex.

5.5 Anti-inflammatory Activity

The anti-inflammatory effect of the fruit aqueous extracts was examined in rats, using fresh egg albumin-induced pedal oedema as experimental test model of inflammation and Diclofenac (DIC, 100 mg/kg p.o) as reference anti-inflammatory agent for comparison. *T. tetraptera* fruit (TTE, 50-800 mg/kg, p.o.) produced dose-related, significant reductions ($p < 0.05$-0.001) of the fresh egg albumin-induced acute inflammation of the rat hind paw oodema. The authors concluded that the fruit aqueous extract possessed anti-inflammatory properties [50].

The anti-inflammatory effect of *Oldenlandia diffusa* and its constituent, hentriacontane **(3),** was reported recently [51]. The authors showed how **(3)** ameliorated the expression of all inflammatory mediators used in their experiments. Compound **(3)** was isolated in substantial yield from the fruit [10] and has also been found to be a component of beeswax, epicuticular wax derived from *Kigelia* species [52], spinach leaves, esparto wax derived from *S. tenacissima* L. and *L'spartum* L. (Gramineae)

[53], *Acacia senegal,* and the anti-inflammatory plants *Stachytarpheta cayennensis* and *Blumea lacera* (Burm.f.) D.C. (Asteraceae). Compound **(3),** in pure form was found to be stable and insoluble in water, and these properties could contribute to its role as a structural component of waxes. It probably exists as a structural component and the major paraffin of the fruit. The properties of **(3)** as an anti-inflammatory agent in *O. diffusa* could explain its contribution to the anti-inflammatory action reported in the fruit, *S. cyannensis* and *B. lacera.*

The findings on analgesic activity, anxiolytic effects and anti-inflammatory actions of the extracts lend scientific support to the ethnopharmacological use of the plant in the management and or control of painful, arthritic inflammatory conditions. Of particular note is that the isolated triterpene glycoside, (**2),** showed properties of a CNS-depressant, an anticonvulsant and an analgesic; it also showed hypothermic and anxiolytic properties.

5.6 Antibacterial Activity

The antibacterial activities of the fruit extracts were investigated by Achi [54], the author used the impregnated paper disc methods. Four typed bacterial strains, *Staphylococcus aureus* (ATTCC 12600), *Bacillus subtilis* (ATCC6051), *Pseudomonas aeruginosa* (ATCC10145) and *Escherichia coli* (ATCC11775) were used in the experiment. It was noted that the antibacterial activity was high against *S. aureus, P.aeruginosa and E. coli* with MIC values at 250 µg/ml against *E. coli, S. aureus and P. aeruginosa*; and 500 µg/ml against *B. subtilis*. The author noted that with the increase of extract concentration the antibacterial activity of the extract increased and suggested that the extract could be useful in preventing the growth of pathogens in food systems.

Studies were conducted to examine the antibacterial activities of the fruit extracts using four human bacterial pathogens, *E. coli, S. aureus, S. typhi* and *P. aeruginosa* [55]. The authors based their results on the zones of inhibition of different pathogens and concluded that the ethanolic extract of the fruit exhibited better antibacterial activity than the water extract and so was more potent against the test organisms.

The antibacterial effects of the aqueous and ethanolic extracts of the fruits were investigated on the pathogens (typed bacterial strains- *E. coli* (NCIB 86), *P. aeruginosa* (NCIB 950) and *S. aureus* (NCIB 8588) in nosocomial wound infections [56]. The drug impregnated disc method was used. The ethanolic extract had significantly greater activity against *E. coli* and *P. aeruginosa* when compared to *S. aeruus* ($p < 0.05$). The minimum inhibitory concentration (MIC) of the aqueous and ethanolic extracts against *E. coli, P. aeruginosa* and *S. aureus* were 500, 250 and 250 mcg/ml respectively ($p < 0.05$). The authors concluded that the fruit extracts had significant antibacterial activities on the pathogens in nosocomial infections.

Hentriacontane **(3)** discussed under anti-inflammatory activity, has also been described as an anti-tubercular drug and a probable anti-tumuor compound [57], this in part may explain the antibacterial properties of the fruit.

5.7 Antimalaria Activity

The extract of the fruit was investigated for antiplasmodial activity alongside different extracts from 10 other West African plants traditionally used against malaria in Ghana [58].The extracts were tested against both the chloroquine-sensitive strain PoW and the chloroquine- resistant clone Dd2 of *Plasmodium falciparum.* The antiplasmodial assay was performed by means of the microculture radioisotope technique. The concentration at which growth was inhibited by 50% (IC_{50}) was estimated by interpolation and IC_{50} values >50 µg/ml for extracts and IC_{50} values > 25 µg/ml for fractions were considered inactive. The mean IC_{50} values [µg/ml] obtained for the petrol/EtOAc (1:1, v/v) fruit extract for the two strains were > 50, suggesting inactivity in this test.

The fruit ethanolic extract was evaluated for its antiplasmodial activity *in vivo* by Okokon *et al.* [59]. It was reported that the extract (300-900 mg/kg) exhibited significant ($p<0.05$) blood schizonticidal activity both in 4-day early infection test and in established infection with a considerable mean survival time when compared with a standard antimalarial drug, chloroquine (5mg/kg). It was noted that the extract from the fruit possessed significant ($p <0.05$) antiplasmodial activity.

In another study, the *in vitro* antiplasmodial activity and cytotoxicity of dichloromethane and methanolic extracts of the stem bark were studied [60]. The antiplasmodial activity of

dichloromethane and methanolic extracts of the stem bark were tested on *P. falciparum* strains FCB (chloroquine-resistant) and 3D7 (chloroquine-sensitive) and on fresh clinical isolates, using the DELI method. The authors found that the dichloromethane extract had IC_{50} values of 10.1±3.2 µg/ml and 13.0±3.1 µg/ml for strains FCB and 3D7, respectively. Cytotoxicity on MRC-5 human foetal cells was weak (CC_{50} = 79.9±24.3 µg/ml), giving good selectivity indexes (7.91 and 6.15 for strain FCB and 3D7, respectively). The methanolic extract had moderate antiplasmodial activity (IC_{50} 34.6±4.7 µg/ml and 29.6±6.9 µg/ml on FCB and 3D7 respectively), but also weak cytotoxicity on MRC-5 cells (CC_{50} 89.4±10.8 µg/ml), giving selectivity indexes of 2.58 and 3.02 respectively. The authors concluded that the results showed that *Tetrapleura tetraptera* stem bark extracts had promising antiplasmodial activity.

These findings could explain the use of the aqueous extracts of the plant in the management of malaria and associated feverish conditions.

5.8 Molluscicidal Activity of *Tetrapleura tetraptera*

Phytochemical screening of the fruit showed that the aqueous extracts frothed copiously suggesting the presence of saponins which could be of interest in the control of schistosomiasis-transmitting snails [7]. This led to the identification of ferulic acid, fatty acids, oleanolic acid and its derivatives from acid-hydrolyzed extracts [8]. This preliminary work encouraged further laboratory and field evaluation of the molluscicidal properties of *T. tetraptera* [61]. It was found that all parts of the plant possessed molluscicidal activity. This and other interests further encouraged more detailed chemical analyses of the fruit, stem bark and root [10-13, 15]. Eight N-acetylglycosides of oleanolic acid, echinocystic acid and the rare sapogenin 27-hydroxyolean-12(13)-en-28-oic acid **-**compounds **(2), (7)-(11), (15)** and **(16),** have been isolated and characterized from *T. tetraptera* in various laboratories*.* It was observed that increased glycosylation of isolated triterpenes increased the solubility of the various saponins and the toxicity of the saponins to *Biomphalaria glabrata* snails, and that saponins from this plant had similar potencies to those isolated from *Phytolacca dodecandra and Swartzia madagascariensis* [11].

The molluscicidal and other related benefits of *T. tetraptera* extracts have been reviewed many times over in the Guardian newspaper (Guardian, Lagos dated 8th March, 2007 and 3rd July, 2008), Science Magazines under different headings- Potential uses of *Tetrapleura tetraptera* Taub. (Mimosaceae), (Science in Africa dated 11th November, 2011); *Aridan*, Success in fighting Bilharzia the natural way (Science in Africa dated 18th November, 2011) and as journal review articles [62-65]. The various experimental work(s), including toxicological evaluation confirmed the potential of this plant for the control of snails (mollusks) and so possible control of schistosomiasis.

Tannins were reported to be abundant in the fruit and stem along with saponins. It was noted that aqueous and methanolic extracts of a series of typical tannin-containing plants exhibited strong molluscicidal properties against the fresh water snail *B. glabrata,* which is the intermediate host of schistosomiasis [66]. The molluscicidal activities of this plant have been linked to the presence of saponins alone. There is the need to identify the contributions of tannins (if any) to the molluscicidal properties of this plant to present a true picture of the molluscicidal effects of the plant.

The information provided in this review confirmed the presence of saponins which exhibited very strong molluscicidal effects against known schistosomiasis-transmitting snails. This in turn gives scientific evidence and support to the traditional use of the plant extracts in the control of schistosomiasis.

5.9 Anti-diabetic Activity

The hypoglycaemic effect of *T. tetraptera* fruit alcoholic extract was studied in normoglycaemic rats [67]. Doses (1000 mg/kg- 4000 mg/kg body wt.) were administered. The extract at doses indicated exhibited a biphasic effect in the rats, causing an initial increase in blood glucose level followed by a falling blood glucose level. The effect at 2000mg/kg was found comparable to that of the standard drug, glibenclamide, between the second and eighth hour of administration and at the tenth hour, the extract (2000 mg/kg-4000 mg/kg) showed a significantly better ($p < 0.01$) blood glucose lowering effect than the standard drug. The author(s) concluded that the findings validate the traditional use of the fruit in the management of diabetes mellitus.

Hypoglycaemic effect of the fruit aqueous extract was examined in rats, employing streptozotocin (STZ)-induced diabetes mellitus as experimental test model and using chlorpropamide (250 mg/kg p.o.) as a reference hypoglycaemic agent for comparison. *T. tetraptera* aqueous extract (50-800 mg/kg p.o.) produced dose-dependent, significant reductions ($p < 0.05$-0.001) in the blood glucose concentrations of both fasted normal and fasted diabetic rats [50]. The authors concluded that the results indicated that the extracts possessed hypoglycemic properties.

In another study by Kuate et al. [68], *T. tetraptera* hydroethanolic extract was evaluated for antidiabetic properties, using experimentally-induced obese and type 2 diabetic rats with characteristic metabolic syndromes. The metabolic syndrome was induced in experimental rats by high-carbohydrate and high-fat diet and the administration of low dose streptozoticin. Oral doses of the hydroethanolic extract (200 and 400 mg/kg) were administered on the type 2 diabetic rats for 28 days, and metformin (300 mg/kg) was used as the standard antidiabetic drug. The body weight, systolic blood pressure, oxidative stress and metabolic parameters were then assessed to evaluate the effect of the extract on the characteristic metabolic syndrome. The authors found that *T. tetraptera* hydroethanolic extract (i), possessed hypoglycaemic ability, (ii), reversed hyperinsulinemia accompanied with obesity and type 2 diabetes status, (iii), attenuated weight gain in rats given high-carbohydrate high-fat diet, (iv), possessed hypolipidaemic effects and reduced tissue steatosis, (v), effectively attenuated lipid peroxidation and suppressed oxidative stress induced by high-carbohydrate diet and STZ, hence exhibiting good antioxidant ability, (vi), improved liver and kidney functions and (vii), improved inflammatory cytokines levels and cardiovascular function and concluded that *T. tetraptera* hydroethanolic extract could be further developed for the management of obesity, type 2 diabetic and hypertension.

Worthy of note is the report on the anti-diabetic effect of the total saponins from *Entada phaseoloides* (L.) Merr. in type 2 diabetic rats [69]. The authors remarked that their study demonstrated both hypoglycemic and hypolipidemic activities of total saponins in type 2 diabetic rats. Saponins from both plants contain N-Acetylglucosamine moieties and oleanene-type triterpenes in their structures and may, therefore, exhibit similar medicinal values. The findings in [68] strongly support this proposition.

These studies have provided the rationale for some of the ethnopharmacological uses of the fruit in the management of type 2 diabetes, inflammation and cardiovascular diseases, stroke and hypertension.

5.10 Hypolipidaemic and Anti- oxidant Activity

Nineteen (19) different commonly used spices were investigated for polyphenol content, *in vitro* anti-oxidant, anti- amylase and anti- lipase activities [70]. Phenolic acid content was determined by the Folin-Ciocalteu method with catechin used as standard, α-amylase inhibitory activity was measured using the starch-iodine method, 2, 2-Azinobis (3-Ethyl-benzothiazoline-6-sulfonic acid)-(ABTS) radical scavenging activity was used to screen for anti-oxidant activity while lipase inhibitory activity was also determined. The authors reported that while the aqueous extracts of the fruit had the highest content of phenolic compounds, the fruit was not potent in anti-amylase activity and also had low potency in anti-lipase activity; and based on the findings, the authors observed that the fruit exhibited properties beneficial to health and so could be used as an alternative and/or complementary strategy in managing risk factors and associated co-morbidities of diabetes mellitus.

The hypolipidaemic and anti-oxidant effects of the fruit were investigated in cholesterol-fed rats [71]. The authors reported that the fruit extract significantly ameliorated ($p < 0.05$) the cholesterol-induced body weight gain and there was an over 50% decrease in serum and post mitochondria fraction (PMF) total cholesterol compared to untreated hypercholesterolaemic rats, LDL- cholesterol was also significantly decreased in the extract-treated animals when compared to hypercholesterolaemic rats. It was also observed that in hypercholesterolaemic rats, a remarkable increase in lipid peroxidation (LPO) and a concomitant decrease in the enzymatic antioxidant status was observed; these indices were, however, significantly attenuated in hypercholesterolaemic rats treated with the extract, These results indicated that the alcoholic extract of the fruit exerted a hypolipidaemic effect, reduced body weight gain and increased the body's anti-oxidant defense system in hypercholeterolemic rats.

The nutritional and nutraceutical potentials of the *T. tetraptera* fruit was investigated along with

other spices [72]. Ferric ion reducing activity (FIRA), hydroxyl radical scavenging activity (HRSA), free radical scavenging activity (FRSA), total phenols, flavonoids, proanthocyanidins and tannins content were analyzed using current techniques. The authors found that total phenols content, expressed as gram gallic acid equivalents(gGAE) per 100g of dry weight (dw) was 22.75±0.32, flavonoids, expressed as g/100 g dw was 2.38±0.08 and tannins, 26.21±0.57 mg/100 g dw. Ferric ion reducing activity, expressed as mg ascorbic acid/g dw was 38.30±1.15, Free radical-scavenging activity (FRSA), expressed in mg Trolox per 100 g dw, was 10.45±0,21 and Hydroxyl radical scavenging activity, expressed as g mannitol/100 g dw, was 1.86±0.09. The authors classified the fruit as having moderate levels of FRSA and FIRA, phenols, flavonoids and proanthocyanins.

The effect of the dry fruit on the plasma lipid profile and enzyme activities in some tissues of hypercholesterolemic rats was investigated [73]. The aim was to assess the effect of the dry fruit on plasma lipid profile and some diagnostic enzymes – Alkaline phosphatase (ALP), Aspartate and Alanine aminotransferase (AST and ALT) in the heart, liver and kidney of hypercholesterolemic rats.The result showed significantly higher levels of plasma total cholesterol, low density lipoprotein cholesterol triglycerides and the LDL/HDL ratio in the hypercontrol rats than the normal control ($p<0.05$). Feeding with 25g/kg and 50g/kg of the dry fruit supplement caused a decrease in the levels of total cholesterol, low density lipoproteins, triglycerides and LDL/HDL ratio with increasing level of HDL when compared to the hypercontrol group ($p< 0.05$). The authors noted that (i), the dry fruit was capable of reducing blood lipids significantly and depending on the therapeutic dose, could be used for the treatment of elevated total cholesterol. (ii), since at 50g/kg, the AST and ALP levels were significantly increased in the liver and the heart, increased concentration of the fruit in the diet could cause damage to some of the organs and (iii), whereas supplements of the dry fruit in the diet could help to prevent against cardiovascular diseases, the plant should be administered in moderate amounts to prevent potential adverse effect.

The variation in the *in vivo* antioxidant properties and α-amylase inhibitory activity of the fruit was assessed [74] at two phenologic stages of the fruit development- the mature green and ripe brown stages. Phenolic antioxidant compounds (total phenol, tannin and total flavonoid) predominated in the ripe brown fruit and conferred it with higher *in vitro* antioxidant activities and α-amylase inhibitory activity than the mature green fruit. The authors contended that the higher potency of ripe brown fruit over the mature green fruit in inhibiting porcine pancreatic α-amylase may be attributed to its higher phenolic levels which possibly were also responsible for the higher antioxidant activities observed in ripe brown fruits. This is in agreement with earlier works [75,76], there were positive correlations between total phenolic content and antioxidant activity, and between antioxidant activity and α-amylase inhibition activity of plant extracts. The authors recommended that for a more effective use of the fruit for the management of oxidative stress and postprandial hyperglycemia in type 2 diabetes, the ripe brown fruit should be used.

The antioxidant and hepatoprotective activities of fruit extracts was investigated [77]. It was observed that the extracts showed varying levels of protection against CCl_4-induced liver damage, as revealed in the reduction in the activities of serum marker enzymes for liver damage- Alanine transaminase, Aspartate transaminase and Alkaline phosphatase; and bilirubin levels when compared with CCl_4- intoxicated control rats. Such defenses were made possible by the presence of flavonoids as experienced in *Morus nigra* [78]. They reported that the extracts decreased the elevation in the activities of liver enzymes and protected against CCl_4-induced liver damage and that the protection was mediated through its antioxidative defenses.

The antioxidant activity of the ethanolic extracts of the stem bark and fruit was investigated [79] using DPPH and FRAP. The authors found that the % DPPH radical inhibition ability of the stem bark ranged from 28.74% to *85*.26% while that of the fruit ranged from 10.56% to 66.01%. This showed that the % antioxidant activity of the stem bark extract was comparable with that of ascorbic acid while that of the fruit extract was about 75%. The authors concluded that the efficacy of the extracts in some of their bioactivities could be attributed to their favourable antioxidant potential.

The importance of antioxidants to health cannot be over-emphasized. The various reports recorded above are justified by the isolation and identification of compounds such as the proteins and antioxidant amino acids-methionine+

cysteine, histidine, flavonoids-*butein*, *naringenin* and *isoliquiritigenin* and phenyl propanoids-scopoletin, ferulic acid, caffeic acid and p-coumaric acid in the plant extracts. The biological/ medicinal values of scopoletin and the amino-acids were highlighted in this review earlier. The isolated flavonoids have also been shown to have different medicinal values; isoliquiritigenin, showed vasorelaxant effect, exhibited aldose reductase inhibiting property, is a potent anti-tumour and an anti-inflammatory agent [80-82]; butein is a potent antioxidant and an anti-inflammatory agent [83] and naringenin, an antioxidant, showed blood glucose lowering property and was reported to lower plasma cholesterol *in vivo,* [84,85]. Oxidative stress has been linked to disease conditions like inflammation, cancer, diabetes, cataracts and aging etc. [86-88]; the presence of these metabolites in *T. tetraptera* may provide the rationale for the traditional use of the plant in these many disease conditions.

5.11 Antigonadotrope Properties of Stem Bark Extracts

The inhibitory effects of the stem bark extracts was investigated [89]. It was observed that the extracts exerted an inhibitory effect on the luteinizing hormone (LH) released by cultured rat pituitary cells, The inhibition was dose-dependent. The authors observed that whatever the saponin concentration, the intracellular LH content remained constant, thus demonstrating a lack of effect on the true release process. An interaction between saponins and LH released into the medium was demonstrated; this led to a decrease in the amount of immunoassayable hormone. The decrease was time and dose dependent suggesting that the inactivation process probably occurred *in vivo*. The authors concluded that this result could explain the anti-gonadotrope properties of the stem bark extracts that are used as natural contraceptives in the Cote d'Ivoire (formerly Ivory Coast) Pharmacopoiea.

5.12 Antimutagenic Activity

The toxicity profile of the stem bark extract was evaluated [13]. The stem bark triterpene glycosides were found toxic to the target snail, *B. glabrata* at different concentrations, except **(11)**. In a forward mutation assay utilizing *S.* typhimurium strain TM677, the authors reported that the stem bark extracts were mutagenic in the absence of a metabolic activating system (S-9) while a methanol extract of the fruit exhibited a weak mutagenic activity only in the presence of S-9. These authors concluded that the stem bark isolates, **(2)**, **(7)**, **(9)** and **(11)** were not mutagenic either with or without metabolic activation.

The toxicity profile of the stem bark alcoholic extracts was examined and found cytotoxic [90]. The authors reported that the acute cytotoxic concentration of the stem bark extracts which killed 50% of brine shrimps within 24hr was 438 mg/ml.

The fruit ethanolic extract toxic profile was investigated on liver function profile and histopathology in male Dutch white rabbits [91,92]. The hepatotoxic effects of 10 days oral administration of the ethanolic extract was studied using twenty healthy male rabbits. It was reported that the ethanolic extract exhibited selective toxicity in male Dutch-White rabbits. The authors observed that the extract caused elevations in serum AST and alteration of various metabolic parameters but did not induce any marked pathological lesions in the liver. The extract, however caused significant ($p < 0.05$) reduction in RBC and WBC. It was suggested that the oral intake of the extract should be at doses equal to or less than 50 mg/kg body weight when the extract possessed haemolytic properties.

In another study, the bacterial reverse mutation effects of *T. tetraptera* extract were evaluated using Ames test [93]. In the *in vitro* Ames test, *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and *E. coli* WP 2uvrA were used with or without metabolic activation by S9 mix. The highest concentration of the extract for the Ames test was established at 5,000 µg/plate. The authors reported that the extract was non-mutagenic to all the five *S. typhimurium* and *E coli* test strains in the presence and absence of metabolic activation. The authors concluded that the extract showed negative results in the bacterial reverse mutation test signifying that it is potentially safe for use as medicinal plant supplement even at high doses.

5.13 Piscicidal Activity of *Tetrapleura tetraptera*

It was observed during laboratory studies that the methanolic extract of the fruit was toxic to fish [61]. Two species of fish, *Tilapia nilotica* and *Tilapia galilae* of varying sizes and length were exposed to serial dilutions of the extract after

acclimatization for two days before experimentation. Results showed an LC_{50} of 0.35 for *T. nilotica* and 0.44 for *T. galilae*, giving the indication that susceptibility of fish could vary with the species, size or even age of the fishes and the concentration of the extracts. Further experiments conducted in the fields showed that only smaller *Tilapia* species were killed and at low concentrations of the extract, the extracts were almost nontoxic to fish.

A survey of plants with piscicidal activities was carried out in Southwestern Nigeria and one of the plants cited was *T. tetraptera* [94]. The trial toxicity tests using 10 out of the 40 piscicidal plants documented produced 100% mortalities of catfish (C*larias gariepinus*) between 4 and 12 hours exposure to 120 ppm concentration. *T. tetraptera* recorded 100% mortality of *C. gariepinus* at 4th hour exposure. It was noted that fish had a longer survivorship at the lowest concentration (40 ppm). The author also noted that application of the documented plant materials on freshwater ecosystems varied and depended on the part(s) of the plant in use, its potency, mode of extraction (pounding, cutting, powdery or whole soaking) and active ingredients.

The toxicity of water extract of the fruits on catfish (*C. gariepinus*) fingerlings was studied [95]. The experiments were carried out under laboratory conditions for 96 hours with 30 fingerlings treated with each of the six graded concentrations of dried fruits. The study showed that the higher the concentration of the extract the higher the mortality of fingerlings while the toxicity of the extract reduced with time. Fifty percent mortality was recorded at 24, 20 and 16 hours for 45 g/ 300 ml, 60 g/ 300 ml and 75 g/ 300ml concentrations of extracts respectively. The treated fingerlings showed erratic swimming and loss of balance at high concentrations of extract. The authors concluded that the fruit had substantial piscicidal potentials to eradicate unwanted fish in aquacultural ponds and can also be used for the harvest of fish in streams, ponds and rivers without causing harm to the environment.

These findings on antimutagenic and piscicidal activities of various extracts and the isolated triterpenes suggest that though these could be toxic to snails and some species of fishes, they are indeed safe for human consumption at reasonable amounts.

5.14 Wound Healing Properties of *Tetrapleura tetraptera*

Wound healing properties of the stem bark extract was investigated [96]. The authors found that topically-applied stem bark extract promoted healing of excision and incision wounds in rats. The study showed an excellent potential of the stem bark therapy on dermal wound healing with a possible mechanism of action related to epithelialization, contraction and tenable strength improvement.

5.15 Other Uses of *Tetrapleura tetraptera* Fruit

The Ghanaian *Prekese* bitters had been formulated with the fruit extract in local gin. It has been shown to have therapeutic action easing hypertension and asthma and exhibiting anti-ulcerogenic and antimicrobial action, and showing other health benefits. Other known products are *Prekese* herbal drink, tea bags, syrup, medicine and spices. The effect of the fruit extract processed at different time intervals on the sensory qualities of Pork sausage was assessed [97].The authors found that the fruit extract had no effect on the nutritional qualities in terms of moisture and crude protein content, and also had no adverse effects on the sensory characteristics of the smoked pork sausages at an inclusion level of 10 ml/kg of meat. The physical and emulsifying properties of the *T. tetraptera* fruit extracts encouraged the determination and comparison [98] of the extracts with a well-known tincture, quillaia tincture B. P. for use in Pharmacy.

The Drug Research and Production Unit, Obafemi Awolowo University, Ile-Ife formulated the dried powdered fruit into soap bases, obtaining two brands of herbal soaps- original *Schisto* toilet soaps, one containing *aridan* fruits alone and the other inadmixture with three other plant parts. These formulated 'medicated soaps' were evaluated for organoleptic properties and foaming ability and it was found that, unlike the other dried plant materials examined, the fruit powder improved the foaming ability of the soaps.

6. CONCLUSION

Tetrapleura tetraptera is a widely used food/drug plant and recent biological/pharmacological studies have generally confirmed ethno-medicinal and folk-loric uses of the plant in various disease conditions; convulsions,

schistosomiasis, pain, microbial infection, inflammation, diabetes mellitus, hypertension, malaria and feverish conditions, impaired immune system etc.; in food as tonic, flavourer, spice and as an economic plant, in soap making and the formulation of *Prekese* bitters, syrup and spices.

The detailed information provided in this review on the chemistry of *Tetrapleura tetraptera* and the various biological properties of extracts and isolated constituents has given justification for the importance of this plant as food and as a useful drug. It is, however, noted that for a full benefit of this natural product to be tapped, more detailed work has to be diligently carried out. Researchers have screened the plant especially the fruit for plant metabolites and have reported the presence of tannins and alkaloids. None of the tannins and alkaloids has been identified in the plant to date. Many triterpenoid glycosides with strong molluscicidal effects have been isolated from *Tetrapleura tetraptera* fruit and stem bark extracts but only **(2)-** aridanin has been studied biologically to any reasonable extent. More biological work needs be carried out on the other isolated glycosides for a full appraisal of the plant and its constituents.

There is no doubt that *Tetrapleura tetraptera* remains a rich source of extracts and chemical compounds that can benefit man in medicine and food.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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