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A REVIEW ON THERAPEUTIC POTENTIALS OF AVOCADO SEED

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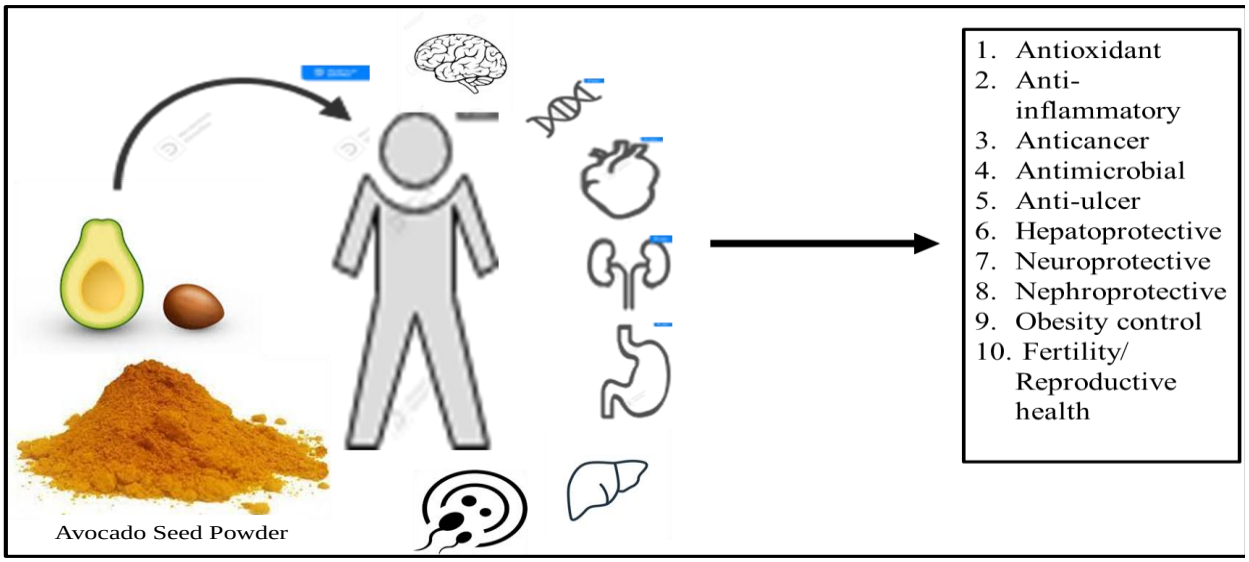
ABSTRACT

This paper highlights the bioactivity of the seeds of Avocado with potential therapeutic values. Searches in PubMed and Google Scholar with specific key words generated a number of literatures which satisfied the inclusion criteria and were used to collect valuable information for the study. Aqueous, ethanol, methanol, ethyl acetate and chloroform extracts of Avocado seeds were documented to be useful in a number of *invitro* studies on cancer and *invivo* models of liver, kidney and reproductive toxicities, ulcerand hypertension. The seeds were also found to maintain oxidative balance in animal models involving oxidative stress and inflammations. In spite the use of Avocado seeds as a 'super food' or functional food and nutraceutical by many cultures in the West, information on its use in Nigeria is limited. This study highlighted areas of further researches to deduce the molecular basis of use and the pharmacokinetics and bioavailability as a dietary supplement which may interact with the food matrix *in-vivo*.

KEY WORDS: Avocado, Bioactivity, Phytochemicals, Seeds, Secondary metabolites, Therapeutic



GRAPHICAL ABSTRACT

INTRODUCTION

Avocado, *Persea americana* Mill is a plant originating from Central America/Mexico but grown in many parts of the world and some states in Nigeria. The folkloric use of the leaves for treatment of hypertension, diabetes and fertility-related issues in Nigeria is documented. The seed is under-utilized fruit seed rich in phytochemicals with medicinal and therapeutic potentials. Avocado *Persia Americana* Mill. Cs. Hass is a plant belonging to the Lauraceae family that originates from Central America/Mexico which is grown in some parts of Northern Nigeria (Kaduna, Plateau, Nasarawa, Taraba, Kogi, Kwara, Niger states), South-East, South-West and South-South regions of Nigeria.Avocado is a plant of economic value and high nutritional and medicinal composition. The plant is locally called *Ubeoyibo* (Igbo), *Piaoyinbo* (Yoruba), *Orumwa* (Bini) and *Ebanmbaraka* (Efik), alligator pear or butter pear.

Different parts of the plant are rich in polyphenols, flavonoids, alkaloids and vitamins [1]. The fruits of avocado is highly consumed in the world due to the presence of unsaturated lipids and its relevance in improving and maintaining healthy heart and circulatory system [2]. The fruit is a berry with a very large fruit and a characteristic olive- green smooth leathery pericarp. The seed forms about 13-18% of the total fruit [3]. Compared with other parts of the fruit, the seed contain the highest antioxidant capacities, phenolic content, and procyanidins [4, 5]. A number of health benefits attributable to the secondary metabolites present in the seeds include

anticancer, anti-oxidant, anti-inflammatory, anti-diabetic, anti-lipidemic and anti-microbial actions [1, 6] and anti-ulcer [7-9] activities.

Avocado seed is documented to be an under-utilized seeds full of medicinal phytochemicals which largely go as waste materials[5, 10]. Only few researches on bioactivity of phytochemicals in the seeds have been conducted compared to other medicinal plants. There is ethno-pharmacological information on the use of seeds for the treatment of health-related conditions in the South Americas [10]. In Nigeria, the seed powder is used as a supplement for cardiovascular diseases and prevention with management of hypertension [11-13]. With increasing awareness on the potential of avocado seed as an antioxidant-rich and safe to consume part of the fruit, the use of the seed as nutraceutical is gaining increasing acceptance [6]. It finds application as herbal teas, or eaten as sliced, dried snack [14, 15] or ground to powder and mixed with fermented corn meal, *ogi* [11]. In order to improve utilization of avocado seed as food in the Nigerian diet, *moi-moi* was produced by adding the 10% of the seed flour to cowpea [16].

This review aims to highlight the bioactivity and therapeutic potentials of avocado seeds with a view to increasing its application in areas of function food, nutraceuticals, nutrigenomics, biosciences and pharmacology for future drug design and clinical studies.

METHODOLOGY

Keywords including ‘avocado seed, bioactivity, pharmacology, plant bioactive, secondary metabolites’, were searched using electronic database, PubMed and Google Scholar articles, were evaluated for the knowledge about the activity, test system, dose, duration, findings and mechanism of action of avocado seed. The articles were selected based on the following inclusion and exclusion criteria. Inclusion criteria: (1) Studies reported *in vitro* or *in vivo* with or without using experimental animals, including humans, cell lines and other mammals; (2) Studies that utilized single and/or multiple cell lines or animals; (3) Studies with Avocado seed as seed powder, aqueous, ethanol or methanolic extracts and (4) Studies with or without proposing activity mechanisms. Exclusion criteria: (1) Duplication of data and titles and/or abstracts not meeting the inclusion criteria and (2) Reports on parts of avocado other than the seed.

A total of twenty-three (23) articles were retrieved from PubMed search database and upon selection, only eighteen (18) satisfied the inclusion criteria. Relevant articles from 2003 –

2023 were searched using Google Scholar and only papers that met the inclusion criteria were further consulted. This study explored the bioactivity of avocado seeds with a view to bringing to lime light its therapeutic potentials.

RESULTS AND DISCUSSION

Bioactivity of avocado seeds

The main molecular families of bioactive compounds present in avocado include phenolic compounds (such as hydroxycinnamic acids, hydroxybenzoic acids, flavonoids and proanthocyanins), acetogenins, phytosterols, carotenoids and alkaloids [17]. Plant bioactive compounds also called secondary metabolites are chemically active compounds which are produced by plants in response to stress with complexity in structure and more restriction in distribution than the primary metabolites (carbohydrates, proteins, lipids, fats) [18]. The study of secondary metabolism in plants is an important source for the discovery of bioactive compounds with a wide range of applications [19] and many therapeutic lead compounds today are natural products or their derivatives. Most of the secondary metabolites have a broad range of their therapeutic activity and they directly interact with the receptors, cell membranes, and nucleic acids [20]. Bioactive compounds (secondary metabolites) are capable of modulating metabolic processes and exhibit antioxidant activities, inhibition of receptor activities, inhibition or induction of enzymes, and induction and inhibition of gene expression [21]. Examples of secondary metabolites with bioactivity include phenols, flavonoids, tannins, alkaloids, steroids, saponins which form a broad classification of these compounds.

Bhuyan *et al.*, comprehensively reviewed and summarized researches in the last few decades on the nutritional and therapeutic properties of avocado and its bioactive compounds [22]. Their paper highlighted the potential of avocado in novel drug discovery for the prevention and treatment of chronic diseases such as cancer, diabetes and cardiovascular diseases in addition to inflammatory/oxidative stress related and microbial infections. Studies have shown that phytochemicals extracted from the avocado fruit selectively induce cell cycle arrest, inhibit growth, and induce apoptosis in precancerous and cancer cell lines [23].

The bioactivity of avocado *in-vitro* or *in-vivo* in studies conducted on the seeds (Table 1) shows activity spanning different aspects of health and diseases. Folkloric use of Avocado seeds is documented among the people of Nigeria as anti-hypertensive [24, 25], anti-diabetic and

weight loss [26]. Anticancer activity of avocado seed extracts was shown in down regulation of the expression of cyclin D_1 and E_2 in LNCaP cells [27]. Avocado seed extract dose-$_{dependently}$ induced apoptosis in LNCaP cells while reducing nuclear translocation of NFκB. Avocado phytochemicals Persin induces G2/M phase arrest in human breast cancer cell lines MCF-7 and T-47D cells while Quercetin and its compounds luteolin and apigenin induced G2/M arrest in several cell types, including U937, lung cancer, prostatic carcinoma cells (PC-3) cell lines and normal tumour fibroblast cells [23]. *In-vitro* cytotoxicity assessment have reduced physiological relevance, capturing only limited aspects of the tumour microenvironment [28]. *In-vivo* studies capture the complexity of the tumour microenvironment and metastatic process in a living system making such studies more reliable even though cumbersome and costly.

Cyclosporin – A (CsA) is an immunosuppressive agent whose usage is associated with hepato- and nephro-toxicities. Molecularly, oxidative stress, inflammation and apoptosis are the main three mechanisms involved in CsA-mediated hepatotoxicity [29]. Owing to the documented antioxidant activity of avocado seeds extracts, oral administration of the extracts ameliorated cyclosporin-A induced hepatoxicity via inhibition of oxidative stress and ER stress [29]. Bhuyan *et al*. reviewed the bioactive metabolites present in avocado seeds and highlighted their health benefits [22]. Further *in-vivo* studies on the anti-hepatotoxic and nephrotoxicity is targeted at providing insights into the molecular basis of action of avocado seeds in toxicity.

Fertility is a measure of reproductive health while infertility is the inability to conceive after 1 year or more of unprotected sex. Avocado seeds improved sperm quality and antioxidant enzymes while decreasing arginase activity after administration in cyclosporin-induced reproductive derangement in male rats [30]. Understanding the mechanism of fertility boosting and spermatogenesis induced by avocado seeds in animal model is important as such study aim to provide useful information on molecular events in reproductive system of mammals.

TABLE 1: BIOACTIVITY OF AVOCADO SEED (*PERSEA AMERICANA* MILL)

S/N	BIOACTIVITY	TEST SYSTEM	DOSE/DURATION	FINDINGS/MECHANISM	REFERENCE
1.	Anti-hepatotoxic	Cyclosporin A – induced hepatoxicity in rats	5% seed powder (4 weeks)	Decreased DNA and liver damage markers, upregulation of expression of BCl2 gene. Inhibition of oxidative stress and pro-apoptotic ER stress.	[29]
2.	Improve fertility	Cyclosporin A – induced reproductive toxicity in male rats	50 – 100 mg/kg b.wt of seed extracts	Increased antioxidant enzyme activities, sperm quality, NO, and serum hormonal level, with a decrease MDA level and arginase activity	[30]
3.	Anti-hepatocarcinoma	DEN/2AAF – induced hepatocarcinoma in rats	50 mg/kg b.wt of hydroethanolic extracts of fruit and seed (alternate days for 20 weeks)	Decreases in antigen Ki-67, cyclooxygenase-2, and nuclear factor kappa-B expression levels, with increases in p53 and BAX levels.	[31]
4.	Neuroprotective	Rotenone-induced neurological disorder in Drosophila melanogaster	5 mg/mL Ethanolic Seed extracts (7 days)	Antioxidant and AChE inhibitory activities.	[32]
5.	Anti-diabetic/Hypoglycaemic	Alloxan – induced diabetes in male rats	26.6 – 106.6 mg/kg b.wt of aqueous seed extract (14 days)	Suppress oxidative stress. Decreased expression levels of IL-6, TNF-α and NF-κB. Suppress β-cell apoptotic death and upregulated glucose uptake by stimulating the PI3K/AKT signalling pathway.	[33]
6.	Antimicrobial /Wound healing	Excision wound infected with Staphylococcus aureus in rat model. Antibacterial activity using disc diffusion assay.	Ethyl acetate, chloroform, Methanol extract of *Persea americana* seed	Inhibition of bacterial biofilm and the perturbation of the bacterial membrane through the leakage of intracellular materials, the inhibition of H^+-ATPases pumps.	[34, 35]
7.	Nephroprotective/anti-inflammatory	Cadmium-induced nephrotoxicity in rats	400 mg/kg b.wt of avocado seeds extract	Exhibited significant anti-inflammatory effects, which was shown by reduced interleukin-2 and tumour necrosis factor α activities.	[36]

8.	Female reproductive health/fertility		20, 100, 500 mg/kg b.wt Methanol seed extract (for up to 90 days)	A dose-dependent decrease in FSH level in day-30 before a significant increase was observed for day 60 and 90. Progesterone increased dose dependently in the treated groups throughout the 90-day treatment duration.	[37]
9.	Anti-ulcer/antioxidants	Indomethacin-induced gastric ulcer in mice		Inhibition of pathways involved in gastric ulcer formation.	[9]
10.	Hypo-cholesterolemic	Hypercholesterolemia model in mice		Significant reduction in levels of total cholesterol, LDL-C, and prediction of the atherogenic index.	[38]
11.	Anti-cancer (breast and hepatocarcinoma cell lines)	MCF-7, HepG2 Cells		Inhibited cell proliferation of MCF-7 and HepG2 cells with IC_{50} values of 62 µg/mL and 12 µg/mL, respectively.	[39]
12.	Anti-cancer (osteosarcoma)	Canine osteosarcoma D-17 cell line	MTT assay of lipid-rich extract of avocado seed (1 to 100 µg/mL) for 24-48 hours	Induced a significant loss of mitochondrial membrane potential and increased superoxide anion production and mitochondrial ROS. Also, induced cell cycle arrest in G0/G1 phase.	[40]
13.	Anti-hypertensive	Rats	Aqueous seed extract 260 mg/kg; 500 mg/kg b.wt (10-14 days)	Improved hypercholesterolemia, reduced mean arterial pressure in rats,	[10, 13, 41]

CONCLUSION

Avocado seeds are rich sources of bioactive secondary metabolites that need to be considered as a dietary inclusion for maintenance of health status and protecting diseases in animals and man. These seeds are waste by-products of local consumption or processing companies which recently gained popularity because of the safety in consumption and enormous health benefits. Several studies have been performed in the past years on phytochemical composition and antioxidant compounds of avocado seeds and their potentials in the treatment and prevention of different diseases. However, there is limited literature on these medicinal potentials in clinical studies. It is worthy to note that molecular basis of action of plant bioactive compounds is a central feature in drug discovery. *In-vivo* studies on various disease signalling pathways, compound

bioavailability and pharmacokinetics of avocado seed bioactive compounds is key to understanding interactions of these phytochemicals with therapeutic potentials.

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