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Neuroprotective Potential of Avocado Peel Correlates with Antioxidant Status in Starvation and Refeeding In Wistar Rats.

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Abstract
This study aimed to evaluate the potency of hydroethanolic avocado (*Persea americana*) peel extracts in starvation and re-feeding on brain oxidative stress markers and to determine its anxiolytic, learning and memory potential by using elevated plus-maze and navigation multiple maze tests respectively in male wistar rats, as an animal model for cognitive function. Sixty rats were divided into six groups A, B, C, D, E and F, having 10 rats each. Groups A and B received distilled water as control and 50mg/kg body weight of the extract orally respectively and were allowed feed ad *libitum*. Groups C-F served as test groups and completed a 48 hr zero-calorie diet programme. Thereafter, Group C was given normal saline while Groups D, E and F were administered graded doses of the extracts and fed intermittently ad libitum for a period of 42 days. After cognitive studies, brain tissues were obtained for elucidation of the effects of the extract on oxidative stress markers. Results revealed that starvation and refeeding with the extracts significantly and in a dose-time-dependent manner, improved learning and memory as reflected by the decrease in time spent in the navigation multiple maze tests. In the elevated plus maze, the extract also significantly and in a dose-time-dependent way, caused anxiolytic effect by increasing the time spent in the open arms and decreased time spent in the closed arms. Significant increase was observed in MDA, F_2isoP, and PC while the opposite was the case for SOD, GPx and CAT after starvation stress in a dose-dependent way. By refeeding, the results revealed that the extracts significantly down-regulated MDA, F_2isoP and PC while up-regulated SOD, GPx and CAT activities dose-dependently. It can be concluded that the administration of Nigerian avocado peel extracts prevented anxiety and improved learning and memory dramatically after starvation and refeeding in rats, possibly through its unique cytoprotective mechanisms such as **antioxidant** efficacy.

Keywords: Avocado peel, anxiety, oxidative stress biomarkers, starvation and refeeding, learning and memory

Introduction
Although in 2015 the countries in the world projected to achieve zero hunger by 2030 [1]. Starvation, generally defined as severe deficiency in caloric energy intake, below the level needed to maintain an organism's life, is increasingly becoming global concern. Moreover, several individuals may starve for various reasons ranging from financial, psychological to religious reasons. Accordingly, 11.3% or roughly 805 million people are undernourished on a daily basis, consuming less than the recommended 2,100 calories each day [2]. By the 2018 Global Hunger Index (GHI) published data, the level of hunger and under nutrition worldwide falls into the *serious* category, at a value of **20.9**, down from 29.2 in 2000. In countries included in the GHI, the share of the population that is undernourished stands at 12.3 percent as of 2015–2017, down from 17.6 percent in 1999–2001 [3]. Population projection in the world is continuingly increasing, currently estimated as 7.7 billion people which is expected to reach 10 billion by 2055 and 11 billion in 2088 [4], leading to many concerns about the effect of physiological and pathophysiological states influenced by the metabolism of starvation and feeding [5].
A review of various literature revealed that starvation may be associated with abnormal neurological functions, a state of psychological and physiological disturbances manifested by

cognitive, emotional, behavioral and somatic elements [6]. Thus aromatherapy with psychoactive properties because of safety, quality and efficacy, has been suggested to be a useful alternative therapy to relieve abnormal neurological functions since synthetic drugs are associated with numerous side effects, like drug tolerance, abuse, sedation, limited efficacy, toxicity and bioavailability problems [7,8]. More so, consumption of avocados may be an effective strategy for cognitive health [9, 10].

Avocado (*Persea americana)* was solely native to Mexico, Central and South America, USA and Europe, today, the fruit is widely grown worldwide including Sub-Saharan Nigeria. Each fruit has a very large central seed or pit surrounded by an edible yellow-green aromatic flavored flesh fruity pulp covered by a purple or dark colored outer skin, or peel. The edible and non-edible parts of the fruits (pulp, seeds and peel) has been recognized to contain potent bioactive compounds and can be consumed as medicinal foods [7, 9-13] and the peel as an antimicrobial agent [11,14]. There is limited literature on the physio-pharmacological reports of avocado peel on central nervous system activity. Therefore, it was thought worthwhile to investigate the effect of Nigerian avocado peel extracts on brain oxidative stress biomarkers in starvation and refeeding and to determine its anxiolytic, learning and memory activities in male wistar rats by using elevated plus-maze model and navigation multiple maze tests respectively for behavioural functions, and to describe different mechanisms of action.

Materials and Methods

Animal and Administration of Hydroethanolic Extract of Avocado Peel

All the procedures involving the rats were approved by the Institutional on Animal Care and Use Ethics Committee. Also, recommendations of European Council Directive 86/609/EC (1986) were followed regarding the guidelines for the protection of animals used for experimental purposes. Prior to the study, food was provided ad-libitum until two weeks to sixty rats weighing between 180- 220g and was divided into six groups, having 10 rats. The groups were designated as groups A, B, C,D, E and F. Group A served as control and received distilled water and Group B received 50mg/kg avocado peel extracts; and both groups received feed ad libitum. Groups C-F served as test groups and administered hydromethanolic extracts of avocado peel as follows: Groups C-F were starved 48hr intermittently, thereafter Group C was given normal saline and Groups D, E and F administered graded doses of the extract and both with feed ad libitum for a period of 42 days. The extract was administered using oral cannula at doses of 50mg/kg, 100mg/kg and 150mg/kg to groups D, E and F respectively intermittently after 48hr starvation. Overall, an experimental trial of 42 days was carried out, with 28 days of starvation and then refeeding with or without the extract for up to 14 days.

Preparation of Hydroethanolic Extract of Avocado Peel

Avocado (*Persea americana*) grown in Nigeria was used in this study. Ripe avocado fruits were cut, and separated in three fractions (peel, seed and pulp). Pulp and seed was discarded, peels were carefully cleaned and hydroethanolic (ethanol: water, 80:20; *v/v*) extracts was used in this study. The peel of avocado was air dried at room temperature for 5 days and then dried in an oven, Panasonic 450®, at 70°C for 15minutes. The peel was then mashed into powder and macerated using hydro-alcohol for 5 days thereafter the filtrate was collected. The filtrated was concentrated using rotary evaporator using hydro-alcohol and continued with heating on the hot plate stirrer to remove the solvent. The obtained dry extracts were re-dissolved in order to prepare stock solutions and administered as follows:

Groups	**Treatments**
A	Normal saline
B	*Avocado peel* extract 50 mg/kg body weight
C	Starved + Normal saline
D	Starved + *Avocado peel* extract 50 mg/kg body weight
E	Starved + *Avocado peel* extract 100 mg/kg body weight
F	Starved + *Avocado peel* extract 150 mg/kg body weight

Treatment history					
Groups	**Refeeding**	**Starvation (48*hr*)**	**Refeeding**	**Starvation (48*hr*)**	**Refeeding**
A	Normal saline + feed *ad libitum*				
B	*Avocado peel* extract (50 mg/kg body weight) + feed *ad libitum*				
C	Normal saline +1.5g pelleted feed	Starved	Normal saline +1.5g pelleted feed	Starved	Normal saline + 1.5g pelleted feed
D,E,F	*Avocado peel*+1.5g pelleted feed	Starved	*Avocado peel*+1.5g pelleted feed	Starved	*Avocado peel*+1.5g pelleted feed

Elevated plus maze model of anxiety

Under laboratory settings, the elevated plus maze and navigational multiple maze tests are a common way to test spatial orientation in experimental animals. The elevated plus maze is an established method to testing exploratory behavior in animals- anxiety. The elevated plus-maze apparatus consists of two open arms (30 x 5 cm) and two closed arms (30cm x 5cm x 15cm) extending from a central platform and is elevated to a height of 50 cm above the floor. Each rat was individually placed on the center of the elevated plus maze with its head facing the open arm. During the 5 min observation period, the time spent in each experimental trail (*t*/seconds ±SEM) in the open and closed arms were recorded.

Navigation multiple maze test of learning and memory

To test learning and memory, the rat was placed in a maze with one escape hatch but many dead ends. The rat starts at the 'Start Point', wandered around in the maze to locate the 'Exit point'. The time taken in each experimental each trail (*t*/seconds ±SEM) by the animal to complete the navigation of the maze was calculated.

Biochemical investigations

After 42 days of the experimental period, the animals were anesthetized using Diethyl-ether and sacrificed. Brain tissue homogenate were prepared using standard procedures [17-18]. The non-enzyme markers- Isoprostanes (F_2IsoP), malondialdehyde (MDA) and protein carbonyl (PCO) and enzyme markers- superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) were assayed by described methods[19-21].

Statistical Analysis

The data collected were expressed as mean ± S.E.M of two independent experiments. For quantitative data statistical analysis was performed using One-Way analysis of variance (ANOVA) and Post Hoc analysis with the aid of IBM®SPSS Version 20.0. The Percentage change (*%*) was also presented.

Results

Effect of starvation on brain oxidative stress biomarkers

Starvation significantly (<0.05) depleted brain tissue antioxidant enzymes superoxide dismutase (-54%), glutathione peroxidase (-34%) and catalase (-22%). The concentrations of malondialdehyde (43%), protein carbonyl (45%) and isoprostanes (18%) were increased significantly (<0.05) compared with control (Table 1). On the other hand, the control animals fed 50mg/kg of the extract, caused significant increase in GPx (41%), SOD (12%) and CAT (3%). Meanwhile MDA (-49%), PCO (-32%) and F2ioP (-33.2%) were significantly decreased after feeding in comparison with the control (Table 1).

Effect of refeeding of the extracts on brain oxidative stress biomarkers

By re-feeding, after starvation, avocado peel extracts significantly caused a decrease in MDA, F_2iop, and PCO with corresponding increase in SOD, CAT and GPx in a dose-related fashion compared with control (Table 1). In starvation and refeeding with 150mg/kg of the extract, significantly increase in SOD (128.2%), GPx (81.1%) and CAT (29.9%) was observed. In contrast, a significant (<p 0.05) decrease in MDA (-49%), PCO (-47.3%) and F2iop (-37.1%) was observed in comparison with starved animals fed normal saline.

Anxiolytic effect of hydroethanolic avocado peel

Table 2 describes the effect of the extract on the behavioral changes in starvation and refeeding using elevated plus maze test. Our result showed that 50mg/kg of the extract caused significant increase in the experimental trial (t) time the animal spent in the open arm (t2, 78% and t3, 195%) and a significant decrease in time spent in the closed arm (t2, -52.4% and t3, - 60.4%) compared to control group of animals. In contrast, the starved groups given normal saline, showed slow cognition, concentration was impaired and thinking becomes very restricted and spent slower time in the open arm (t2, -53.7% and t3, - 65.9%). Meanwhile, in the closed arm there was an increase in time spent (t2, 4.8% and t3, 43.8%) compared with control. By refeeding, the extract significantly increased time spent in the open arm (t2 and t3) while decreasing in time spent in the closed arm (t2 and t3) dose-dependently in comparison with the starved and given normal saline. In starvation and refeeding, 150mg/kg of the extract caused significant increase in time spent in the open arm (t2, 374% and t3,757%) than was the case in the closed arm (t2, -55% and t3, -78%) compared with the starved groups fed with normal saline.

Effect of hydroethanolic avocado peel extract on learning and memory

Table 3 depicts the effect of the extract on learning and memory. The control starved rats given normal saline all wandered around and couldn't find the correct escape hole. The animals spent longer time in the navigation multiple maze test (t2, 32.5% and t3, 80%) compared with control group. Healthy rats given the extract (50mg/kg) were able to find the hole fast and spent less tine in the navigation multiple maze tests (t2, -50% and t3, -57%) in comparison with control group of animals. By refeeding, the extracts in a dose-dependent significantly reduced the experimental trial time spent and at 150mg/kg, t2 was - 43.3% and t3, -75% compared with starved control group of animals given saline.

Table 1: Effect of avocado peel on antioxidant enzyme biomarkers

Treatments	SOD (u/ml)	CAT (u/g)	GPx (µg/m)	MDA (µg/ml)	F_2isoP (µg/ml)	PC (µg/ml)
Control	224±4.2	111±0.3	56±0.1	140±0.2	190±0.3	120±0.2
50mg/kg AP	250±1.3[a]	114±1.2[a]	79±0.3[a]	72.0±1.2[a]	127±1.7[a]	82.0±0.1[a]
Starved +Saline	103±1.4[a]	87.0±2.3[a]	37±1.0[a]	200±1.4[a]	224±1.3[a]	174±1.4[a]
Starved +50mg/kg AP	140±1.7[a]	80.0±1.4[a]	37±1.2[a]	192±1.0[a]	180±0.2[a]	151±1.7[a]
Starved +100mg/kg AP	230±0.8[a]	100±1.2[a]	60±0.4[a]	150±0.4[a]	167±0.1[a]	147±2.1[a]
Starved +150mg/kg AP	235±0.7[a]	113±1.4[a]	67±0.3[a]	102±1.4[a]	141±2.1[a]	92.0±0.4[a]

Key; AP-avocado peel extract, SOD-superoxide dismutase, CAT- catalase, GPx-glutathione peroxidase, MDA- malondialdehyde, F_2isoP-isoprostane F_2, PC-protein carbonyl [a]-values are statistically significant (P≤0.05) compared to *control* (*n*=10)

Table 2: Effect of the extract on time spent in the open and closed arms using elevated plus-maze

	Open arm			Closed arm		
Treatments	***Trail 1***	***Trail 2***	***Trail 3***	***Trail 1***	***Trail 2***	***Trail 3***
Control	24±0.2	41±0.6[a]	41±0.3	47±0.2	42±0.1	48±0.1
50mg/kg AP	21±0.1	73±0.2[ab]	121±0.4[ab]	41±0.1	20±0.4[ab]	19±0.3[ab]
Starved +Saline	27±0.3	19±0.3[ab]	14±0.1[ab]	43±0.4	44±0.1	69±0.8[ab]
Starved +50mg/kg AP	28±0.7	34±0.1[ab]	47±0.8[b]	44±0.3	42±0.1	37±0.3[ab]
Starved +100mg/kg AP	24±0.2	83±0.4[ab]	118±2.1[ab]	40±1.1	34±0.3[ab]	27±0.3[ab]
Starved +150mg/kg AP	20±0.4	90±0.7[ab]	120±0.6[ab]	41±0.4	20±0.2[ab]	15±0.1[ab]

Key; AP-avocado peel extract, trials (in seconds±SEM);[a]- value statistically significant at P≤0.05 compared to *control*; [b]- value statistically significant compared to previous trial within same treatment group.

Table 3: Effect of the extract on time spent using navigation multiple maze tests in learning and memory

Treatments	*Trail 1*	*Trail 2*	*Trail 3*
Control	41±4.2	40±4.1	40±4.3
50mg/kg AP	31±1.1[a]	20±4.3[ab]	17±2.1[ab]
Starved +Saline	40±2.3	53±5.4[ab]	72±6.2[ab]
Starved +50mg/kg AP	40±2.1	40±4.3	40±4.2
Starved +100mg/kg AP	43±1.3	32±3.4[ab]	27±2.4[ab]
Starved +150mg/kg AP	41±3.2	30±4.4[ab]	18±2.1[ab]

Key; AP-avocado peel extract, trials (in seconds ± SEM);[a]- value statistically significant at P≤0.05 compared to *control*; [b]- value statistically significant compared to previous trial within same treatment group.

Discussion

The study aimed to determine the effect of 48 hr intermittent starvation and refeeding using avocado peel extracts on brain activity and cognition in experimental animals. Avocado *(Persea americana)* peel is usually bio-waste, but its nutritional importance can be said to be functionally equivalent to its edible portion [7,8,10,11,12,14]. Indeed, the physio-pharmacologically bioactive constituents of avocado peel phytochemical may be responsible for the biological activities and this theory may not be completely excluded from the outcome of this study. To our knowledge, this is the first study to examine physiological and psychological changes after 48 hr starvation and refeeding with avocado peel extract in rats. The findings of the present study revealed that starvation stress assessed in an *in vitro* model of rat's brain (tissue homogenates) significantly increased oxidative stress, reactive oxygen species levels and lipid peroxidation evident by increased production of malondialdehyde (MDA). On the contrary, there were diminished activities of the free radical scavenging factors such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx). This is suggestive that food deprivation or starvation can change the way the body responds to starving conditions in maintaining the energy homeostasis through regulating nutrient metabolism perhaps to promote the chance of survival in agreement with the previous reports [5]. Nevertheless, studies have associated food deprivation or starvation with biochemistry marker neuropeptide Y (NPY) signals released by neurons in the hypothalamus in the brain [22] and expression of the hormone ghrelin gene produced in the stomach [23] on mechanism of hunger responses. While hypothalamic neuropeptide Y (NPY) signalling activates reticular neurons in the medulla oblongata to promote feeding and mastication during the hunger response or reduces energy expenditure by stopping heat production and promotes feeding behaviour [22], gene expression levels of ghrelin is enhanced progressively up to 7 days of starvation, and declined during refeeding [23]. Notwithstanding, it is plausible that the ghrelin-hypothalamic neuropeptide Y (NPY) activities could be modulated in a special way as a survival mechanism in starvation, resulting in the observed brain tissue oxidative injury (increase in MDA). However, how NPY signalling in the hypothalamus elicits the hunger responses has remained unknown [22]. Preponderance of MDA and reduced activities of SOD and GPx after starvation stress can cause oxidative stress, which may play a critical role in the pathophysiology of starvation-refeeding syndrome [23].

The observation in the study further revealed that the effects of avocado peel extract are opposite to that of starvation in its "remarkable" ability to down-regulated brain MDA during feeding and up-regulated SOD, CAT and GPx activities on refeeding. This might perhaps be considered as one of the possible mechanisms of starvation management in a dose-dependent way. Evidently, our study demonstrated also that avocado peel and its physio-pharmacologically bioactive constituents possess neuroprotective effects in starvation and refeeding via reducing brain oxidative stress. These findings are also suggestive that avocado peels could be used as an alternative to treat starvation. Notwithstanding, it has been suggested that *Persea americana* peels could be a great alternative in the substitution of synthetic antioxidants [11, 12, 14].

Generally, learning can be defined as the acquisition of experience, which allowed an animal to change its response to specific stimuli or situations. Memory, on the other hand, can be defined as the ability to store and retrieve information from the past. In the present study we examined the effect of avocado peel extracts in starvation and refeeding on anxiety, learning and memory in experimental animals by using elevated plus maze and navigation multiple maze tests respectively. Our results showed that avocado peel extracts enhanced cognitive responses by a short term resolution in the experimental animals in the navigation multiple maze tests, time-dependently, an indication of increased in the rate of learning and memory formation. These psychogenic responses were also reflected by the ability of the animals fed the extracts to show less signs of anxiety complexes by remaining within the open arm of the elevated plus maze for a long period of time and decreased time spent in closed arm, in dose-related way, indicating its anxiolytic potential. Studies have implicated the neurotransmitter N-acetylaspartylglutamate (NAAG), the most abundant peptide transmitter in the brain as biochemical marker for cognitive impairment [25]. Although the role NAAG plays in cognition is not quite understood, it has been suggested plausibly that by simply inhibiting its breakdown and having more of this neurotransmitter improves memory and learning. It is therefore possible that the extract may increase NAAG levels in the brain in starvation and refeeding, thereby improving learning and memory in the rats. From these findings, the extract has the potential to speed development of new nutritional drugs for the management or treatment of cognitive impairment in starvation and hunger or other neurological conditions. It is encouraging that the extract could be a way to enhance cognition. However, more studies are needed to elucidate this mechanism of action.

Conclusion

Using elevated plus maze and navigation multiple maze test methods respectively, hydroethanolic extracts of avocado

peel has been demonstrated to possess anxiolytic activity and improved learning and memory in starvation and refeeding in experimental animals, in a dose-dependent manner. These findings were achieved plausibly through the cytoprotective antioxidant efficacy of the peels of avocado. It is thus worth pursuing avocado peel as a natural treatment due to its anxiolytic effect and improvement of learning and memory in starvation and refeeding.

Conflicts of interest

The authors declare that no competing interests exist.

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