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Effects of Sub-acute Administration of Onion Waste Quercetin on the Hippocampus of Mice: A Histological Approach

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Highlights

- The study evaluates the effects of onion waste quercetin (OWQ) on the brain of mice.
- OWQ at 190 mg/kg promotes the degeneration of brain cells in mice.
- OWQ at 95 mg/kg was found to prevent neuronal cell degeneration in mice.

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Abstract

Quercetin is a flavonoid with a great capability of crossing the blood-brain barrier. It is reported to exert numerous beneficial effects on both animal and human health. The study evaluates the effects of onion waste quercetin (OWQ) on the histology of the hippocampus and dentate gyrus of mice. Twenty mice were assigned into four groups (n=5). The groups were given distilled water, and OWQ at 95mg/kg, 190mg/kg, and 380mg/kg respectively for 28 days. The brain of each mouse was harvested afterwards, weighed, and processed for light microscopy. The normal and degenerating cells of the dentate gyrus and hippocampus Cornu Ammonis (CA1 & CA3) were counted. The micrographs of the dentate gyrus showed normal molecular, granular, and polymorphic layers in the control mice, as well as the mice, treated with OWQ with few degenerating cells in the granular layer of OWQ-treated (190mg/kg) mice. The CA3 area of the hippocampus showed normal molecular and polymorphic layers in OWQ-treated mice. However, the granular layer of the mice that received OWQ at 190mg/kg showed numerous degenerating cells. OWQ especially at 95mg/kg was found to significantly increase the number of normal cells of the dentate gyrus and hippocampus (CA1 & CA3) of the brain related to the control at $P< .05$. It also significantly decreased degenerating cells relative to the control ($P< .05$). Conclusively, OWQ was found to significantly reduced degenerating cells in the dentate gyrus and hippocampus. Nevertheless, further studies are required to evaluate the possible biochemical mechanisms for this histological event.

1. INTRODUCTION

Neurodegenerative diseases (NDDs) are chronic disorders that lead to progressive damage to the nervous system structures and functions, resulting in locomotors and cognitive defects [1]. There are several causes of neural degeneration which comprised cellular and molecular events such as altered cell signalling, gene expression, impaired mitochondrial functions, neuronal apoptosis, increased oxidative stress, ageing, aggregated misfolded proteins, and environmental factors [2]. Degenerative neurons are hardly restored, thus resulting in NDDs, prominent among them are; Alzheimer's disease (AD), epilepsy, Parkinson's disease, dementia, Amyotrophic lateral, and multiple sclerosis [3]. The NDDs are a major public health concern because of the increased rate of morbidity and mortality in developed countries, as well as increased life expectancy [4]. Reports on the global statistics of illnesses, revealed that NDDs are the second most common cause of mortality globally, which claimed about 6.9 million lives annually [5]. Further, the treatment of NDDs is expensive; as AD alone costs about $100 billion annually [6].

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Quercetin is a flavonol found in vegetables, fruits, and flowers such as onions, apples, red lettuce, berries, and tomatoes as glycosides or sold as a dietary supplement in the aglycone form [7,8]. Their concentration may differ in different plants, sometimes even in the same plants but growing in a different environment and/or different parts of the plant [9]. All flavonols are polyphenols called flavonoids which are known to play an important role in reactive oxygen species scavenging [7,10]. The dietary intake of flavonol was estimated to be between 16-20 mg/day and quercetin accounts for more than 60 % [11, 12]. However, increase consumption of quercetin-rich foods can upsurge the daily intake to more than 200 mg/day [7]. Previous studies revealed that flavonoids have the capability of crossing the blood-brain barrier (BBB) to exert an antioxidant effect within the brain thereby preventing the onset and progress of many neurodegenerative diseases such as Alzheimer's, ischemia, Parkinson's disease, and cognitive impairments [13-15]. Quercetin is one of the flavonoids with the greatest capability of crossing the BBB and is reported to exert numerous beneficial effects on both animal and human health [15, 16]. The activities of quercetin include hepatoprotection, nephroprotection, and anti-diabetic properties. It also serves as a natural antioxidant with therapeutic effects on many diseases such as alcoholic liver disease, and neurodegenerative, and autoimmune diseases [17-20].

Onion, being one of the most abundant sources of quercetin produces waste that is unsuitable for land disposal. The waste constitutes a global health problem due to the growth of phytopathogenic fungi [21]. In response to public health and environmental problems, the European Commission introduced a way of promoting the recycling of onion waste to produce fertilizers [22]. Furthermore, onion waste can be used for the commercial production of quercetin to serve as a food supplement in animal production. Despite the numerous beneficial effects of quercetin, too much consumption may be detrimental to animals and their health. Hence, knowledge of the toxicity of different sources of quercetin can provide a clue to regulating its consumption. The present study evaluated the effects of onion waste quercetin (OWQ) on the body and brain weight as well as on the histology of the hippocampus of mice.

2. MATERIALS AND METHODS

2.1. Quercetin Extraction and Standardization

Quercetin was extracted from onion waste as described in our previous study [23]. Ground onion waste (1 g) was dissolved in cold ethyl acetate (20 ml) for 24 hours. The mixture was shaken for 30 minutes, filtered, and evaporated to dryness. This procedure was repeated until thin layer chromatography (TLC) showed a single spot for OWQ that corresponds to the standard quercetin as described in our previous study [19].

2.2. Experimental Design

Twenty (20) male BALB/c mice were housed in the Biochemistry Department Animal House, University of Maiduguri to adapt for two weeks. The mice were allotted to four groups (n=5). The mice groups were orally given distilled water, and OWQ at 95 mg/kg, 190 mg/kg, and 380 mg/kg respectively for 28 days. The brain of each mouse was harvested 24 hours after the last administration, weighed, and fixed in Bouin's fluid for light microscopy preparation. The brain index of each mouse was calculated as follows; $\text{Brain index} = \frac{\text{Brain weight}}{\text{Body weight}} \text{ x } 100$.

2.3. Histological Procedure

The fixed mice brain was divided into 2 equal right and left halves and grossed for easy location of the hippocampus. The grossed tissues were dehydrated in graded alcohol, and the clearing and embedding were done with xylene and paraffin wax respectively. About 5 μm sections were cut, stained with hematoxylin and eosin (H&E), and mounted in dibutyl phthalate polystyrene xylene.

2.4. Cell Count and Photomicrographs

The normal and degenerating cells in the dentate gyrus (DG), as well as the Cornu Ammonis (CA1 & CA3) areas of the hippocampus, were counted at x200 magnification in 10 regions of each slide with a light microscope (Olympus BH2). Cells with a dense crescent or round-shaped nucleus and cells that are

detached from surrounding tissues were considered degenerating cells [24]. Photomicrographs were taken with a microscope camera (AmScope M500) at x200 magnifications.

2.5. Statistical Analysis

One-way analysis of variance and Dunnett's posthoc test was conducted on the data using GraphPad Prism 7 (GraphPad, San Diego, USA). The results were presented as Mean±standard error (SE) with statistical significance at P<.05.

3. RESULTS

3.1. Body Weight and Brain Index

There was no significant change in the body weight of mice treated with OWQ relative to the control in weeks 1-4 (P>.05). A non-significant change in brain index was also detected in mice that received OWQ related to the control at P>.05 (Figure 1).

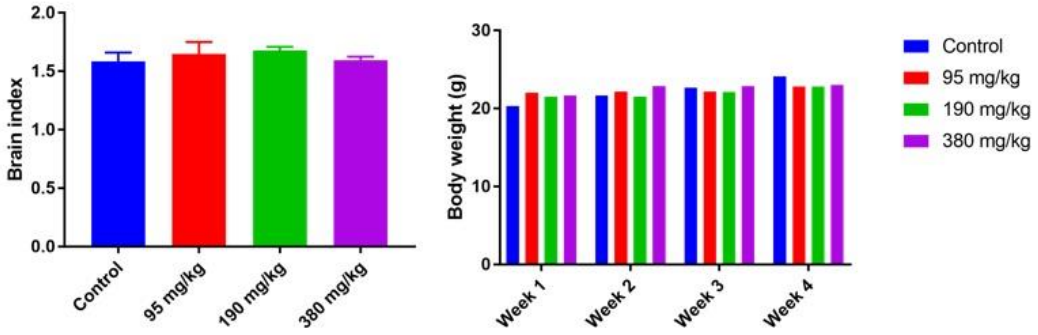

Figure 1. *Brain index and body weight of mice treated with Onion waste quercetin at different doses. Data presented as mean±SE. *** designates a significant change with the control at P< .05*

3.2. Histology and Cell Count

Photomicrograph of the DG showed normal molecular, granular, and polymorphic layers in the control mice, as well as the mice, treated with OWQ. Few degenerating cells were observed in the granular layer of the control and mice that were given OWQ at 190 mg/kg (Figure 2). The number of normal granular cells in the DG region of mice that received (95 and 380) mg/kg OWQ significantly increased compared to the control (P< .05). Conversely, no significant change was detected in the number of normal cells in mice that received OWQ at 190 mg/kg compared to the control at P> .05 (Figure 3). The degenerating cells within the granular layer of the dentate gyrus were significantly lower in mice treated with OWQ compared to the control at P< .05 (Figure 3).

The micrograph of the hippocampus (CA1 area) of the control and treated mice revealed normal molecular, granular, and polymorphic layers (Figure 4). The photomicrograph of the CA3 region of the hippocampus showed normal molecular and polymorphic layers in all the experimental groups. The granular layer of the mice that received OWQ at 190 mg/kg showed numerous apoptotic cells (Figure 4).

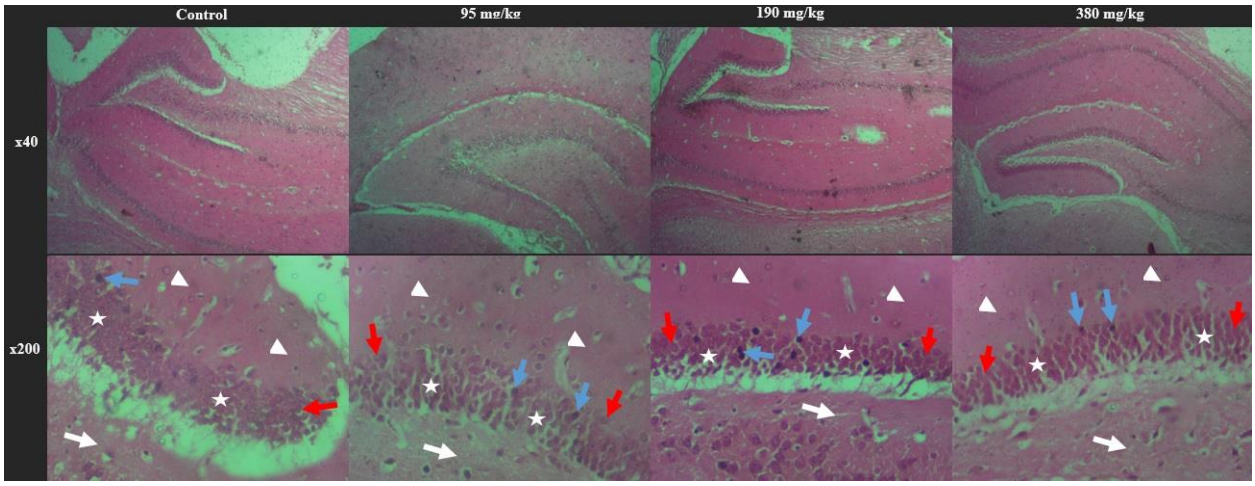

Figure 2. *Micrographs of the dentate gyrus of mice treated with Onion waste quercetin at different doses showed a normal molecular layer (arrowhead), granular layer (star), polymorphic layer (white arrows), normal cells (red arrows), and degenerating cells (blue arrows). H&E x40 magnification (scale bar= 820µm) & x200 magnification (scale bar= 164 µm)*

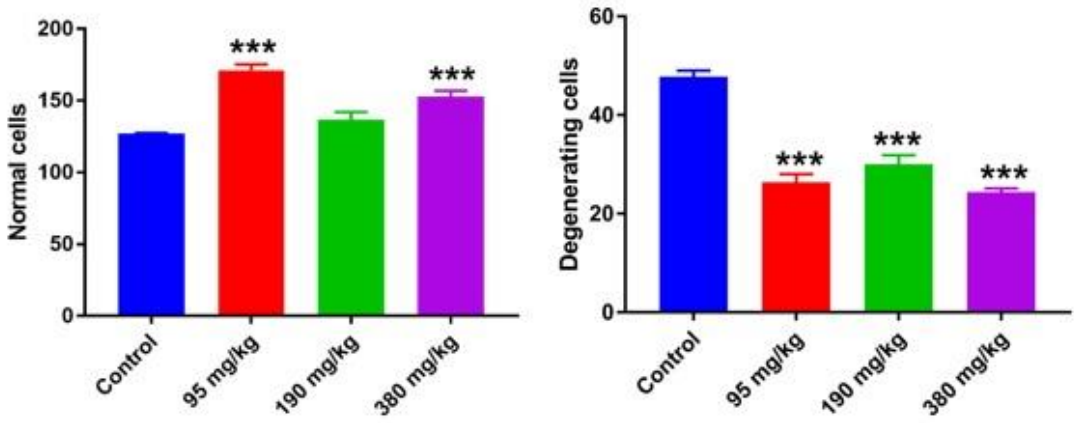

Figure 3. *The number of normal and degenerating cells within the granular layer of the dentate gyrus of mice treated with Onion waste quercetin at different doses. Data presented as mean±SE. *** designates a significant change with the control at P< .05*

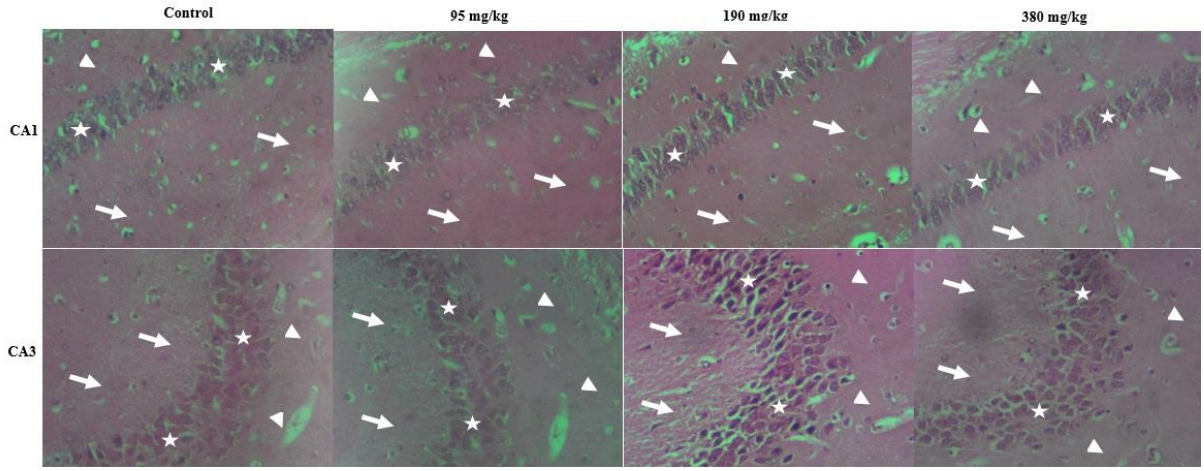

Figure 4. *Micrographs of the CA1 and CA3 areas of the hippocampus of mice treated with Onion waste quercetin showed a normal molecular layer (arrowhead), polymorphic layer (white arrows), normal cells (red arrows), and degenerating cells (blue arrows). The CA3 area of mice treated with 190 mg/kg Onion waste quercetin showed numerous degenerating cells. H&E x200 magnification (scale bar= 164µm)*

The number of normal cells within the granular layer of the CA1 region of the mice that received OWQ was significantly higher compared to the control (P< .05). A nonsignificant decrease was observed in the number of degenerating cells in the granular layer of CA1 in the control relative to the mice treated with 95 mg/kg and 190 mg/kg of OWQ at P> .05. Nevertheless, a significant decrease in degenerating cells was observed in the mice treated with 380 mg/kg OWQ compared to the control at P< .05 (Figure 5). The normal granular cells in the CA3 region of the 95 mg/kg and 380 mg/kg treated mice were not significantly changed relative to the control. However, the number of normal cells in the granular layer of mice treated with 190 mg/kg OWQ was significantly lower compared to the control (Figure 5). The number of degenerating cells within the granular layer of the CA3 region of the mice treated with (190 & 380) mg/kg was significantly higher compared to the control. Conversely, the degenerating cells in the granular layer of mice treated with 95 mg/kg were not significantly changed compared to the control (Figure 5).

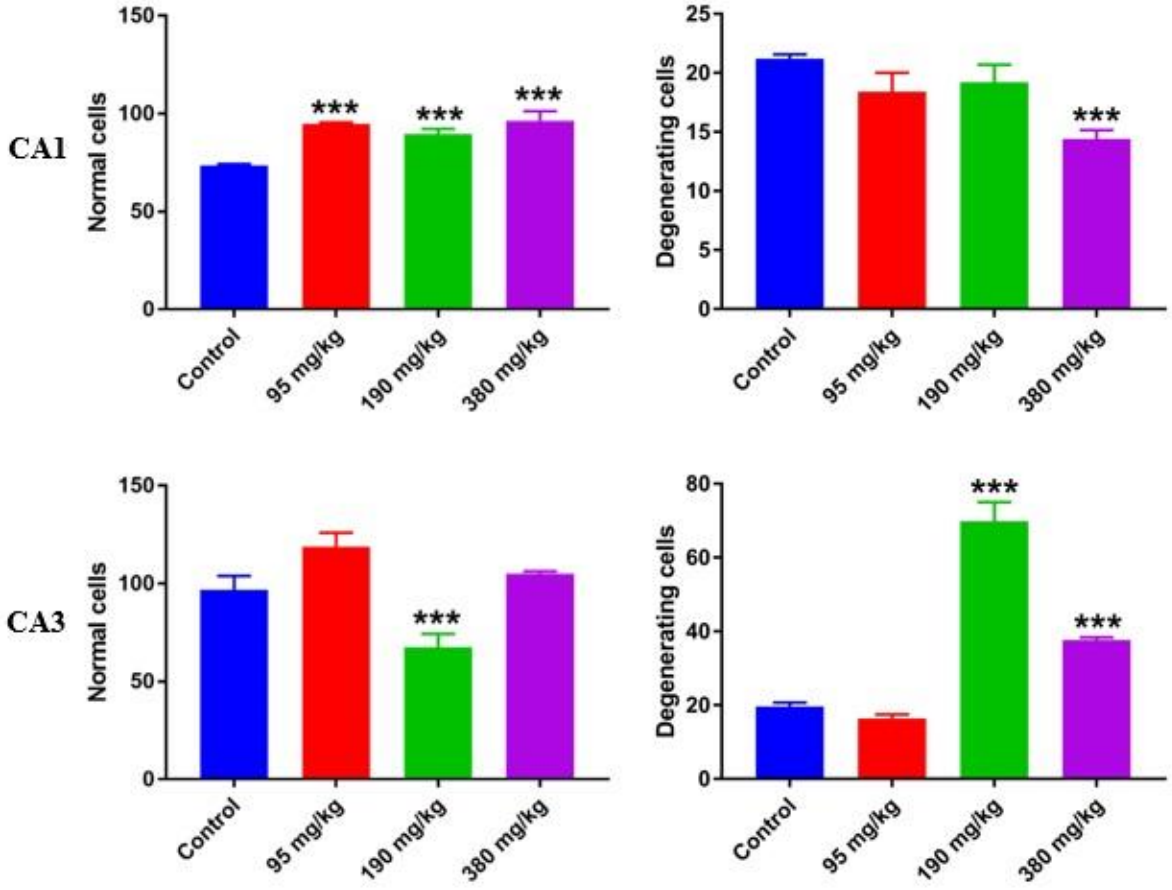

Figure 5. *The number of normal and degenerating cells within the granular layer of the CA1 and CA3 regions of the hippocampus in mice treated with Onion waste quercetin at different doses. Data presented as mean±SE. *** designates a significant change with the control at P< .05*

4. DISCUSSION

The outcomes of the existing study revealed that OWQ improves brain function by preventing the degeneration of the dentate gyrus and CA1 region of the hippocampus. The result suggests that OWQ can be used as an alternative remedy to prevent the progression of neurodegenerative diseases.

The body weight and brain index study were conducted to estimate the role of OWQ on body and brain weights. The result revealed that OWQ has not significantly increased body and brain weight in mice. A previous study reported quercetin to attenuate fluoride-induced body and brain weight loss in rats [25]. Quercetin was also found to prevent the body and relative brain weight loss induced by 3 nitro propionic acids in a rat model of Huntington's disease [26]. However, quercetin did not significantly prevent iron oxide nanoparticles-induced body weight loss in rats [27]. We suggested that quercetin's effect on body and brain weight depends on dosage, frequency, and period of administration as well as the route of

administration. While prolonged quercetin consumption was reported to increase its intake by about 10 folds [7]. Some studies reported an increased bioavailability of quercetin when conjugated with superparamagnetic iron oxide nanoparticles or polysorbate-80 [28, 29]. While others reported increased brain delivery of quercetin by 3.5-5.4 folds when combined with nano lipid carriers and/or solid lipid nanoparticles [30, 31]. This study hypothesized that increased bioavailability and brain delivery of quercetin may enhance weight gain and increase relative brain weight.

Scoring of viable and degenerated cells was conducted on the hippocampus and dentate gyrus was performed to ascertain the effects of 28 days of administration of OWQ. The result showed that OWQ increase the normal cell count within the granular layers of the hippocampus and dentate gyrus in OWQ-treated mice compared to the control, suggesting that OWQ prevented neurodegeneration in the hippocampal and dentate gyrus regions of the brain. Neuronal cell degeneration is a normal process that occurs in injured brain cells but is known to be higher in Alzheimer's, Huntington's, and Parkinson's disease [32-34]. The resultant effect of neural loss includes progressive loss of motor function, cognitive impairment, and dementia [35]. Neurodegeneration may also occur as a result of injury, inflammation, and oxidative stress. A previous study showed that quercetin significantly improves albumin, total protein and globulin levels as well as significantly decreased urea and creatinine levels in lead-treated rats [36]. Therefore, the increase in albumin and globulin levels that was reported in the previous study might be the reason for more normal cells compared to the degenerating cells that were observed in the present study. In the present study, OWQ was found to prevent neuronal cell degeneration in OWQ-treated mice compared to the control. Previous studies also reported the neuroprotective potential of quercetin. Quercetin was reported to ameliorate MPTP-induced behavioural abnormalities in rats by improving antioxidant and anti-inflammatory activities [37]. Quercetin was found to inhibit pancreatic beta cell apoptosis and significantly decrease proapoptotic markers in diabetic rats [38]. The possible mechanism through which OWQ maintains the pool of normal cells in the DG and hippocampal region of the brain is by acting as a free radical scavenger and also donating electrons to prevent oxidative stress. It might act by its anti-inflammatory activities as reported in previous studies [33, 37] thereby preventing neuronal cell damage. Based on the different effects observed by quercetin in the CA1 and CA3 regions of the hippocampus, we hypothesized that the biological activities of quercetin may change or vary depending on the type of cell and/or tissue.

The current study is limited to the morphology and number of normal/degenerating cells in the hippocampus, a region responsible for learning and memory. Considering the positive outcome of the current study, further research can be conducted to estimate the anti-inflammatory and antioxidant actions of OWQ. The effects of OWQ behavioural changes and other regions of the brain such as the cerebellum and cerebral hemispheres could also be studied. Conclusively, onion waste quercetin was found to significantly reduced degenerating cells in the dentate gyrus and hippocampus of mice brains. Nevertheless, further studies are required to evaluate the possible biochemical mechanisms for this histological event.

CONFLICTS OF INTEREST

No conflict of interest was declared by the authors.

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