



## COMPARATIVE OESTROGENIC EFFECTS OF *Allium sativum* and *Allium cepa* IN OVARIECTOMISED RATS

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### ABSTRACT

Oestrogens are steroid hormones that influence the growth, differentiation, and functioning of many target organs, including the male and female reproductive organs. Menopause, an important sign of aging in women is characterized by oestrogen depletion, which is associated with many menopausal problems. Oestrogen supplements that are mostly used are not readily safe and have been reported to cause serious health hazards. Phytoestrogens are plant compounds that are essentially correspondent to oestradiol (17- $\beta$  oestradiol) and can relate with oestrogen receptors to elevate and/or prohibit oestrogenic responses. This study therefore aimed at evaluating the possible therapeutic efficacy of *Allium sativum* and *Allium cepa* on oestrogenic activities of adult ovariectomised wistar rats. Adult Wistar rats were ovariectomized, then administered various doses of the extracts for 28 days, then sacrificed and tissues harvested for analysis. Results show *Allium cepa* and quercetin to increase endometrial thickness, increase neural cells in synaptophysin stained cells of hippocampus and dentate gyrus. A conclusion of *Allium cepa* possessing similar estrogenic properties as estradiol group in these ovariectomized rats was drawn, which can offer some ameliorative effects of estrogen deficiency.

**Keywords:** Oestrogen, Ovariectomised, *Allium sativum*, *Allium cepa*

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### INTRODUCTION

Oestrogens are steroid hormones that influence the growth, differentiation, and functioning of many target organs, including the male and female reproductive organs (Yiğitaslan et al., 2016). Oestrogen is implicated in the development of breast, ovarian, endometrial, and prostate cancer, while oestrogen deficiency has been associated with osteoporosis, neurodegenerative diseases, cardiovascular diseases and obesity (Yiğitaslan et al., 2016). Sex hormones play a vital role in regulating attainment of peak bone mass and in protecting against bone loss with increasing age, mainly by suppressing bone resorption. Although oestrogen is mainly thought to act

on cells of the osteoclast lineage, there is scientific attestation to propose that oestrogen excites bone formation in rodents and some affirmations to suggest that high-dose oestrogen stimulates bone formation in humans (Idris, 2014). Like all steroid hormones, oestradiol is a cholesterol derivative and is mainly produced by granulosa cells of the ovaries. Oestradiol is carried from the ovaries to target cells in the blood. Through its effects on transcription, oestradiol acts as a growth hormone for female reproductive organs including the vaginal lining, cervical glands, lining of the fallopian tubes, the endometrium, and the myometrium. (Imaoka et al., 2009).

Menopause is the most important sign of aging in women and oestrogen levels are greatly reduced. Depleted oestrogen level has been associated with many menopausal problems such as osteoporosis, vagina dryness, hot flushes etc. Oestrogen supplements that are mostly used are not readily safe and have been reported to cause serious health problems such as cardiovascular diseases, breast pain, vaginal itching and discharge, stomach cramps, changes in menstrual period, vaginal bleeding. (Nanette S. et al, 2016)

Oestradiol is known globally to alleviate the symptoms of menopause. Due to known side effects of the use of oestradiol as medication, there has been rapid increasing enthusiasm amongst consumers regarding medical interventions, peculiarly in the use of supplements and herbs for the treatment of menopausal symptoms. Herbal and plant-derived therapies that are consumed as food are frequently considered safer. Therefore, this study aims to evaluate the possible therapeutic efficacy of *Allium sativum* and *Allium cepa* on oestrogenic activities of adult ovariectomised wistar rats

Phytoestrogens are plant compounds that are essentially correspondent to oestradiol (17- $\beta$  oestradiol) and can interact with oestrogen receptors to elevate and/or prohibit oestrogenic responses (Jefferson et al., 2012). These compounds are consumed as an essential part of a normal diet and are commonly used as supplements in promoting alleviation of menopausal symptoms. Major phytoestrogen groups such as isoflavones (found in legumes and soybean products) and flavones (found in quercetin, luteolin) have recently been discovered to have effects on reproductive health (Jefferson et al., 2012).

Onion and garlic are worldwide-consumed vegetables, and serve as a rich source of dietary quercetin known as strong anti-oxidant with ability to chelate metals and

scavenge free radicals, which in turn inhibits lipid peroxidation. Studies have presented other biological activities of quercetin that may be beneficial to health. It can inhibit platelet aggregation and/or broad spectrum of enzymes and has been demonstrated to have anti-inflammatory properties. Through these actions quercetin may contribute to protection from aging, vascular diseases and certain forms of cancer (Mostafa & El-gayed, 2010). Onion is rich in two groups of phytochemicals (flavonoids and the alk(en)yl cysteine sulphoxides) that are beneficial to human health. The former is divided into two major groups, the flavonols and the anthocyanins which have attracted interest in recent years (Young et al., 2014). Onion also known as *Allium cepa*, belongs to the family Amaryllidaceae and is a specie of the genus, *Allium*. It is related to a great number of other species of similar odour and taste and they include garlic, leek, chive, welsh onion (Pareek et al., 2017).

Garlic, commonly known as *Allium sativum* belongs to the plant family *Liliaceae*, which is a genus of 500 species. It has been used for many centuries, and their therapeutic and medicinal values were recognized as far back as the era of ancient Egypt. Garlic (*Alliums sativum*) is a member of the Liliaceous family. It is a specie in the onion genus, *Allium*. Its close relatives include the onion, shallot, leek, clive and Chinese onion (Hajiuon, 2014). Garlic has played an important dietary and medicinal role throughout the history of mankind. Garlic has been used since time immemorial as a culinary spice and medicinal herb (Dixit, 2018). Several studies have shown that garlic contains active hypocholesterolemic and hypoglycemic components, known as diallyl disulfide and dipropyl disulfide (Hawad, 2015). Quercetin, a natural pentahydroxyflavone is believed to exhibit estrogenic and anticancer activity by acting as an effective radical-scavenger against oxidative cell damage. Any structural and chemical similarities between the quercetin

and synthetic estrogens can also provide insights to their mode of action (Mostafa & El-gayed, 2010).

Quercetin is a phytoestrogen that applies both *in vitro* agonistic and antagonistic activities on estrogen receptors. Quercetin is a phytoestrogen belonging to the flavonol subclass of flavonoid compounds, and it exerts many potential beneficial effects on human health. It is found in a variety of fruits and vegetables, particularly in onions. *In vivo* and *in vitro* studies have suggested a wide range of biological effects of quercetin including antioxidant anticancer, antihypertensive, anti-inflammatory, and antimicrobial effects. Phytoestrogens have been suggested to bind to and activate ER $\alpha$  and ER $\beta$ . However, there are inconsistent results in the literature regarding the effects of quercetin on ERs. Quercetin has shown agonistic or antagonistic activity on these receptors. Initial studies on the estrogenic activity of quercetin have reported only anti-estrogenic effects on an estrogen-sensitive breast cancer cell line (MCF-7), while subsequent studies have found that quercetin exerts both estrogenic and anti-estrogenic effects in a dose-dependent manner (Yiğitaslan et al., 2016)

The hippocampus is a brain structure with profound structural and functional plasticity evident across the lifespan in humans and rodents. The integrity of the hippocampus is implicated in learning and memory, anxiety, and stress regulation. Furthermore, the hippocampus is implicated in disease states that result in cognitive dysfunction and

synaptic function that exhibit sex differences (e.g. autism, schizophrenia, depression). (Sheppard et al., 2019). In female mammals, including rodents and nonhuman primates, estrogen historically acts on the brain to elicit reproductive behavior, including solicitation of the opposite sex and mating behavior. More recently, estrogen effects on non-reproductive behaviors have gained recognition. These include anxiety and depressive-like behaviors, as well as cognitive behaviors (Spencer et al., 2009). Several cognitive processes appear to be dependent on the level of E2 such that cognitive impairment occurs when E2 concentrations are above or below an optimal level. Numerous clinical research studies have examined memory and cognitive function in women whose levels of E2 have been altered either through ovariectomy or menopause. In general, the results of these studies show a decrease of cognitive function in women following surgical removal of their ovaries or menopause, and that these deficits can be reversed by estrogen replacement therapy (ERT) if the therapy is initiated immediately following ovarian hormone loss (Linda A. Bean, Lara Ianov, 2015). Estrogens rapidly increase synapse density both *in vivo* and *in vitro* suggesting that pre-synaptic input (i.e. synaptic transmission to estrogen-treated neurons) may also be involved in the 17 $\beta$ -estradiol mediated changes (impairments or enhancements) in learning and memory that have been observed within the same rapid timeframe (Sheppard et al., 2019).

## MATERIALS AND METHODS

This research was performed at the animal house of the College of Health Sciences, University of Ilorin. Ethical approval was obtained from the University of Ilorin ethical review committee, with an approval number of UERC/ASN/2018/1472. The guidelines of the Institutional Animal Care and Use Committee (IACUC) were strictly followed

throughout the handling of the animals (IACUC, 2011). The research was carried out accordingly in line with the guidelines of the University of Ilorin Ethical Review Committee.

### Procurement and preparation of extracts

The premarin (conjugated oestrogen) tablets were purchased at a standard pharmaceutical store, Aromokeye in Ilorin. The premarin tablets were made into powder using a homogenizer, then dissolved in phosphate buffer solution (PBS), Quercetin was procured from a standard laboratory in Ilorin. Garlic was purchased at a local market (Yoruba Road market) in Ilorin, then authenticated by the Department of Plant Biology, University of Ilorin (voucher number UILH/001/1125). The garlic extract was prepared according to a method described by (Uduak, 2014), with some modifications. The garlic cloves were air dried under a shady environment until all the moisture was dried off. After drying the garlic cloves were peeled and washed properly. In making the garlic solution, 100g of garlic was blended with deionized water with the aid of a blender till a homogenate was formed. The resulting solution was filtered using a sieve and was measured upto 100ml. The residual components was then aired to dry and weighed. The garlic extract gotten from the residue was used in obtaining high and low doses of garlic solutions for the research. Similarly, *Allium cepa* was purchased along Yoruba road, Ilorin and authenticated at Plant Biology department, University of Ilorin with a voucher number: UILH/002/1332. To prepare *Allium cepa* extract solution, 100grams of *Allium cepa* was blended with distilled water. The resulting mixture was filtered and made up to 100ml, which was later dissolved and was administered at 1.14mg/kg and 1.17mg/kg body weight daily (Uduak, 2014) at low and high doses respectively.

### **Animal care**

A total of 36 (thirty-six) adult female Wistar rats weighing  $160g \pm 10g$  were procured from Afolabi farm, Oko Olowo Ilorin. The rats were bred in the animal house of College of Health Sciences, University of Ilorin. They were housed in wooden wire-gauzed and mosquito netted cages and allowed to

acclimatize for two (2) weeks under normal atmospheric conditions. The rats were fed with pelletized feed (growers mash) bought from Ogo-Oluwa feeds, Sango Ilorin, and had access to clean water liberally. The animal care was as stipulated by the National Institutes of Health guide for the care and use of laboratory animals (IACUC, 2011).

The weights of the animals were checked at the commencement of administration and just prior to sacrifice.

### **Ovariectomy procedure**

Prior to the surgery, the rats were anesthetized with ketamine (20mg/kg) intraperitoneally using insulin syringes. The lower abdomen along the midline was shaved of hair, then the area was cleaned with ethanol. Ovariectomy was preceded by a single midline dorsal skin incision, 2cm long, approximately halfway between the middle of the back and the base of the tail, according to the method described by (Lasota, 2004). The muscles were then incised, then a small longitudinal peritoneal incision about 1cm was made. After peritoneal cavity was accessed, the adipose tissue was pulled away to access the urinary bladder, then the uterus was accessed posterior to this. Following the identification of the uterus, it was traced cephalad until the right uterine tube and the ovary surrounded by a variable amount of fat were easily located and partly lifted up, aided by gentle retraction. Using non toothed forceps, the fallopian tube was then double ligated close to the inferior part of the ovary, then the ovary was carefully excised. Haemostasis was ensured. The same procedure was repeated for the left ovary.

The uterine horn with the fallopian tubes were then returned to the peritoneal cavity after the removal of ovaries. The incision was closed in two layers: muscle was closed using chromic catgut (absorbable) suture while the skin was closed with non-absorbable nylon

2/0. Asepsis was ensured throughout the procedure.

On completion of the procedure, the animals were placed individually in clean dry recovery cages with absorbent towels. They were provided warmth using light bulbs (heat source) and heated water bottles, thus minimizing hypothermia and maintaining body temperature. The animals were closely observed for 12 hours, and full recovery was ensured. Their heads were ensured to be up in the absorbent towel as this could compromise respiration. They were turned periodically, checking for discomfort or pains until they were able to maintain sternal recumbence. They were provided with feed and clean water and their dietary intake were monitored. The animals became stabilized and were placed in clean bedded cages. The post-surgical care routine was done for 14 days prior to commencement of the administration.

### **Animal grouping and administration protocol**

A total of thirty-six ovariectomised Wistar rats were randomly drawn into eight groups two weeks following the surgical procedure. Eight boxes containing six animals each were grouped as follows The groups were; Control (C), Oestradiol (E), Low Garlic (LG), High Garlic (HG), Low Quercetin (LQ), High Quercetin (HQ), low onion (LO) and high onion (HO). Animals in the experimental groups were administered using a ball tip needle via stomach gavage consecutively for 28 days.

Administration doses (Uduak, 2014) were:

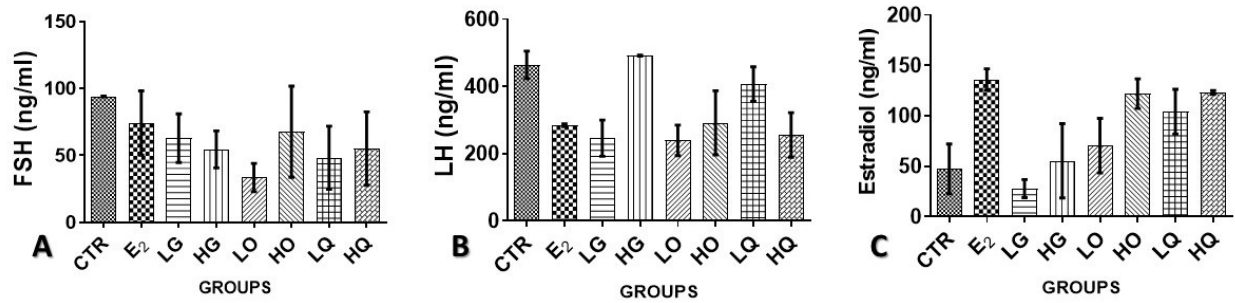
- 10mg/kg body Weight of Oestradiol daily
- 1.14mg/kg body weight of (LG) daily
- 1.17mg/kg body Weight of (HG) daily
- 10mg/kg body weight of (LQ) daily
- 30mg/kg body weight of (HQ) daily
- 1.14mg/kg body weight of (LO) daily
- 1.17mg/kg body weight of (HO) daily
- 1ml/g body weight of physiological saline was given to the Control group (C) respectively.

### **Animal sacrifice and sample collection**

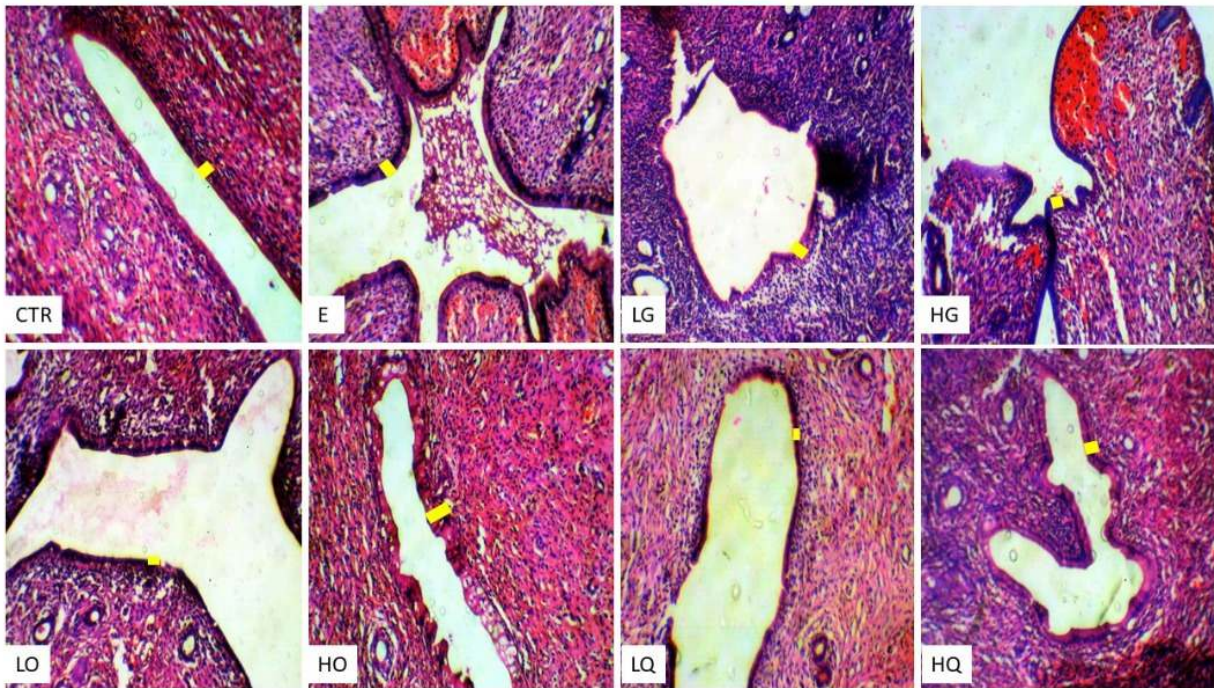
Sequel to completion of treatment, the rats were anaesthetized using 20mg/kg of ketamine (intraperitoneal). Blood samples were collected in plain specimen bottles, via cardiac puncture for hormonal analysis.

A midline incision in the scalp from the nasal bone and running caudally to the occipital bone was made on the head of the rat. The occipital, parietal and temporal skull plates from the brain were separated. Still holding the head firmly for stability and leverage, the occipital and parietal plates are pulled away from the brain and most of the dorsal surface of the left and right hemisphere is exposed. Once the plates were displaced, dura matter that were attached to the temporal plates were looked for and gently cut away with surgical scissors. The entire brain was quickly extracted using a spatula which was placed between the ventral surface and the bottom of the skull plates. A scapel was then used to remove the cerebellum and a spatula to pull away the midbrain, brainstem, thalamus thus revealing the hippocampus. Once the hippocampus was free, remaining blood vessels, cortex and white matter were gently trimmed away. The hippocampus was then fixed in 10% buffered formalin for immunohistochemical analysis.

## RESULTS

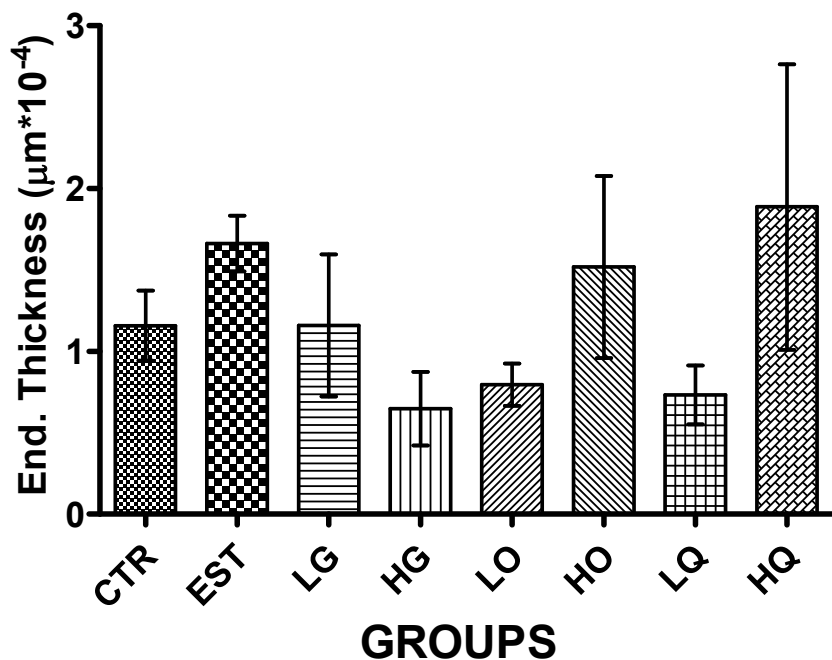


**Figure 1:** Hormonal analysis showing summary of Follicle Stimulating Hormone (A), Luteinizing Hormone (B) and Estradiol (C) levels amongst the groups. (CTR – control; E – estradiol; LG – low garlic; HG – high garlic; LO – low onion; HO – high onion; LQ – low quercetin; HQ – high quercetin).

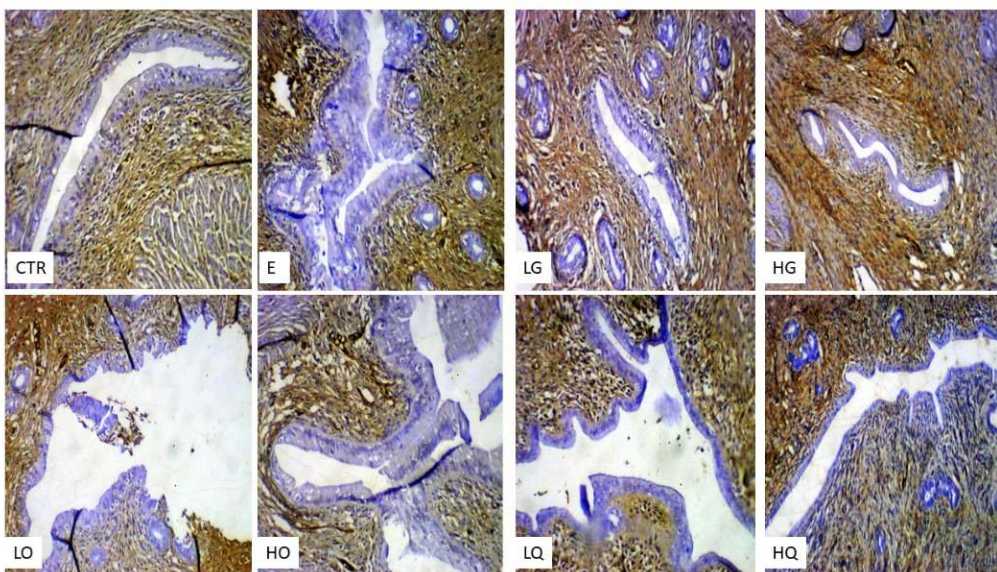


**Figure 2a:** Shows the representation of the endometrial thickness. It was observed that the endometrium was thickest in animals exposed to HQ while its thinnest in animals exposed to HG.

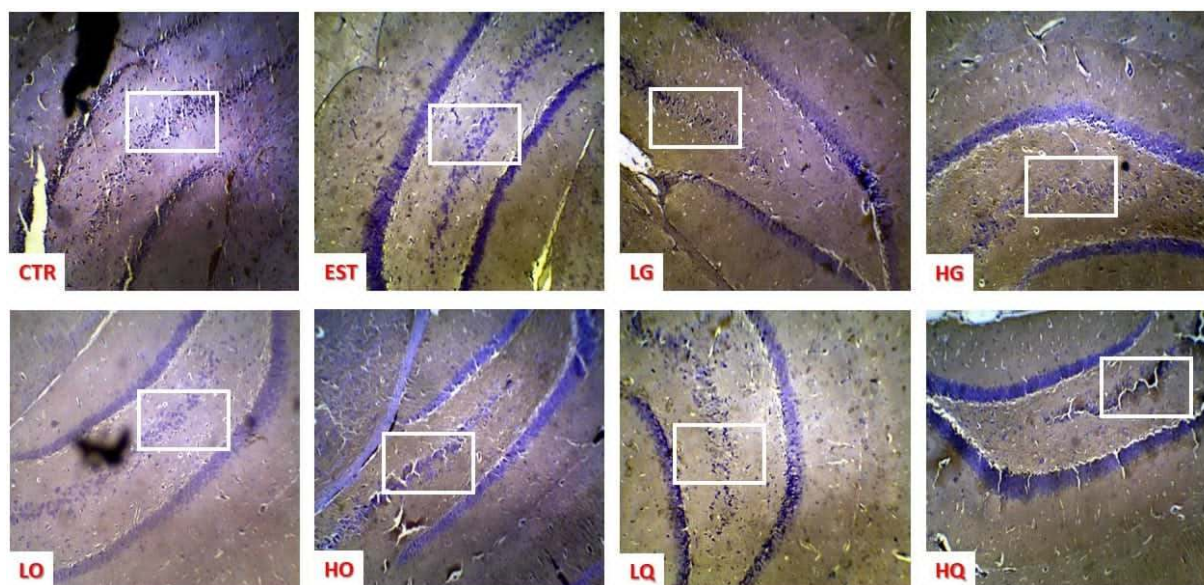
### Histomophometry (Endometrial Thickness)



**Figure 2b:** Showing Histomophometry of endometrial thickness. There is no statistical significant difference in the endometrial thickness of control animals compared to experimental animals. However, the endometrium is thickest and thinnest in animals exposed to high quercetin and high garlic concentrations respectively compared to other experimental groups, while high onion had a thicker endometrium similar to estradiol group.



**Figure 3:** Showing immunohistochemical stain for estrogen in the endometrium. The illustration above shows that animals exposed to HQ, E and LQ exhibit densely stained endometrial lining compared to other groups of experimental animals while HO is moderately stained more than the control group. However, the HG, LG and LO staining density is similar to the that of the CTR group.



**Figure 4:** Showing immunohistochemical staining of the hippocampus for estrogen.

Neural cells in synaptophysin-stained hippocampus showed cell bodies of small and medium size. The distribution, cytoarchitecture and morphology of the cells in CTR appeared similar to LO, LQ. Neural cells in EST, HO and HQ are however darker, copious and tightly packed compared to the CTR. Population of hippocampal cells in the LO group are decreased though cells distribution and morphology is similar to that of CTR.

Synaptophysin revealing antibody for integral protein at the pre-synaptic regions showed possible existence of neuroendocrine cells in all the present hippocampal cells. Though binding appeared weak, there is convincing evidence of synaptophysin-stained hippocampal cells in CTR and EST. While immunopositive-stained cells are moderate in LO, LQ compared to either CTR, high doses of onion and quercetin showed increase in population of these calcium-binding glycoprotein as there is pronounced expression of synaptophysin-

stained cells in HO and HQ when compared to CTR.

Neural cells in synaptophysin-stained dentate gyrus showed cell bodies of small and medium size. The distribution, cytoarchitecture and morphology of the cells in LQ, HQ and EST are darker, copious and tightly packed when compared to CTR. Also, compared with EST, population of dentate gyrus cells in the LO and LQ groups appeared to be decreased; though cell distribution and morphology seem to be similar to CTR.

Synaptophysin revealing antibody for integral protein at the pre-synaptic regions showed possible existence of neuroendocrine cells in all the present dentate gyrus cells. While immunopositive cells are moderate in LO and LQ compared to EST, HO and HQ which appeared to increase the population of calcium-binding glycoprotein as there is pronounced expression of synaptophysin-stained cells in HO, HQ and EST

## DISCUSSION

Synthetic oestradiol, an oestrogen therapy is the gold standard therapy procedure used to

treat oestrogen related problems both in menopausal women and women of all ages



with low serum oestrogen levels. It has been proven to be effective in the treatments of depressive disorders, osteoporosis, urogenital atrophy and other disorders associated with low levels of serum oestrogen. As efficacious as the therapy may be, literatures have reported various detrimental side effects that it may pose to health such as headache, breast pain, vaginal itching and discharge (Al, 2018).

This study aimed at finding possible natural alternatives such as plants that are of daily consumption, which may have subtle or similar oestrogenic properties. In the present study, we observed that there was no substantial increase in the endometrial thickness of the uterus in the treated animals as compared to the control group. Even so, the uterus of the animals in the High Onion (HO) group showed an increase in the endometrial thickness, which was elevated than that of the control, and alike to that of the estradiol group. The garlic groups however did not show appreciable increase in the thickness of the endometrium. This is consistent with the works of Al, 2018, which reported that garlic extracts whether low or high did not show appreciable effects on the endometrium (Al, 2018). Similarly, Alrefaie et al., in 2011 also documented that garlic extracts did not show any significant changes in the endometrial and myometrial thickness of the uterus as compared to control and oestradiol groups. The oestrogenic effect of onion observed in the endometrial thickness in this study agreed with that of Alrefaie et al., 2011 as they also administered high dose onion extract to their study rats through intravenous injections at a concentration of 30mg/kg per body weight (Alrefaie et al., 2011).

The uterus of the animals in the HO and quercetin groups were better protected than the control group. Yiğitaslan *et al.*, reported that quercetin given administration showed an increase in the endometrial thickness of the uterus when compared with other

experimental animals (Yiğitaslan et al., 2016). This is corroborated by our findings in this current study. Genistein, a phytoestrogen, was also observed by to have resulted in high endometrial thickness when administered at high dose and no effects observed at low dose in rodents (Fanti et al., 1998). The uterus of the animals in the High Quercetin (HQ) group displayed high endometrial thickness as compared to the EST and HO groups.

Next was that we studied the serum hormone levels of some reproductive hormones. A reduction in the concentration of serum FSH and LH while increase in the oestradiol levels in the animals used for the investigation were noticed when compared to the animals in the control group. This is in conformity with the work of Ma et al., (2013). They observed that *Pueriera mirifica*, a phytoestrogen containing plant when administered orally as a hormone replacement, reduced the concentration of serum FSH and LH in ovariectomized rats. Also, it was also stated in another work of (Al, 2018), who recorded a decrease in serum FSH and LH levels in the trial animals subjected to doses of garlic and oestradiol when compared to the control group. The reason for this reduction can be explained by the exogenously administered oestrogen and possibly oestrogen component of the plants (onion and garlic) administered to the experimental animals, which suppresses the natural endogenous production of the gonadotrophins via a negative feedback mechanism.

In this study, an increase in oestrogen levels in the experimental groups was recorded when compared to the control animals. This has been shown in the work of Zheng, Huang, Zheng, & Li, (2016). They observed that the oral administration of olive oil and garlic increased the serum oestrogen concentration when compared to the group exposed to oestradiol. However, they reported a significant increase in the FSH and

LH concentration in the animals, which contradicts the findings of this study, as an increase in oestradiol should normally send signals to the pituitary gland, thereby lessening the levels of FSH and LH.

Oestradiol has been declared to have cognitive enhancing and neuroprotective effects. Oestradiol, when administered to ovariectomized rats, increases synaptic proteins and synaptogenesis in the synaptophysin-stained hippocampal pyramidal and dentate gyrus neurons that mediate cognition and memory protection (Chindewa & Lapanantasin, 2008). The present study indicates that therapeutic treatments using High Onion (HO) increases synaptic proteins, neural cells, thus having lasting impact on cognition and memory on the hippocampus, which was similar to findings in the oestradiol and HQ groups, when compared to the control and other treated groups. Hwang et al., (2017) observed that Dangguijakyak-san (DJS), a herbal extract when administered at high doses to ovariectomized rats, initiates an increment in the deposition of synaptic proteins at the hippocampus and the dentate gyrus. DJS reduces the value memory deficits and facilitated synaptic activation via the incentive of hippocampal estrogen synthesis in the rats. Witty *et al.*, (2013) observed that oestradiol, when administered to ovariectomized rats, put forths lasting impacts on cognition. They displayed that provisional exposure of rats to exogenously administered oestradiol after cessation of ovarian function results in lasting increases in level of oestrogen receptor (ER  $\alpha$ ) and growth receptor (IGF-1) in the hippocampus. This helps in enhancing spatial hippocampus dependent memory.

Similarly, Frick *et al.*, (2002) reported that dose of oestrogen administered to aged ovariectomized rats at supra-physiological (high) doses, based on the large size of the uteri. The resulting effect on the hippocampus after synaptophysin expression

were increased dentate granule density, increase in the depositions of synaptic protein, thus playing a role in hippocampus dependent memory improvement. This supports the current study, which observed that the onion extract administered at high doses to the experimental animals improved dentate granule density, thereby culminating into improvement in memory and cognition.

Due to side effects associated with the synthetic oestrogen, keeping natural oestradiol at optimum levels is crucial for normal physiological function. Unfortunately, keeping oestrogen at a balance in postmenopausal women can pose a lot of challenges because low levels oestrogen is a normal physiological process in this cohort. Therefore, natural oestrogen mimetic products could serve as the alternative to synthetic oestradiol. Flavonoids such as onion and garlic have substantial amount of quercetin, an important constituent of oestrogen. Therefore, these natural foods have exhibited some oestrogenic properties.

The findings from this study indicates that different doses of quercetin were able to produce different effects on the uterus. The effects observed following the administration of low dose of quercetin were the exact opposite of the effects produced following the administration of high dose of quercetin. At low dose, quercetin caused a significant decrease in the endometrial thickness, the density of stroma and the size of uterine glands were poorly formed with luminal and glandular epithelia acquiring atrophic appearance. However, following the administration of high dose of quercetin, the endometrial thickness was increased, the glands were well formed, the stroma was dense and the epithelia were hypertrophied and hyperplastic. The oestrogenic effects of high dose quercetin observed in this study agreed with that of Shahzad et al., 2015. Changes that occur in the uterus under low dose quercetin influence could affect the morphology and therefore could interfere

with the normal endometrial function and development. We concluded that quercetin exerted both oestrogenic and antiestrogenic effects on the uterus, depending on dose administered. Several other flavonoid compounds such as kaempferide and apigenin were also reported to display both oestrogenic and antiestrogenic effects, depending on doses (Collins-burow et al., 2009). The oestrogenic activity of quercetin at high dose could be used to replace synthetic oestradiol, for example, in the therapy of postmenopausal oestrogen deficiency, in a similar way as high onion.

## CONCLUSION

Oral administration of onion extract has been demonstrated to have some agonistic oestrogenic effects on the uterus as evidenced by increased tallness of the endometrium which is similar to what is observed in the oestradiol group while garlic

extract does not appreciably increase endometrial thickness the way synthetic oestradiol does. Also, administration of estrogen like substances increases concentration of neurons that mediate cognition and memory protection.

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## CONFLICT OF INTEREST

The authors declare that there was no sponsorship from any organization nor governing body, and that the research was self-sponsored.

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