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OXIDATIVE STRESS-ACTIVATED DEPRESSION IN FEMALES: THE ROLE OF ANTIOXIDANT PLANT MATERIALS IN FERTILITY INVOLVES THE HYPOTHALAMIC-PITUITARY-GONADAL UPREGULATION

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ABSTRACT

Depression is associated with fluctuating hormonal levels in females, and this may be responsible for some of the infertility issues that usually characterize such individuals. Treatments with known antidepressants have not yielded the desired results as failure and adverse reactions are continually being reported. And since depression-associated infertility is usually associated with oxidative stress, natural antioxidants may play important protective or recovery roles. Such antioxidants are available in phytochemicals and polyphenol compounds in plants. This review evaluates the actions of some plants with antioxidant-rich properties, and their role towards protecting or promoting the female reproductive activities possibly arising from oxidative stress-induced depressive states. The plant extracts and their polyphenols modulate depression leading to improved reproductive outcomes by inhibiting proinflammatory cytokines, increased expression of BDNF, deactivation of microglia cells, down-regulation of hypothalamic-pituitary-adrenal (HPA) axis activities and ultimately improving hypothalamic-pituitary-gonadal (HPG) signals and hormonal release.

Key words: Oxidative Stress; Depression; Reproduction; Polyphenols; Hypothalamic-Pituitary-Adrenal Axis

INTRODUCTION

Depression is a mental health disorder characterized by depressed mood, mood swings, and anhedonia among others, leading to a plethora of emotional instability and suicide [1, 2]. It affects the female population more, probably associated with the fluctuating hormonal and other stress-related activities they are exposed to [3-6]. This has made studying of depression in female paramount because of the associated infertility issues that often arise, as depression tends to peak in the reproductive stage of life [7, 8].

Depression is of idiopathic aetiology with multifaceted predisposition from genetic, environment and diseases [9]. Oxidative stress arising from free radical accumulation, have been associated with depression pathophysiology. Oxidative stress arises as a result of unbalanced and excessive generation of reactive oxygen species and free radicals due to failure or inadequate endogenous antioxidant response. Such actions trigger inflammation, neuronal degeneration and death, and onset of depression [10, 11].

Oxidative stress affects whole body systems [12]. However, specific actions involve the hypothalamo-pituitary-gonadal systems [13, 14]. Oxidative stress leads to microglia and neuroinflammatory markers activation in the hypothalamus and the attendant release of corticotrophin releasing hormone (CRH). CRH released into the blood activates receptors in the anterior pituitary and the release of adrenocorticotropic hormone (ACTH) that subsequently stimulates the adrenal gland leading to glucocorticoids release. Glucocorticoids initiate a cascade of metabolic processes leading to gonadotropin release and inhibition, which alters the reproductive cycle [15, 16].

The reproductive cycle alteration due to fluctuating sex hormones is responsible for some of the infertility issues arising from depression, which has led to a sex-hormone status hypothesis for depression in women [7]. Literature on this depression hypothesis is largely from animal studies, which are quite conflicting still leaving the mechanism open to varied hypotheses.

Depression is generally managed pharmacologically with antidepressants such as norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors and the serotonin norepinephrine re-uptake inhibitors [9]. These antidepressants have been known to adequately manage depressive symptoms, but often fail due to delayed efficacy and side-effects [17]. On the other hand, oxidative stressors are ineffectively taken care of. Investigations of alternative curative approaches that improve clinical results against depression include micronutrients and phytomedicines, which are some of the major complementary remedies involved in the treatment of depression individually or as adjuvant to antidepressants [18, 19].

Different researchers have suggested the benefits of herbs or their phytochemicals in the management of depression [18, 20, 21]. This alternative in phytomedicine, which is rich in antioxidants essential for oxidative stress management may help depressive outcome. Plant-based antioxidant-rich compounds have been reported to show promising results in reproductive cycle preservation and depression treatments [22-25]. Reports of such plant studies, however did not explore the roles of oxidative-induced depression and the associated reproductive issues. This review discusses the roles of plant-based phytochemicals and their compounds potency in managing oxidative stress-induced depression leading to female reproductive function protection.

METHODOLOGY

Relevant research data on locally consumed plant extracts and their polyphenol derivatives on original research of animal studies and clinical trials were sourced from repositories. These repositories included PubMed and PubMed Central, African Journals Online, Directory of Open Access Journals, Journal Storage, Food Science and Technology Abstracts, Google Scholar, ResearchGate, Scientific Electronic Library Online, Scientific Information Database, Science Direct, Scopus, Semantic Scholar, SpringerLink, and Web of Science. Key words/phrases utilized include plants with antioxidant, antidepressant, and reproductive functions, and plant-derived polyphenols with antidepressant and reproductive functions (Fig. 1). Data which lacked a parameter of interest were excluded from the review.

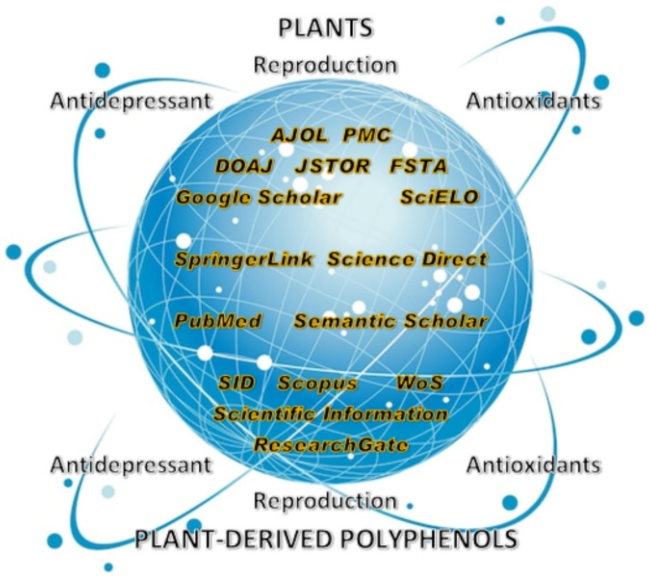

Fig. 1: Search terms and repositories consulted. AJOL - African Journals Online; DOAJ - Directory of Open Access Journals; FSTA - Food Science and Technology Abstracts; JSTOR – Journal Storage; PMC - PubMed Central; SCIELO - Scientific Electronic Library Online; SID - Scientific Information Database; WoS- Web of Science

But before venturing into the medicinal plants and their antidepressant, anti-oxidative stress and reproductive functions, let us delve into how depression, oxidative stress and hypothalamic-pituitary-gonadal and adrenal axes interrelate.

Oxidative Stress and Depression

Cellular metabolic processes result in the build-up of unstable molecules known as reactive oxygen species and free radicals [26, 27]. These free radicals and reactive oxygen species (ROS) include superoxide (O_2) radical, hydrogen peroxide (H_2O_2), hydroxyl (OH) radical, and nitric oxide (NO) among others [28, 29]. In normal conditions, their production is maintained within acceptable limits by endogenous antioxidants including the enzymatic superoxide dismutase (SOD), catalase (CAT) and glutathione among others. Due to the unstable nature of free radicals and reactive oxygen species, they are highly reactive thereby upsetting other molecules stability and functional state [26-29]. Moreover, if the free radical production is unmatched especially when enhanced by environmental stressors like physical or psychological abuse, diseases, or traumatic events, oxidative stress ensues, this leads to the generation or aggravation of diseases conditions, including abnormality of brain functions, neuronal signalling and depression [30, 31].

The mitochondrion serves as the main source of ROS production, which stimulates inflammation, promoting oxidative stress [12, 32]. These processes cause microglia and other immune cells to express pro-inflammatory cytokines and chemokines in order to recruit various other immune cells [33, 34]. As antioxidants are inadequately supplied or are unable to match these, it leads to oxidative and inflammatory damage to DNA, protein, or lipid oxidation [33, 34].

The immune system plays a role in the pathophysiology of depression by altering normal neuronal networks [34]. Cytokines such as interleukin (IL)-1β, IL-6, and tumour necrosis factor-α are activated in oxidative stress [35, 36]. In the brain, neuroinflammation activates inflammatory pathways via nuclear factor-κB and mitogen-activated protein kinase family stress kinases to promote cell damage and formation of proinflammatory molecules, eventually resulting in cell death [37-39]. This promotes the onset and development of depression and its associated comorbidity.

Oxidative Stress and Hypothalamic Function

The hypothalamic-pituitary-gonadal (HPG) axis regulates reproductive activities, and in females initiate and modulate the release of ovarian hormones and other reproductive functions [8, 40, 41]. The HPG axis also promotes healthy brain function such as neuroprotection, neurogenesis, neuronal differentiation, survival and cognition [42-44], and these roles are regulated by hypothalamic neurons that synthesize releasing hormones [44, 45]. The hypothalamic neurons of the paraventricular nucleus synthesize oxytocin, while those of the supraoptic nucleus release antidiuretic hormone (ADH) [46-48]. The arcuate nucleus contains neurons that produce releasing hormones transmitted to the anterior pituitary [49] Such releasing hormones include thyrotrophic-releasing hormone, corticotrophin-releasing hormone, gonadotropin-releasing hormone (GnRH), prolactin-releasing hormone, growth hormone-releasing hormone, and growth hormone-inhibiting hormone (somatostatin) [44, 45, 50] These hormones bind to their receptors in the anterior pituitary, and elsewhere including cells of the immune system [51] (Fig. 2).

The GnRH is particularly important as it regulates reproductive functions [52] The hypothalamic neuropeptide, kisspeptin is reported as a potent stimulator of GnRH and gonadotropin secretions [53, 54]. Kisspeptin is released by the arcuate and anteroventral periventricular nuclei, which binds to its receptor, initiating a cascade of signalling through the phospholipase C pathway, which recruits secondary messengers, inositol triphosphate and diacylglycerol to mediate intracellular calcium release and protein kinase C activation [53-55]. This activates the GnRH neurons leading to GnRH release [55, 56]. Hence, the negative feedback regulation of GnRH by gonadal hormones is through their receptors in the kisspeptin neurons [57, 58].

Also regulating GnRH release is another hypothalamic neuropeptide, gonadotropin-inhibitory hormone (GnIH), which in mammal is appropriately called RFamide-related peptide-3 [59-61]. The GnIH neurons are located in mammalian dorsomedial nucleus of the hypothalamus. The GnIH binds to the GPR147 receptors, suppressing adenylyl cyclase formation of cAMP and inhibiting protein kinase cascades leading to the inhibition of GnRH release [60]. Interestingly, oestrogen also

has a negative feedback regulation of GnIH[59].

There is interplay between the HPG and hypothalamic pituitary adrenal (HPA) axes with feedback and interactions [62-64] The HPA axis plays an important role in the body's adaptation to stress [65, 66]. The hypothalamic paraventricular nucleus (PVN) release corticotrophin-releasing hormone (CRH) due to stressful stimuli, pain or fright[67-69]. CRH binds to its receptor in the anterior pituitary resulting in the release of adrenocorticotropic hormone (ACTH) that subsequently stimulates the adrenal gland leading to glucocorticoid release. Glucocorticoids also act at the PVN to rapidly inhibit CRH neuronal activity via membrane glucocorticoid receptors [69, 70].

The normal HPG-axis activity is compromised in oxidative stress and depression [10, 71]. Oxidative stress induces GnRH inhibition resulting in luteinizing hormone (LH), follicle stimulating hormone (FSH), and reproductive function inhibition [14, 72, 73]. Oxidative stress results in GnIH neurons activation by circulating glucocorticoid, which binds to its glucocorticoid receptor [74]. This circulating glucocorticoid is up-regulated in depression with a down-regulation of its negative feedback controls [70, 75]. Thus, HPA axis over activation, as observed in depression negatively impacts on reproduction[76] (Fig. 3).

The cytokines, interleukin (IL)-1β, IL-6, and tumour necrosis factor-α suppresses the HPG axis [77]. Their upregulation decreases gonadotropin level and GnRH release by acting on receptors in the kisspeptin neurons [78, 79], and inhibiting GnRH activation and gonadotropin secretions[53, 54]

Oxidative stress also stimulates hypothalamus neurons to modulate important neurochemicals including the monoamines, serotonin, dopamine, and norepinephrine [80-82]. Oxidative stress leads to the oxidation of tryptophan eliciting the tryptophan-kynurenine pathway and dopamine depletion, which is associated with depression pathogenesis [71, 83, 84]. Oxidative stress rapidly increases norepinephrine metabolism and release, which in the hypothalamic PVN stimulates the release of corticotrophin-releasing hormone (CRH)[85, 86].

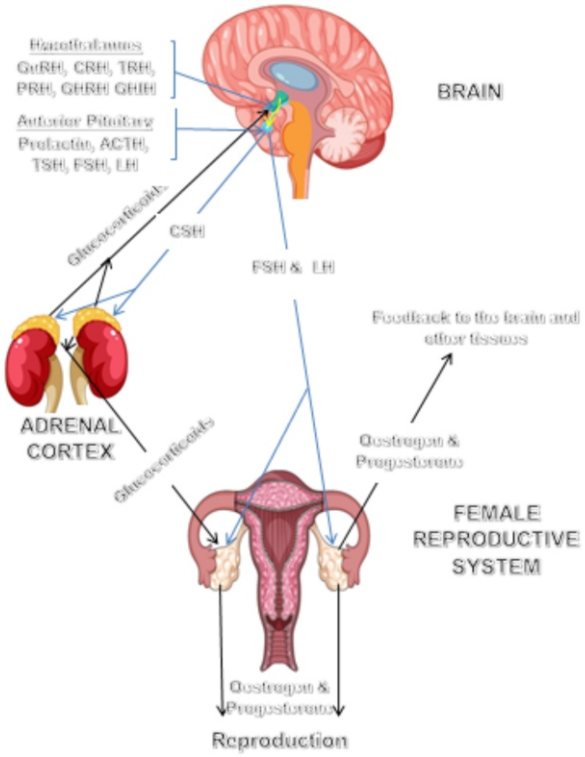

Fig. 2: Anatomical and physiological representations of the female hypothalamo-pituitary-gonadal axis and its interaction with the hypothalamo-pituitary-adrenal axis. The hypothalamo-pituitary-gonadal-adrenal axes involve the release of gonadotropin-releasing hormone (GnRH) and corticotrophin-releasing hormone alongside other releasing hormones: thyrotrophic-releasing hormone (TRH), prolactin-releasing hormone (PRH), growth hormone-releasing hormone (GHRH), and growth hormone-inhibiting hormone (GHIH). GnRH activates its receptor in the anterior pituitary to secrete luteinising hormone (LH) and follicle stimulating hormone (FSH), while CRH activates the release of adrenocorticotrophic hormone (ACTH). FSH and LH stimulate the ovary and uterus, activating the release of oestrogen and progesterone to complete the oestrous cycle and reproduction. Feedback goes to their receptors in the brain and other body tissues. ACTH acts on the adrenal cortex, causing glucocorticoid release for metabolic activities that also act on the ovary and provide feedback to the hypothalamus. Other anterior pituitary hormones activated by their releasing hormones include thyroid-stimulating hormone (TSH), prolactin (PRL), growth hormone (GH), and melanocyte-stimulating hormone (MSH).

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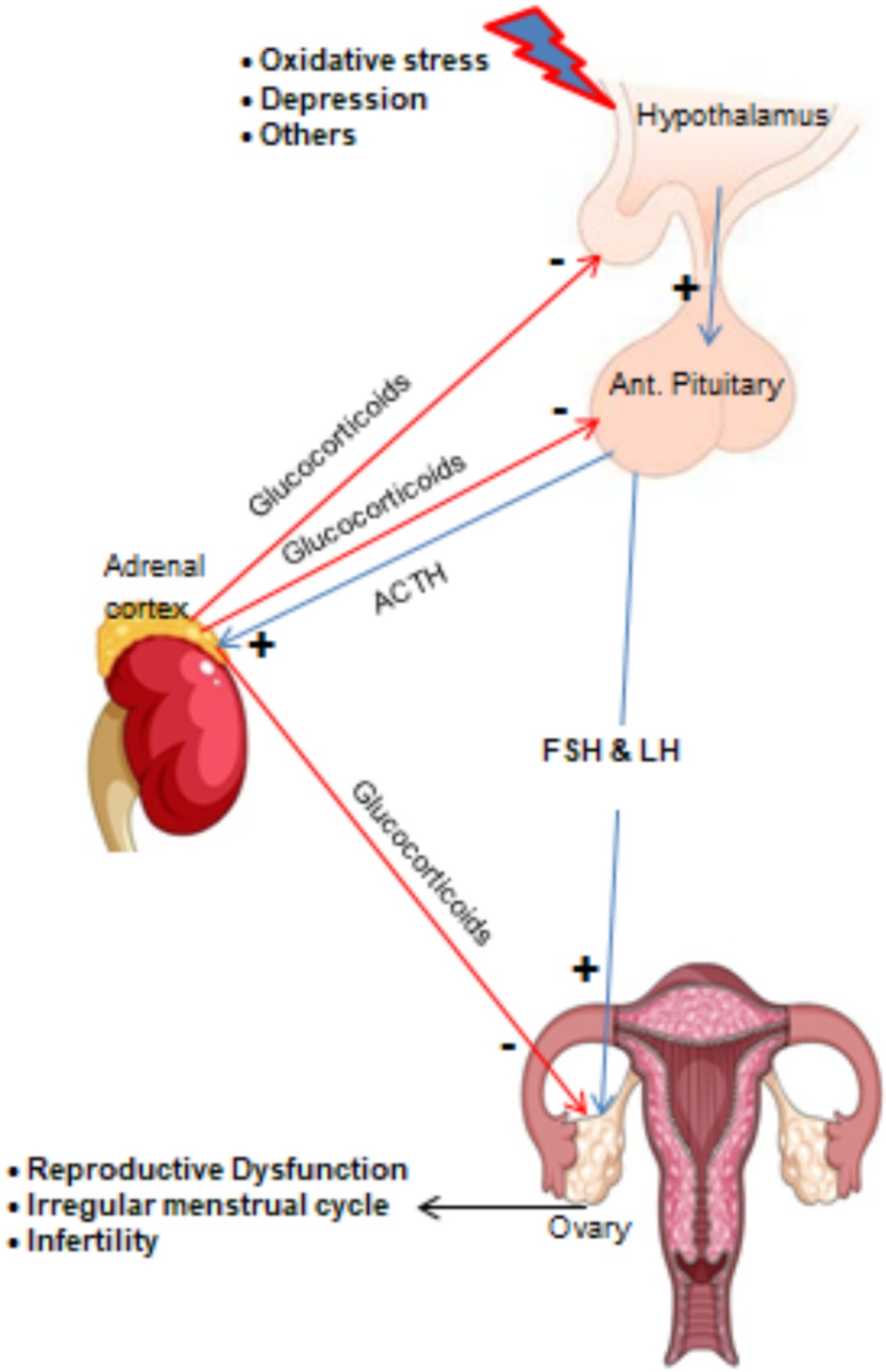

Fig. 3: Oxidative stress activates the HPA axis that inhibits the HPG axis at the hypothalamus, pituitary and ovary due to enhanced glucocorticoids release. Follicle stimulating hormone (FSH); luteinising hormone (LH); adrenocorticotrophic hormone (ACTH)

The cytokines, interleukin (IL)-1β, IL-6, and tumour necrosis factor-α suppresses the HPG axis [79]. Their upregulation decreases gonadotropin level and GnRH release by acting on receptors in the kisspeptin neurons [80, 81], and inhibiting GnRH activation and gonadotropin secretions [55, 56]

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Oxidative Stress and Pituitary Function

The pituitary gland is the master endocrine gland that releases hormones, which controls several other glands in the body [87-89]. It is in turn regulated by the hypothalamus through the releasing hormones or oxytocin and ADH [89]. The hypothalamic preoptic neurons release of GnRH activates the release of pituitary gonadotropins, FSH and LH [50, 52], which are essential in gonadal functions regulation. These gonadotropins are also instrumental in modulating behavioural and neuronal change [90, 91].

There is interplay between FSH and LH. In the female, FSH and LH bind to their receptors in the ovary and activate the G-protein cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) pathway mediating gametogenesis [92, 93]. While FSH triggers proliferative signals, follicular growth and maturation, LH increased angiogenic potential of granulosa cells of the ovary for follicular maturation. These hormonal actions lead to steroid production and ovulation [94].

The influence of LH on the ovarian theca cells leads to the androgen, androstenedione synthesis, which converts to oestradiol under FSH influence [95]. A critical level of oestradiol is needed to elicit an "LH surge," which initiates ovulation. This is through its positive feedback regulation by oestradiol activating the kisspeptin neurons [96]. After ovulation, the mature follicle becomes the corpus luteum, which synthesis progesterone and is stimulated by LH or human chorionic gonadotropin if a pregnancy occurs [97]. Oestradiol secretion also inhibits pituitary secretion of FSH, which in turn causes the concentration of FSH in other developing follicles to drop and consequently their developmental arrest [95].

Oxidative stress interferes with the FSH and LH by the pituitary. This is mostly through multiple proinflammatory mediators trigger elicit glucocorticoid release and it subsequent inhibition of GnRH.

Oxidative Stress and Gonadal Function

The gonads are the reproductive organs, which are the testes in males and ovaries in females. They are responsible for the production of the germ cells, spermatozoa and oocytes required for sexual reproduction [98, 99]. Other roles include testosterone, oestrogen and progesterone secretion, which are responsible for sexual secondary characteristics [100]. The receptors of these hormones are widely distributed throughout body, and especially in the brain [101-105]. Oestrogen plays vital roles in fertility of females including ovarian follicles stimulation, vaginal and uterine wall maintenance, and breast development and function [106]. This hormone exerts its actions by binding to oestrogen receptors, which in turn activate transcriptional signalling processes that result in the control of gene expression, although non-gene pathway is also involved [107][108].

Another hormone, progesterone binds to either nuclear progesterone or non-nuclear progesterone receptors expressed in several reproductive organs including the placenta and ovary [109]. Progesterone regulates developmental processes and proliferation and differentiation during the reproductive cycle and pregnancy [110]. However, there is need for a balance between oestrogen and progesterone levels for optimal function.'—[111] In the healthy endometrium, progesterone and oestrogen signalling coordinate in a tightly regulated, dynamic interplay to drive a normal menstrual cycle and promote an embryo-receptive state to allow implantation during the window of receptivity [112].

Oestrogen, testosterone and progesterone have effects on different neuronal pathways including the HPG and HPA axes [113]. They influence HPA axis function and reactivity to stress [114, 115]. These sex hormones neuromodulatory role in the female explains emotional changes often associated with reduced levels [7, 116]. ROS plays an essential role in signal transduction and metabolic pathways in processes such as follicular development, oocyte maturation, ovulation, implantation, steroidogenesis, and maintenance of pregnancy [64, 117]. Oxidative stress leads to ovarian cycle disruption through the inhibition or decreased secretion of LH and FSH [118-120]. The E2-induced increase in GnRH and LH that controls ovulation in females, and this is susceptible to oxidative stress [117, 118]. Oxidative stress influences embryo development through key transcription factors modification and expression [121], and in the implantation and fertilization of eggs [122] leading to the pathogenesis of female infertility.

Depression affects oestrogen level [123], menstrual cycle [124], ovarian cycle and the synthesis and secretion of gonadotropins, including menstrual flow abnormality and premenstrual symptoms [125]. Depression also activates increase in cortisol secretion and lower oestradiol in the follicular phase [126].

Oxidative stress is also highly pathogenic and associated with reproductive diseases such as polycystic ovary syndrome [127] and endometriosis as well as pregnancy complications including spontaneous abortion and preeclampsia [112, 128, 129]. It is possible that oxidative stress actions in reproductive organs is either gonadal activation of kisspeptin or RFRP-3 neurons resulting in dysfunctional downstream GnRH and LH secretion [63, 130, 131], which in addition enhance circulating glucocorticoid that disrupts the positive feedback mechanisms at hypothalamic kisspeptin circuits necessary for LH surge generation [63].

Phytomedicine and Hypothalamic Pituitary Gonadal Axis Regulation

Phytomedicine is the alternative medical practice of using herbs and their compounds in the management of disease conditions [132, 133]. Herbs or their phytochemicals have been recommended in the management of depression, especially in resource-limited settings [18]. This is because herbs have been shown to improve the symptoms of depression in preclinical and clinical trials. Such herbs with antidepressant properties also promote reproductive health through the HPG axis [18, 20, 21, 134]. Reviews of experimental and clinical trials of some commonly utilized plants with wide range of medicinal properties in this part of the world are illustrated from the next paragraph and their general actions is shown in Fig. 4.

Anti-Depression-Like and Reproductive Health Actions of Some Plants on Hypothalamic Pituitary Gonadal Axis

Basella alba of Basellaceae family possesses antidepressant activities, and its extract has been reported to attenuate chronically activated immune system and free radical generation due to stress in rats [135]. The phenol extract of *Basella alba* effectively ameliorated the depressive-like behavioural features of chronic unpredictable stress [136] and improved testicular testosterone secretion and fertility [137]. *Carpolobia alba* of Polygalaceae family also possesses antidepressant activities, as its extract inhibited inflammation and oxidative stress in rats [138], while also improving

testicular testosterone secretion and fertility[137].

Crassocephalum crepidioides of the family Compositae, showed antioxidant and neuroprotection properties [139], and improved sperm quality and gonadotropins, and gonadometric indices in the West African dwarf bucks [140]. *Cyperus esculentus* of the Cyperaceae family, preserved neurons, synaptogenesis, and spatial learning against sertraline-induced oxidative damage [141], and preserved spermatogenesis with improved testosterone level of hyperglycaemic rats –[142].

Gongronema latifolium belongs to Asclepiadaceae family, whose leaf extract showed antioxidant action by decreasing MDA and NO levels and increasing CAT, SOD, and GPx activities [143], while promoting reproduction by increasing serum testosterone, FSH, and LH[144]. *Massularia acuminata* of the Rubiaceae family promotes antioxidant enzymes, SOD and CAT in aluminium chloride-induced oxidative stressed rats [145] and improves male reproductive activities, sperm quality as well as improved serum testosterone, FSH and LH [146].

Moringa oleifera (Moringaceae), whose leaf extract has neuroprotective properties [147], and is reported with antidepressant effect in mice, hypothesized to be through the noradrenergic-serotonergic neurotransmission pathway [148]. It also protects reproductive functions in males through increased FSH and LH concentration and improved semen volume, sperm count and motility in the rabbit[149].

Petroselinum sativum Hoffm. (Apiaceae) is phenolic extract showed anxiolytic and antidepressant-like effects in mice[150], and anti-inflammatory activity, as well as oestrogenic effect [151]. *Psidium guajava* (Capparaceae) showed antidepressant activity assessed using forced swim test and tail suspension test [152], and increased in the levels of reproductive hormones (testosterone, LH, FSH), sperm mobility and epididymal sperm concentration and promotes female fertility.[153]

Rauvolfia vomitoria (Apocynaceae) leaf and bark extracts promote tissues GSH, SOD and CAT, while decreasing malondialdehyde (MDA) and nitrite concentrations in the female rat[154]. In the male rat, *Rauvolfia vomitoria* improved testosterone level, seminal parameters and male sexual performance [155, 156]. *Solanum aethiopicum* (Solanaceae) whose extract protects against oxidative stress by reducing endoplasmic reticulum stress and regulating the Nrf2 and Nf-κB molecular pathways[157], attenuates brain dysfunction and improves behavioural outcomes in chronic mild stress depressed rats[158, 159], while its leaf extract improved serum levels of testosterone, FSH, LH and histology of the rat testis [160].

Vernonia amygdalina (Asteraceae) promotes anti-depressive like actions on animal models [161] and improved sperm quality and increase in oestrogen levels in rats [162, 163].

Zingiber officinale (Zingiberaceae) and its rhizome extract reversed brain oxidative stress and cognitive deficit against aluminium chloride-induced neurotoxicity in mice[164, 165], it improves semen quality and increases fertility of sperm by disrupting the production of free radicals, levels of gonadotropin hormones (LH, FSH) and testosterone[166, 167].

Anti-Depression-Like and Reproductive Health Actions of Some Plant-Derived Polyphenols on Hypothalamic Pituitary Gonadal Axis

Phenols and polyphenol compounds are secondary metabolites of medicinal plants, which majorly provide the antioxidants necessary against oxidative stress and oxidative stress-induced depression.[168] Phenolics are natural antioxidants and made up of secondary metabolites reported with antioxidant actions in depression and depression-like conditions, and these include flavonoids, phenolic acids, tannins, and coumarins among others [168, 169]. Phenolic compounds such as carvacrol, eugenol, rutin, resveratrol, and ferulic acid are known to attenuate depression-like condition possibly by decreasing or inhibiting proinflammatory cytokines interleukin (IL)-1β, IL-6, and tumour necrosis factor-α, decrease MDA and increased oxidative stress markers (SOD and glutathione), modulation of HPA axis, suppression of mediated dopaminergic brain pathways, increased hippocampal brain derived neurotrophic factor, deactivation of microglia cells [170, 171]. Other routes through which phytochemicals exhibit their actions are activation of oestrogen receptors, decreased monoaminergic activity and enhanced levels of 5-HT and adrenaline. These polyphenols also inhibit MAPK signalling pathway-mediated oxidative stress and inflammation in depression.

Carvacrol, a phenolic monoterpene attenuates neuroinflammation, oxidative stress and depression and anxiety like behaviours in challenged rats, maintained spermatogenesis, and improved sperm parameters and testosterone levels [171]. Eugenol, an allyl chain-substituted guaiacol improved apurinic endonuclease 1, SOD and amyloid beta-40 (Aβ-40), while inhibiting TNF-α, IL-1, inducible nitric oxide synthase (iNOS), and myeloperoxidase levels in compromised rats [172]. It improved ovarian release of oestradiol and antimullerian hormones, as well as increased production of FSH and LH[173].

Rutin is a glycoside that increases antioxidants concentrations to ameliorate chronic unpredictable stress-induced behavioural deficits, improving cognition, and locomotor and muscle coordination skills[174], promote ovarian cell steroidogenesis, and reduced apoptosis resulting from experimental-induced endometriosis [175, 176]. Resveratrol, a stilbene, inhibits monoamine uptake, and downregulated HPA axis by increasing BDNF production and increase in mRNA expression levels of synaptotagmin 1 and synapsin 1 in the hypothalamus[177-179]. Resveratrol improved depressive behaviour in CUMS rats by downregulating HPA axis hyperactivity, increasing brain-derived neurotrophic factor (BDNF) expression and decreasing IL-6, C-reactive protein, and TNF-α concentrations —[179]. It restores oocyte quality in aging mice, while preventing age-induced quality decline in human clinical trial[180, 181].

Ferulic acid, a hydroxycinnamic acid derivative increased IL-10 concentration and reduced IL-6, IL-1β, TNF-α, and serum concentrations of ACTH and corticosterone through increased expression of glucocorticoid receptors in male rats [182]. Improved sperm viability and motility [183], increased serum oestradiol level[184].

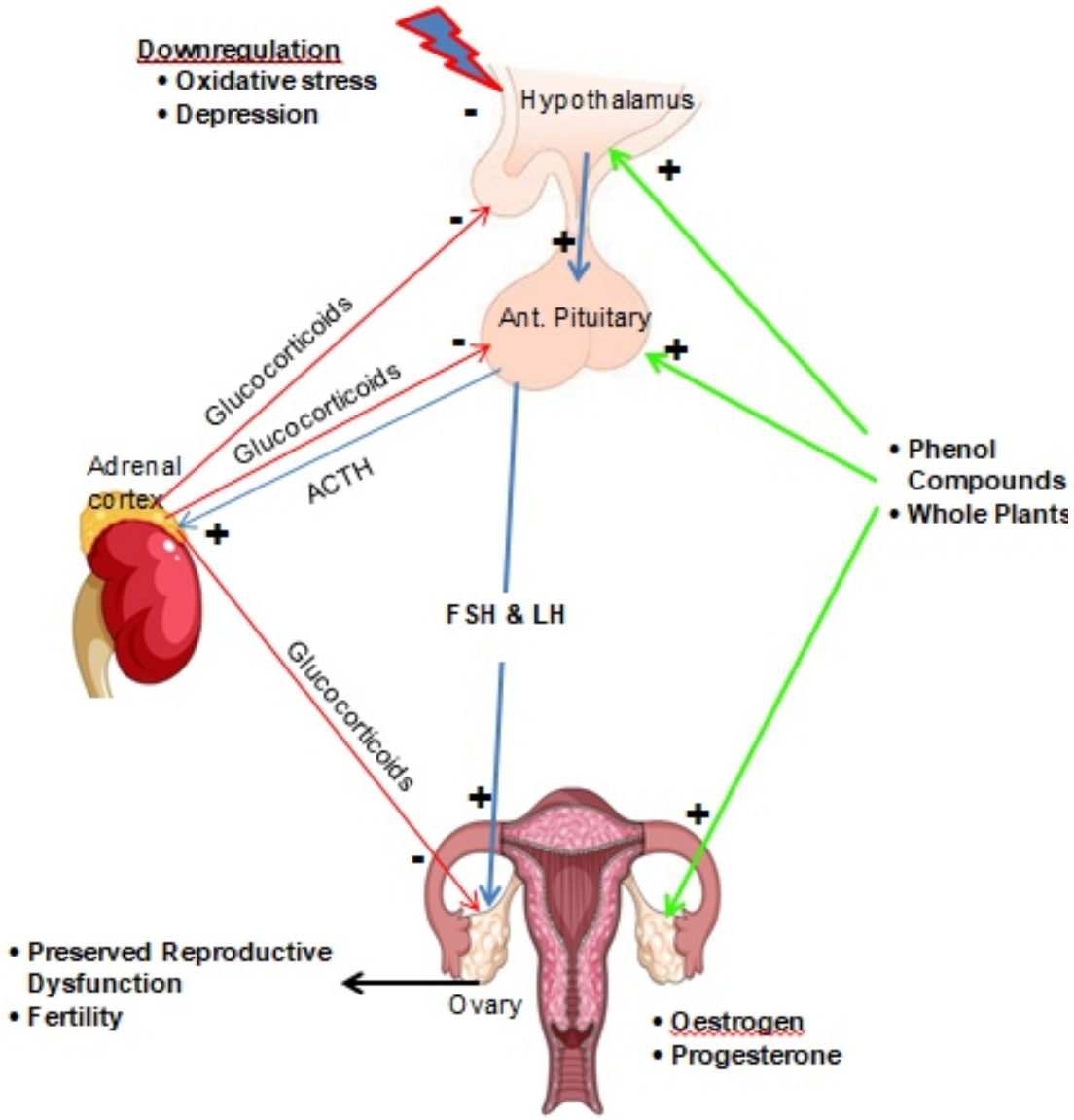

Fig. 4: Phytomedicine actions on the hypothalamo-pituitary-gonadal axis. Whole plants or the phenol compound derivatives act on the hypothalamus promoting GnRH release, which enhance the release of FSH and LH by the anterior pituitary to promote oestrogen and progesterone release. These preserve the reproductive cycle and enhance fertility.

Petroselinum sativum Hoffm. is a member of the Apiaceae family. Its phenolic extract showed anxiolytic and antidepressant-like effects in mice [152], and anti-inflammatory activity, as well as oestrogenic effect [153]. *Psidium guajava* of the Capparaceae family showed antidepressant activity assessed using forced swim test and tail suspension test [154], and increased in the levels of reproductive hormones (testosterone, LH, FSH), sperm mobility and epididymal sperm concentration and promotes female fertility. [155]

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Future Prospects of Phytochemicals and Plant-based Polyphenols in Reproduction

The use of photochemicals is intriguing, and may provide the needed succour in the management of depression and its interrelationship with female reproductive issues. This is because they tend to regulate immune system deactivation of reproductive functions. Currently, most phytochemicals and polyphenol compounds have been shown to follow established mechanism of action identified by antidepressants towards protection of reproductive functions in both male and females. Although most of these studies were conducted independent of relationship between depression and reproductive health, it is believed that further research linking depression alleviation and reproductive health will help established natural antioxidants that can serve this dual purpose. This will allow for clinical trials to support conventional claims, investigate possible synergistic effects of compounds, and create standardized formulations.

CONCLUSION

Depression and reproductive ill-health are interrelated as both are influenced negatively by oxidative stress arising from ROS and free radicals activities. Oxidative stress activates proinflammatory cytokines, microglia and oxidation of tryptophan eliciting the tryptophan-kynurenine pathway, dopamine depletion, and norepinephrine release in the hypothalamic nucleus, which in turn stimulates the release of CRH favouring the activation of pituitary adrenal pathway and glucocorticoid release that inhibits HPG pathway leading to poor reproductive activity and infertility. Plant extracts and their polyphenols have shown great potential in managing depression and reproductive health challenge associated with oxidative stress. However, more studies that directly link plant extracts and their polyphenols ameliorating these two disease states at once will provide additional information for clinical trials to commence.

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Declarations

Conflict of Interest/Competing interests

Authors do not declare any conflict of interest.

Ethics approval

No Ethical concern as this is a review research. Therefore Ethical approval was not sought.

Consent to participate

Not applicable.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Code availability

Not applicable

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