



REVIEW ARTICLE

Cognitive decline during *Rajonivrutti* (Menopause) and the role of *Mudga* (*Vigna radiata* L.) in neuroprotection

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Abstract

Perimenopause is a midlife transition of womanhood, marking the reproductive senescence, and is also a vital period in the neuroadaptive landscape of the aging female brain. Numerous estrogen-regulated neuro-endocrine functions are dismantled during this period, including sleep patterns and circadian rhythm, thermoregulation, cognition, memory, etc. During the transition to menopause, the decline in estrogen levels can lead to cognitive ageing, manifested as difficulty in concentrating, and loss of episodic memory and executive functions. These physiological manifestations can turn pathological in a small proportion of perimenopausal women. Women are more prone to the development of late-onset Alzheimer's disease (AD) in advanced age due to apolipoprotein E (APOE)-4 genotype, higher longevity, and estrogen-mediated hypometabolic state predisposing deposition of A-beta plaques, involved in the pathogenesis of Alzheimer's disease (AD). According to *Ayurveda*, *Rajonivrutti* is the period of cessation of menstruation in a woman and is considered a *Swabhavika Vyadhi* (natural manifestation). *Ahara* (diet) is the *Prana* (vital source) and the key regulator of health and well-being. *Mudga* is a dietary supplement mentioned in *Nithyasevani Ahara dravya* by *Acharya* Charaka. It is a potential drug that can be adopted as *Ahara Rasayana* in perimenopausal women owing to the potential ability to mitigate climacteric symptoms including vasomotor (VMS) and cognitive decline due to its rich phytoestrogen content, anti-inflammatory, and antioxidant properties.

Introduction

Puberty and menopause are developmental transitions from both endocrinological and neurological perspectives, involving sequential activation and deactivation of complex regulatory pathways. (1) The variability, duration, and intensity of menopausal symptoms can affect the susceptibility to various diseases including neurodegenerative consequences later in life, as a substantial proportion of women is vulnerable to neurological shifts. This is mainly contributed by the disruption of glucose metabolism in estrogen-dependent areas of the brain including the hippocampus, hypothalamus, posterior cingulate, medial temporal, and entorhinal cortex. Symptoms including depression,

insomnia, and subjective variations in memory could act as a prodrome of neurodegenerative diseases including Alzheimer's disease (AD), Multiple Sclerosis, Parkinson's disease, etc.(2,3) Studies prove that women who had estrogen use after menopause could preserve regional cerebral glucose metabolism, which in turn could act as a protective factor in the development of AD(4)

Menopause is the vital period of transition from *Madhya ayu* to *Jara avastha* (middle age to old age), with susceptibility to pathological manifestations relating to *Pitta* and *Vata dosha*. Manifestations of *rajonivrutti* are classified under 3 domains - *dosha kshayaja*, *dhatu kshayaja*, and *manasikalakshana*. The cognitive defects manifested including *smriti-vignanahani* is attributed to *Vata* and *Pitta kshaya*. The intake of *ahara* with *deepana*, *panchana*, *medhya*, *balya*, *vayasthapana* properties is beneficial during this period. Acharya Charaka quotes it under *Swabhavika Vyadhi* and Chakrapani specifies it to be *Nishpratikiya*; which means ordinary treatment modalities have no effects, specifying the relevance of *Pathya krama* and *Rasayana karma*.

AIM AND OBJECTIVES

Menopause is the period during which *agni vaishmya* leads to impaired formation of *rasadhatu*, which further causes impaired production of its *upadhatu arthava*, and the subsequent production of other *dhatu*s. Intake of an easily digestible, absorbable nourishing diet, which does not increase the vulnerability of weight gain and metabolic issues is advisable. Estrogen deprivation in women during menopause presents with imbalances beyond reproductive senescence including risks of cardiovascular diseases, osteoporosis, loss of elasticity of skin, cognitive decline, mood disorders including anxiety and depression, etc. Dietetics that can nourish the channels that carry *rasadhatu (rasa ayana)* is advisable in this period. As stated by the principle '*vridhi samanai sarvesham*'; (the concept that the growth and nourishment of the human body could be carried out only by substances having similar properties), the estrogen deprivation in menopause and the cognitive deficits manifested thereby, could be counteracted by estrogen-like compounds found in nature, i.e, the phytoestrogens, which is found in abundant in *mudga*. The role of *Medhya Rasayana* (nootropics drugs that enhance cognition) and *Naimittika Rasayana* (disease-specific nootropic) in stress-induced and neurodegenerative conditions has been studied so far. This review aims to throw light on the management of cognitive decline in menopause with *mudga* which is a *Nityopayogi dravya*, which is a promising field of research in Ayurveda.

Hormonal changes in menopause

The term menopause comes from the Greek words *pausis*, which means pause, and *men*, which means month. (5) Perimenopause can extend up to 3-5 years and is the transition period characterized by increased blood levels of FSH, anovulatory cycles, significantly reduced fertility, and erratic menstrual periods, with multitudes of symptoms that vary substantially per individual and impact the physical, mental, and social well-being.

From an endocrine perspective, perimenopause is characterized by variations in the female reproductive axis (Hypothalamo-Pituitary-Ovarian-Uterine Axis) manifested as a sharp decline in levels of circulating hormones and an increased variability in the length of the menstrual cycle. Decrements in concentrations of the primary ovarian hormones, estrogen (estradiol and estrone) and progesterone, along with fluctuations in the level of hypothalamic and pituitary gonadotropic hormones are manifested, resulting in variation in ovulation. The circulating levels of DHEA, androstenedione, and total and free testosterone are found to be highest during the third decade of life and decline thereafter. By the age of 50, the total serum testosterone level decreases by 50%. This is manifested as a diminished sense of well-being, depression, decreased energy, decreased muscle and strength, decreased sexual desire, sexual receptivity, sexual arousal and orgasm, loss of pubic hair, and changes in cognition and memory.(6) FSH shows a pulsatile pattern of secretion and its level stabilizes only after menopause. Variations in the internal endocrine milieu influence cognitive decline during midlife.(7)

Brain as a target of gonadal steroid estrogen

Estrogen receptors are present in the brain, playing a crucial role in functions beyond reproduction, including memory and cognition. The genomic activities of estrogen are mediated by two receptors - estrogen alpha (ER α) and beta (ER β) which are seen particularly abundant in the hypothalamus, the primary thermoregulatory center and regulator of sleep and circadian rhythms.(8) It is also present in those brain regions pivotal to learning and memory, including the prefrontal cortex, hippocampus, amygdala, posterior cingulate cortex, serotonergic neurons of the raphe nucleus, and adrenergic neurons of the locus coeruleus. Estrogen receptors in the brain play an important role in reproductive neuroendocrine functions through ER β immunoreactivity expressed in GnRH, CRH, vasopressin, oxytocin, and prolactin-containing neurons in the hypothalamus.(8) ER β also modulates non-reproductive neurobiological systems, acting as a neuroprotective and neurotropic factor, influencing memory and cognition, crucially involved in the hormonal and behavioral responses associated with stress, etc.(8)

Cognition, cognitive aging, and dementia

Cognition is the mental process of acquiring knowledge through thought, experience, and the senses. It comprises various aspects of higher intellectual functions including attention, memory, decision-making, planning, reasoning, judgment, comprehension, etc. Cognitive deficit implies the impairment of different domains of cognition, which manifests as difficulty in learning and concentrating, memory deficits, mental confusion, agitation, difficulty with daily tasks, mood changes, etc.(9) Dementia is a severe form of cognitive impairment where normal functioning in society is nearly impossible without treatment.

Age-associated erosions of cognitive abilities begin insidiously in middle age and accelerate through old age affecting executive functioning and episodic memory predominantly.(10) Episodic memory enables individuals to consciously recall past experiences.(11) Executive functions or cognitive control refers to the top-down mental processes that are controlled, non-automatic, and involved in problem-solving behavior. It aids in staying focused, facing unanticipated challenges, and resisting temptations. Cognitive flexibility, working memory, response inhibition, monitoring of task performance, and interference control are the core executive functions.(12)

Cognitive decline and the risk of Alzheimer's disease (AD) in Perimenopausal women

Age-related cognitive changes in perimenopausal women can progress to pathological neurodegenerative diseases due to associated co-morbidities, genetic predisposition, or other underlying pathology. In a cross-sectional study conducted by the Study of Women's Health Across the Nation (SWAN) in women aged between 40 to 55 years, 44% of early perimenopausal, 41% of late perimenopausal, and 41% of postmenopausal women were endorsed with complaints of forgetfulness.(13) AD is a neurodegenerative disorder that contributes to 60-70% of cases of dementia, and women comprise two-thirds of it, regardless of age and ethnicity.(14) Females are at a higher risk of developing late-onset Alzheimer's disease (AD), due to their increased longevity than males and due to changes in brain biochemistry due to hormonal variations.(15)

Due to the disruption of estrogen-regulated systems, menopausal transition causes several neurological symptoms, such as impairment in cognitive domains, and disturbances of sleep and circadian rhythm. The master regulatory system of brain energy metabolism, the ovarian-estrogen-neural axis, is disrupted during menopause, leading to a hypometabolic state that causes an adaptive starvation reaction with elevated fatty acid metabolism, producing ketone bodies as an alternate fuel. (16) This raises the chance of developing AD later in life by

producing oxidative stress-induced toxicity that leads to neuronal death and the deposition of A β in the form of senile plaques. (17) APOE-4, a genetic variant of the apolipoprotein E gene which is the most important known risk factor for Alzheimer's disease and other neurodegenerative disorders, has been shown to substantially decrease brain connection and accelerate brain atrophy in women more strongly than in males, even in the absence of dementia. (18) The early age of menopause was observed to influence Alzheimer's amyloid pathology and cognitive impairment as well. (19)

Hormone Replacement Therapy (HRT) - boon or a bane?

The extent of menopausal symptoms and the need for intervention can be highly variable. Whether the risks of HRT outweigh its benefits is an area of active debate. The most extensive research regarding this topic was done by two RCTs. One with a 15-year tracking over 161,800 healthy, postmenopausal women by the National Institutes of Health as part of the Women's Health Initiative (WHI), in which women were randomly assigned to receive either a hormone medication containing both estrogen and progestin (Prempro™) or a placebo and the second one with an Estrogen-Only intervention with women assigned randomly to receive estrogen alone (Premarin™) or a placebo, with 27,000 healthy women enrolled. (16) These trials were stopped following the identification of specific health risks, including cardiovascular disease and breast cancer even though HRT was found to be protective for colorectal cancer and hip and vertebral fractures. The positive effects of HRT on AD risk show that early administration of E2 in middle age provided neuroprotection to the hippocampus, however, long-term estrogen depletion during post-menopause could render the brain unresponsive to HRT. (17)

Alternative to HRT - Role of dietary phytoestrogens

Phytoestrogens are plant-derived polyphenolic compounds that mimic estrogen activity due to their structural similarity with 17- β -estradiol.(18) These plant-derived xenoestrogens, also known as dietary estrogen can produce beneficial properties of estrogens without producing their classical side effects (endometrial & breast cancer, cerebral and cardiovascular accidents, etc.).(19) Global research over the last four decades has identified its beneficial effect in preventing cardiac disease and menopausal symptoms.(20) Isoflavones and lignans are two major classes of phytoestrogens, isoflavones are found in soybeans, and lignans in flaxseed, whole grains, legumes, fruits, vegetables, etc.(20) Dietary phytoestrogens can be beneficial in reducing symptoms of menopause and render neuroprotection (21) against AD and PD, as demonstrated in animal models. Phytoestrogen can inhibit COX-2 cyclooxygenase, an enzyme that catalyzes the synthesis of compounds involved in the inflammatory process, inhibits induced cytotoxicity, Tau

hyperphosphorylation, and autophagy, preventing apoptosis due to brain ischemia, and acting on ER-beta, can upregulate dopamine synthesis(22)

Rajonivrutti

Ayurvedic literature has defined the classical symptoms of menopause by the term 'Rajonivrutti'(cessation of menstruation). It is otherwise termed "Nishphala", denoting loss of ovarian reserve, and "Gatartava", denoting the end of menstrual cycles.(23) The period of this essential physiological manifestation in a woman's lifetime is around 50 years.(24,25) *Rajonivrutti* is further classified into 2 types -*Kalaja* and *Akalaja*. *Akalaja Rajonivrutti* (premature cessation of menstruation) happens as a result of *abhighata* or karma. *Kalaja rajonivrutti* (natural menopause) is a *swabhavika vyadhi* and can be understood by the 'Swabhavoparama Vada' (the theory of natural destruction or self-destruction). All the *karya dravya* (formed elements), whether in a state of *sama* or *vipareetha aavastha* (equilibrium or disequilibrium), will be destroyed progressively due to its momentary nature. Hence, birth, growth, and senescence, influenced by *kala* (period) are inevitable processes and are irreversible.(21)

As *rajonivrutti* is a period of progression from *Madhya* to *vridha ayu*, dominance of *vata* and *pitta* dosha is manifested, along with *dhatu kshaya lakshanas*. Vitiating of *rasadhatwagni* results in the vitiated formation of its *upadhatu arthava* which could be equated to the whole menstrual and ovarian cycles influenced by the hormonal milieu. The *doshaja lakshana* manifested includes *vata vridhi lakshana* including *balakshaya, sandhivedana, anidra* etc. and *pittaja lakshanas* like *Trishna, ushnanubhiti, glani* etc.(26) *Saptadhatukshaya lakshana* are also manifested with *manasika lakshanas* like *soka, medhahrasa, alpaharshana* etc. even though Chakrapani quotes this manifestation as 'nishpratikriya', but can be made *yapya* and managed appropriately by following *hita bhojana* and *vihara, dinacharya, ritucharya, sadvritta* and *rasayana karma*.(27) Intake of *ghrita* and *ksheera, Madhura, Soumya sheetaveerya ahara*, and *yoga* and *pranayama* can be adopted as a daily regimen.

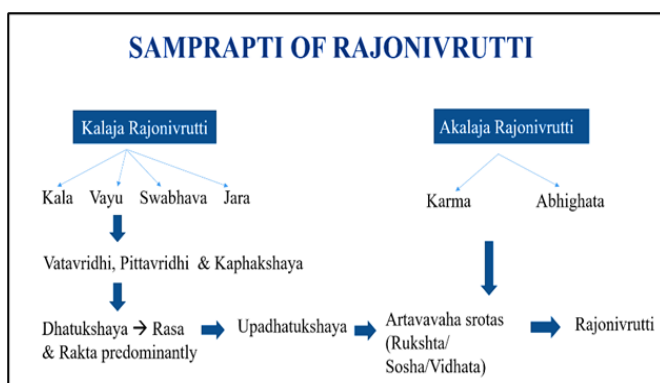


Fig. 1 : SAMPRAPTI OF RAJONIVRUTTI

Ahara rasayana in rajonivrutti

Rasayana is among the 8 branches of Ayurveda that deal with delaying aging, improving intellect, preventing disease, and maintaining positive health.(28)

Rasayana therapy acts by 3 ways -(29)

1. Regulation of *agni-correcting* metabolism at *jataragni, bhootagni* and *dhatwagni* level
2. *Srotoshodhana* - purifying and activating microchannels, thereby enhancing tissue perfusion
3. *Poshana* - rejuvenating and revitalizing *saptadhatu* and *upadhatu*

It is classified into 3 types based on drug, diet, and lifestyle - (29)

1. *Ahara Rasayana* - dietary and nutritional interventions
2. *Achara Rasayana* - based on social and personal code of conduct
3. *Dravya/Aushadha Rasayana*-based on herbal formulations

Chakrapani quotes *pratikarma* as the *chikitsa* adopted before the materialization of a disease. *Ahara* is of prime importance in maintaining the balanced state of all the human body's physiological functions, including metabolic and excretory processes. A balanced diet and adequate fluid intake are vital to address metabolic imbalances, deranged fat deposition and decreased basal energy needs in perimenopausal women. *Agni* transforms the *vijatiya panchabouthika ahara* into *sajathiya panchabouthika dhatu*, along with *poshana* of *bala, varna, ojus* and thereby, *Arogya*. Menopause is a phase characterized by nutritional deprivation and increased risk of developing obesity and associated metabolic diseases simultaneously. To reduce the associated risk factors, nutritional interventions following dietetics such as incorporating *nityopayogi dravya* in diet and adopting principles of *aharavidhidhana* and *visheshayatana* are essential for overall well-being. *Aharavidhidhana* is the etiquette to be followed while consuming food, including consuming wholesome food in optimal quantity, at a devouring pace, paying attention while eating, etc. and *visheshayatana* including methods of food intake per the nature of food, processing, according to season, age of the individual and other dictums of food intake. Considering the biorhythm of *tridoshas*, *rajonivrutti* is a transition from the predominance of *pitta* to *vata* dosha. Hence, adhering to *Hita, Satmya, and Avirudha Ahara* is essential to mitigate the risk of malnutrition in the elderly.

Role of mudga as a dietary supplement in menopause

In Ayurveda, *ahara* is considered one of the three pillars of life. As mentioned in Western medicine as 'let food be thy medicine and medicine be thy food,' Acharya Lolimba has

stated that if the diet is given properly, there is no need for separate medication.(30) *Panchabhoutika ahara* is being endogenized and converted to *vijathiya ahara rasa* in *avasthapaka* (stage of digestion) and *sajathiya sara* in *nishtapaka* (metabolism), thereby nourishing *panchabhoutika sareera*. *Pathya* refers to a wholesome diet and regimen that detoxifies the body by pacifying vitiated *Doshas*. Acharya Charaka has enlisted *nityahitopayogi dravya* for the maintenance of *swasthya* and prevention of diseases that include - *Shashtika shali* (a variety of rice maturing in 60 days), *Godhuma* (wheat), *Yava* (*Hordeum Vulgare* Linn), *Mudga* (*Vigna radiata* L.), *Saindhava* (rock salt), *Amalaki* (*Embolica officinalis*), *Antariksha jala* (rain water), *Ghrta* (ghee), *Go-dugdha* (cow's milk), *Madhu* (honey) and *Jangala Mamsa* (meat of animals dwelling in arid climate).(31)

Mudga is considered *Vara* (superior) among the *shimbi dhanyavarga* (legume group).(32) It is having *Kashaya Madhura Rasa Laghu ruksha vishada Guna*. *Veerya* is *Sheeta* with *Katu vipaka* (*Madhura vipaka* - API)(33) *Doshaharatwa Karma* is *Kapapittahara*, but does not exclusively increase *vata*. *Mudga* imparts *Deepana*, *pushtibalaprada*, *raktamutramayaghna* actions, and by thorough analysis of *rasadi panchaka*, it shows *vichitrapratyayarabdha karma*. (34,35) By correcting *jataragni*, helps in *Dhatu Pushti* countering degenerative physical changes like osteoporosis. The *raktamutramayagna karma* aids in relieving urogenital symptoms like dysuria, vaginal burning, itching, urinary incontinence, recurrent urinary tract infections, etc. Cooked *mudga* is easily digestible and absorbable, as *agnimandya* is a basic symptom of menopause. Hence *mudga* in a menopausal diet could be used as soups, sprouts, or porridges.

The potential health benefits of legumes owing to the bioactive food compound and antioxidant properties contribute to defense against chronic degenerative diseases. (36) *Mudga* commonly known as green gram or moong bean is a rich source of protein and carbohydrates with low-fat content, consisting of 347 kcal, 10-12% water, 24-25% proteins, 60-65% carbohydrates, 16-17% dietary fibres, 1.2-2% fats and a rich source of Vitamin B1,B2,B3,B6,B9 and minerals like Iron, Magnesium, Phosphorus, Potassium, Calcium, and Zinc. Starch is the principal carbohydrate. Raffinose, stachyose, verbascose, etc. are soluble carbohydrates that disappear on soaking, fermentation, and germination. It produces lower calories compared to other cereals due to low glycemic index, plasma C peptide, and glucagon which are advantageous for obesity and diabetic individuals, (equal to 630 g/kg of dry weight). The consumption of mung bean has been reported as a potential antidiabetic agent (type II diabetes) due to the decreased digestibility of bean's carbohydrates, more amylose, resistant starch composition, high dense dietary fibers, and generation of Short Chain Fatty Acids (SCFA) in the gut, which

inhibits high blood sugar levels and prevents high glycemic and insulinemic effects.

Green gram promotes the synthesis of LDL cholesterol and is rich in dietary fibers. The protease inhibitors present in green gram prevents the replication of cancer cells as seen in breast carcinoma and prevent osteoporosis by promoting bone formation. It contains magnesium, which lessens the resistance to blood flow, and the high potassium content helps control blood pressure. The microbial flora facilitates the fermentation of dietary fibers and resistant starch in the gut resulting in the production of SCFA (butyrate), which has the potential effects on colon and breast cancer.

The contribution of *mudga* in cognitive aging of menopause could be understood under 2 major headings -

◇ Role in Ovarian-Estrogen Neural Axis

- *Katu Vipaka + Vishada guna + Kaphapittahara* → helps clarify *sookshma srotas* → contribute to the anti-inflammatory & antioxidant activity of *mudga*
- *Dhatupushtibalaprada* → attributed by Isoflavone & lignan → acts as Selective Estrogen Receptor Modulators → that enhances synaptic regulation & the production of neurotrophins (factors that regulate the development, maintenance, and function of the vertebral nervous system)

◇ Role in Enteric Nervous System (ENS)

Varsha is the *Rithu* that has the least *agnibala* (digestive capacity) of all. (37) The dietary fibers in *mudga* modulate gut microbiota composition and promote Short-Chain Fatty Acids (SCFAs) production.(38) Acharya has advised the use of *Mudga* due to its probiotic action that enhances gut microbiota via vagal innervation of the Gut-Brain Axis or Enteric Nervous System, which helps in enhancing neuroplasticity (the brain's ability to reorganize and rewire its neural connections) and the production of neurotransmitters. (Fig.2) (39) The polyphenols in mung beans, particularly flavonoids, were shown to promote the growth of beneficial gut bacteria like *Lactobacillus* and *Bifidobacterium* and contribute to the antioxidant properties.(40) The proven antistress activity of *mudga* also contributes to this aspect.(41)

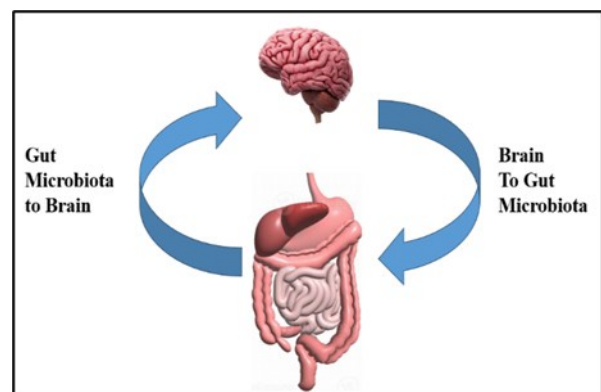


Fig. 2 : Gut-Brain Axis

Conclusion

Menopause is a transition period of womanhood, a physiological stressor that involves significant hormonal changes that impact a woman's physical and emotional well-being. In majority of women, menopause is symptomatic and is characterized by VMS (hot flushes, cold sweats, and night sweats), somatic (joint aches and pain, body composition (weight gain), skin (increased aging and wrinkling, frontal balding, and hirsutism), genitourinary (vaginal dryness, vulvovaginal atrophy (reduced vulval fat, reduced vaginal rugae, and blood flow), and sexual (dyspareunia causing sexual dysfunction), musculoskeletal (osteoporosis, rheumatoid arthritis), metabolic syndrome (Insulin Resistance) and increased risks of Cardiovascular diseases (CVD), breast, ovarian and cervical carcinoma. The decline in ovarian estrogen levels also contributes to CNS manifestations including memory loss, difficulty in concentration, reasoning and judgment, activities of daily living, and mood instability, depression, sleep deprivation. The cognitive decline during *Rajonivrutti* (menopause) is a major concern, that can even turn pathological, as two-thirds of individuals with Alzheimer's disease are women. *Mudga*, alleviates the majority of symptoms of the perimenopausal era by *tridoshagna* and *vichitrapratyayarabdha* property. *Deepana karma* kindles the *jataragni*, thereby regulating *bhutagni* and *dhatwagni*, which form the key regulator of all metabolic pathways. The phytochemical constituents of *mudga* like flavonoids, phenolic acids, organic acids, and lipids contribute to its antioxidant, antimicrobial, anti-inflammatory, and anti-diabetic activity. The cumulative effect of the phytoestrogens of *mudga* acting on the Selective Estrogen Receptor Modulators (SERM) when consumed regularly. The brain estrogen glucose metabolism which is dismantled in menopause leads to adaptive starvation reaction and fatty acid metabolism in the brain, and the subsequent oxidative damage is known to promote the accumulation of A β pathology and neuronal dysfunction, leading to an increased risk of AD later in life. Through its antioxidant action, anti-inflammatory effects, and potential to support neurogenesis, the phytoestrogens in *mudga* help to counteract the cognitive impairments often associated with menopause.

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