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EFFECT OF PHYTOESTROGENS IN COWPEA (*Vigna unguiculata*) ON BREAST CANCER IN MENOPAUSE

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ABSTRACT

Perimenopausal or early postmenopausal women can be prescribed Hormone Replacement Therapy to help them manage moderate to severe menopausal symptoms. One of the primary concerns is that Hormone Replacement Therapy may escalate breast cancer risk. Natural polyphenols' anticancer properties are now a popular issue in many research labs over the last two decades. Polyphenols may be useful in the development of anticancer drugs. Cowpea (*Vigna unguiculata*) contains a high concentration of flavonoids, phenolic compounds, and antioxidants. Phytoestrogens can bind to mammalian ER and act as inadequate aromatase inhibitors, that might lower the breast cancer risk through limiting circulating estrogen levels.

1. Introduction

Menopause symptoms are caused by the eventual depletion of oocytes inside the ovaries. This results in a chronic hypoestrogenic state, which causes menopausal symptoms in the short term and has a long-term impact on cardiovascular and bone health [1,2]. Hormone Replacement Therapy (HRT) can be prescribed to women with perimenopausal or early postmenopausal to help them menopausal symptoms. The potential increased risk of breast cancer associated with HRT is one of the primary sources of concern among health care providers and patients [1].

Medicinal plants and herbs have long been recognized as a primary source of bioactive molecules with therapeutic potential. The anticancer properties of natural polyphenols have received worldwide attention during the last two decades [3]. Meanwhile, polyphenols may be useful in the development of anticancer drugs, which contain one or more aromatic ring and hydroxyl functional groups [4].

Cowpea (*Vigna unguiculata*), also known as black eye pea, is a herbaceous annual plant and a widely cultivated legume grown in the tropics, where it is an important protein source in the foods of millions of people [5]. Cowpea has excellent nutritional and nutraceutical properties and several agronomic, environmental and economic benefits, contributing to food security and environmental preservation, so that it can become a strategic promotion for food security and population health on all continents [6]. The cowpea contains phytoestrogens, which may reduce the risk of breast cancer by lowering circulating estrogen levels by their ability to bind to estrogenic receptors (ERs) α and β and act as weak aromatase inhibitors [7].

2. Menopause

Physiology of Menopause

Menopause is a physiological change in women as they approach reproductive age caused by the cessation of ovarian endocrine activity because of the total depletion of the limited supply of ovarian follicles, which includes a significant decrease in estrogen production and an endometrial cycle decline [8,9].

Transition of menopause is typically marked by menstrual irregularities, an increase in follicle-stimulating hormone (FSH), and the initiation of menopausal symptoms. During the transition, the hypothalamic-pituitary axis would seem to drop sensitivity to both positive and negative estrogen feedback, which lead in anovulatory menstrual cycle patterns [9]. The decrease in estrogen during menopause can cause a variety of short- and long-term complaints in women. In the short term, a drop in estrogen levels during the perimenopausal and postmenopausal periods causes a cluster of symptoms known as climacteric syndrome. In the long run, low estrogen levels can increase the risk of

cardiovascular disease, osteoporosis, Alzheimer's disease, genital atrophy, and non-genital organ degradation [2]. Most women experience postmenopausal symptoms due to a decrease in estrogen. Vaginal dryness, hot flashes, vaginal itchiness, dyspareunia, and dysuria are examples of postmenopausal symptoms. These symptoms can be extremely distressing for patients and have a negative impact on their sexual function, daily activities, interpersonal relationships, quality of life, sleep, and mood [10].

Hormone Replacement Therapy (HRT) and Breast Cancer Risk

Menopause's hypoestrogenic problem can be treated with HRT, which is known to be costly and, in the long run, can increase the breast cancer risk. Many therapies have been developed to address this decrease in biological estrogens, and these therapies are becoming more comprehensive, incorporating lifestyle changes including exercise and diet [8]. Menopause is accompanied by a significant and drastic decrease in the production of ovarian hormone. Menopause at a young age is a protective risk factor for breast cancer. According to descriptive epidemiology, the trend of increasing age-related breast cancer risk after menopause is slowing. HRT use can leave a woman in a premenopausal state, without the benefits of menopause in terms of reducing cancer risk [11].

The risk of breast cancer must also be considered before initiating hormone therapy. Nonhormonal treatments for bothersome symptoms should be recommended for women with a history of breast cancer or who are at high risk of developing the disease [9]. According to the 2015 NICE guidelines, HRT with estrogen and progestogens regimen is linked to a higher risk of breast cancer. The risk appeared to be linked to the duration of treatment and decreases after HRT discontinuation [12]. The risk of breast cancer on HRT regimens containing estrogen and progestin is increasing every year, so clinical recommendations state the use of HRT within 5 years is a low risk [9].Oestrogen-only HRT appears to have little or no increased risk of breast cancer. Vaginal oestrogen therapy does not increase the risk, but combined HRT appears to increase the risk of breast cancer in a time-dependent manner. Using micronised progesterone and dihydrogesterone in combined HRT appears to be related with a reduced risk of invasive breast cancer when compared to other progestogens [1].

3. Bioactive Compound in Cowpea

Flavonoids, including isoflavonoids (genistein, daidzein, and equol) and flavonols (quercetin), account for 60% of dietary phytoestrogens. Isoflavonoids can be found in soybeans, beans, peas, peanuts, lentils, lettuce, cabbage, kale, vegetables, onions, fruits, clover, grains, spices, Kudzu, cow's milk and eggs, while the quercetin can be found in legumes, berries, cherries, apples, whole grains, cruciferous vegetable (sprouts, cabbage and broccoli), peppers, cocoa, citrus fruits, cranberries, asparagus, onions, olive oil, and red wine [13].

Cowpea (*Vigna unguiculata*) has a high polyphenol content, which includes phenolic acid derivatives and flavonol glycosides. This legume is rich in flavonoids, phenolic compounds, and antioxidant activity [14]. The phenolic acids in cowpea seed make up a large portion of the total phenolic compounds. The basic structures of main phenolic acids (benzoic and cinnamic acid derivatives) identified in cowpea, as well as aldaric acid ester (feruloylgalactaric acid). Gallic acid, vanillic acid, and p-Hydroxybenzoic acid are benzoic acid derivates. Derivates of cinnamic acid, including ferulic acid (Fig.1) [15].

The most abundant flavonoids in cowpea are flavonols (quercetin, myricetin), flavan-3-ols, and anthocyanins (delphinidin, cyanidin, petunidin, malvidin, and peonidin). In Cowpeas, the quercetin derivatives (glycosides and acylglycosides), are the most essensial group of flavonols. Glycosides (kaempferol and myricetin) are found in small amounts in some cowpea varieties [15].

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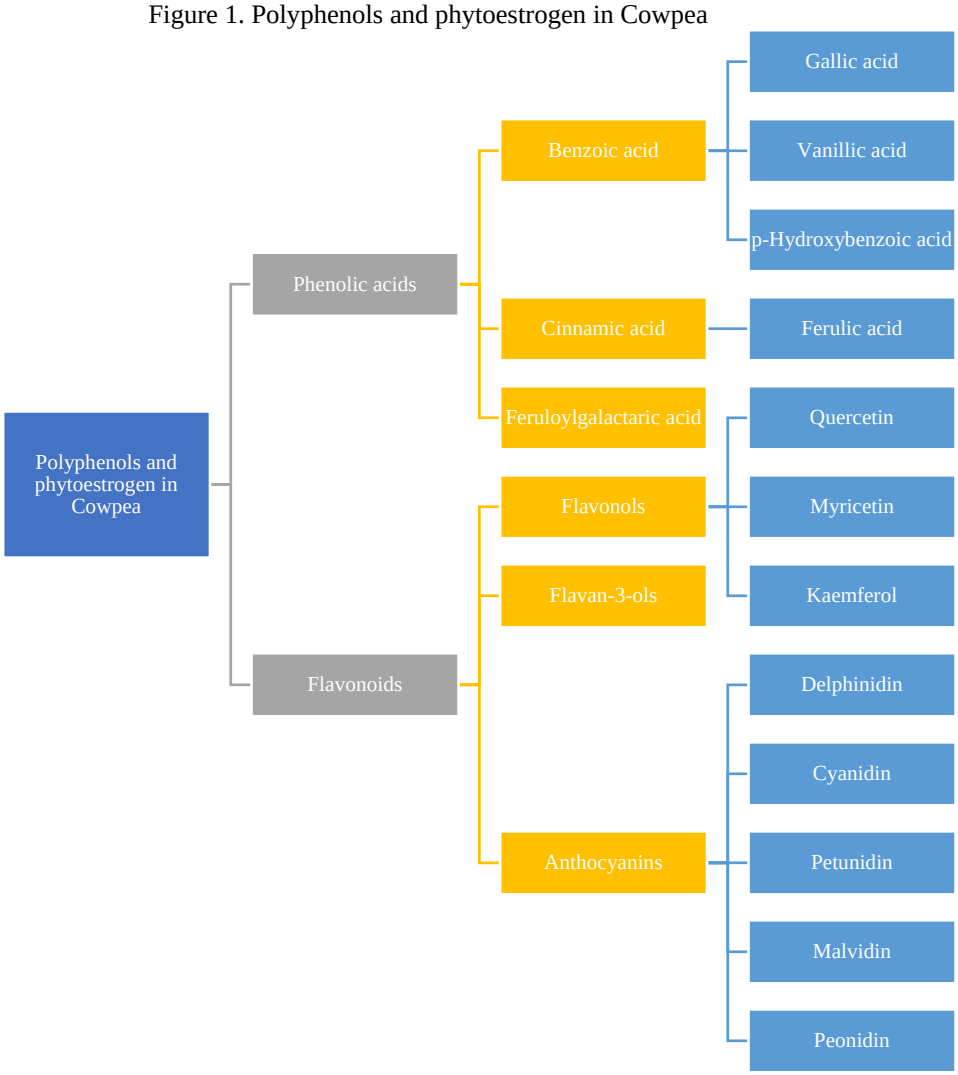
Figure 1. Polyphenols and phytoestrogen in Cowpea



Phytoestrogen

Phytoestrogens known as non-steroidal polyphenolic molecules that are structurally similar to endogenous estrogens sufficient to bind to estrogen receptors (ER). However compared endogenous estrogens, their affinity for ER is much lower [16]. Phytoestrogens show have an ER-β preference over ER-α, as well as ER agonist and antagonist actions that some have compared to selective estrogen receptor modulators (SERMs). Phytoestrogens are structurally similar to 17β-estradiol and mimic estrogen binding to its receptors, resulting in estrogenic effects in target organs [2,8,17].

Today, the use of natural compounds containing hormones or phytohormones, such as phytoestrogens, is widespread. Plant compounds with estrogen-like activity are known as phytoestrogens [8]. Polyphenols, including soy-derived isoflavones, also known as phytoestrogens, have received a great deal of attention due to their capacity to prevent carcinogenesis [17]. Phytoestrogens have many properties, including anti-inflammatory, antioxidant, anti-fungal, anti-viral, anti-bacterial, anti-hypertensive, and anti-convulsant properties, and have shown potential effects in the many disease prevention including osteoporosis, breast cancer, cancer, menopausal symptoms, stroke, obesity, diabetes, heart disease, and neurodegenerative disorders including Alzheimer's disease [13,18].

Role Phytoestrogen in Breast Cancer

Epidemiological and interventional studies have found that phytoestrogen consumption reduces breast and endometrial cancer risk [16]. Phytoestrogens have the potential to affect multiple cell systems, including signaling pathways, epigenetic regulation, steroid production, and apoptosis [7]. Phytoestrogens bind with ER-β preferentially and form heterodimers with ER-α, decreasing cell

proliferation in breast and uterine tissue. Tyrosine kinase inhibition in breast cancer cells, antioxidant properties, and G protein-coupled estrogen receptor 1 interactions have been observed, suggesting that they may protect against tumor genesis [16].

Many of phytoestrogens compounds can bind to mammalian ER and are weak aromatase inhibitors, which may reduce the risk of breast cancer by reducing the levels of circulating estrogen. Cancer cell growth and angiogenesis are inhibited, while apoptosis is stimulated. The tumor suppressor gene p53, cyclin-dependent kinases (p21/p27), pro- apoptotic and anti-apoptotic genes such as Bax and Blc-2 are all known protein targets for phytoestrogens. Furthermore, their protective effects are mediated by alters in the genes epigenetic patterns with essensial roles in this disease, including breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) [7]. Table 1 shows the bioactive compounds in cowpea that play a role in breast cancer.

Table 1. Role of Cowpea Bioactive Compounds in Breast Cancer

Bioactive Compounds	Role in Breast Cancer
Quercetin	- Decrease in proliferation via apoptosis by dose- and time-dependent [19] - Bax up-regulation [19] - Bcl-2 down-regulation [19] - Inhibits insulin receptor signaling, which reduces MDA-MB-231 breast cancer cells proliferation [4] - Reduced tumor [4] - Inhibited breast cancer cell growth and migration by reversing epithelial-mesenchymal transition, which was associated with the modulation of β-catenin and its target genes (e.g., cyclin D1 and c-Myc) [20] - Inhibited angiogenesis of breast cancer xenografts in mice by suppressing VEGFR2 [21]
Kaemferol	- Promote apoptosis in MCF-7 breast cancer cells [22,23] - Significantly inhibited uptake of glucose mediated by GLUT1, which could be another mechanism underlying its anti-proliferative effects [22,23]. - Prevent breast cancer caused by exogenous estrogens such as 17-estradiol or triclosn both in in vivo and in vitro research [24]. - Inhibited breast cell invasion by decreasing MMP-9 expression and activity via the PKCδ/MAPK/AP-1 cascade [25].
Delphinidin (anthocyanins)	- Promote apoptosis [4] - Decrease HER2 cell proliferation [4] - Decrease tumor growth [4]
Gallic acid (benzoic acid, phenolic acids)	- Inhibited cell proliferation [26] - Promoted apoptosis in MCF-7 breast cancer cells via both the extrinsic and intrinsic pathways [26].

4. Conclusion

Cowpea phytoestrogens may alter multi-target mechanisms involved in the development, prevention, or treatment of breast cancer. Cowpea phytoestrogens emerge to be a potential menopausal health treatment. Cowpea's potential for preventing, treating, or developing breast cancer needs to be investigated further, and needs a randomized controlled trials using standardized interventions at agreed-upon doses over longer time periods are required.

References

1. Vigneswaran K, Hamoda H. Hormone replacement therapy – Current recommendations. Best Pract Res Clin Obstet Gynaecol. Baillière Tindall; 2022;81:8–21.

Contents lists available at STIKes Kepanjen

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journal homepage: https://ehealth.stikeskepanjen-pemkabmalang.ac.id/index.php/path/index

2. Sujiati T, Siswanto B, Hidayat A, Widowati AR. The Effect of Isoflavone in Cowpea (Vigna unguiculata) Powder Supplement on Post-Menopausal Vaginal Maturation Index at Malang, Indonesia. Asian J Heal Res [Internet]. Ikatan Dokter Indonesia Wilayah Jawa Timur; 2022 [cited 2022 Dec 4];1:12–7. Available from: https://a-jhr.com/a-jhr/article/view/10

3. Qin T, Rasul A, Sarfraz A, Sarfraz I, Hussain G, Anwar H, et al. Salvianolic acid A & B: potential cytotoxic polyphenols in battle against cancer via targeting multiple signaling pathways. Int J Biol Sci. Australia; 2019;15:2256–64.

4. Zhou Y, Zheng J, Li Y, Xu D-P, Li S, Chen Y-M, et al. Natural Polyphenols for Prevention and Treatment of Cancer. Nutrients. Switzerland; 2016;8.

5. Boukar O, Belko N, Chamarthi S, Togola A, Batieno J, Owusu E, et al. Cowpea (Vigna unguiculata): Genetics, genomics and breeding. Plant Breed [Internet]. John Wiley & Sons, Ltd; 2019 [cited 2022 Dec 4];138:415–24. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/pbr.12589

6. Kebede E, Bekeko Z. Expounding the production and importance of cowpea (Vigna unguiculata (L.) Walp.) in Ethiopia. http://www.editorialmanager.com/cogentagri [Internet]. Cogent; 2020 [cited 2022 Dec 4];6. Available from: https://www.tandfonline.com/doi/abs/10.1080/23311932.2020.1769805

7. Montes-Grajales D, Martínez-Romero E, Olivero-Verbel J. Phytoestrogens and mycoestrogens interacting with breast cancer proteins. Steroids. Elsevier; 2018;134:9–15.

8. Noviana NN, Suprobo NR, Wiyasa IWA. The Genistein Daidzein in Kudzu Root (Pueraria lobata) Extract Decreased Malondialdehyde Plasma Levels in Hypoestrogenic Rats. Asian J Heal Res [Internet]. 2022 [cited 2022 May 31];1:7–11. Available from: https://www.a-jhr.com/a-jhr/article/view/6

9. Santoro N, Roeca C, Peters BA, Neal-Perry G. The Menopause Transition: Signs, Symptoms, and Management Options. J Clin Endocrinol Metab [Internet]. Oxford Academic; 2021 [cited 2022 Dec 6];106:1–15. Available from: https://academic.oup.com/jcem/article/106/1/1/5937009

10. Thesen R, Morck H, Zagermann P. Estradiol. Pharm Ztg [Internet]. StatPearls Publishing; 2022 [cited 2022 Dec 6];132:2958–9. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549797/

11. Kotsopoulos J. Menopausal hormones: definitive evidence for breast cancer. Lancet. Elsevier; 2019;394:1116–8.

12. National Institute for Health and Care Excellence. Menopause: diagnosis and management (NICE guideline 23) [Internet]. 2015 [cited 2022 Dec 6]. Available from: https://www.nice.org.uk/guidance/ng23

13. Lephart ED, Arráez-Román D. Phytoestrogens (Resveratrol and Equol) for Estrogen-Deficient Skin—Controversies/Misinformation versus Anti-Aging In Vitro and Clinical Evidence via Nutraceutical-Cosmetics. Int J Mol Sci 2021, Vol 22, Page 11218 [Internet]. Multidisciplinary Digital Publishing Institute; 2021 [cited 2022 Dec 4];22:11218. Available from: https://www.mdpi.com/1422-0067/22/20/11218/htm

14. Folberth C, Yang H, Gaiser T, Yusnawan E, Inayati A, Baliadi Y. Total phenolic content and antioxidant activity in eight cowpea (Vigna unguiculata) genotypes. IOP Conf Ser Earth Environ Sci [Internet]. IOP Publishing; 2021 [cited 2022 Dec 5];924:012047. Available from: https://iopscience.iop.org/article/10.1088/1755-1315/924/1/012047

15. Awika JM, Duodu KG. Bioactive polyphenols and peptides in cowpea (Vigna unguiculata) and their health promoting properties: A review. J Funct Foods. Elsevier; 2017;38:686–97.

16. Rowe IJ, Baber RJ. The effects of phytoestrogens on postmenopausal health. Climateric [Internet]. Taylor & Francis; 2021 [cited 2022 Dec 7];24:57–63. Available from: https://www.tandfonline.com/doi/abs/10.1080/13697137.2020.1863356

17. Thangavel P, Puga-Olguín A, Rodríguez-Landa JF, Zepeda RC. Genistein as Potential Therapeutic Candidate for Menopausal Symptoms and Other Related Diseases. Mol 2019, Vol 24, Page 3892 [Internet]. Multidisciplinary Digital Publishing Institute; 2019 [cited 2022 Jun 29];24:3892. Available from: https://www.mdpi.com/1420-3049/24/21/3892/htm

18. Sutrisno S. The Advantages and Disadvantages of Phytoestrogens. Asian J Heal Res [Internet]. 2022 [cited 2022 May 31];1:1. Available from: https://www.a-jhr.com/a-jhr/article/view/23

19. Duo J, Ying GG, Wang GW, Zhang L. Quercetin inhibits human breast cancer cell proliferation and induces apoptosis via Bcl-2 and Bax regulation. Mol Med Rep [Internet]. Spandidos Publications; 2012 [cited 2022 Dec 7];5:1453–6. Available from: http://www.spandidos-publications.com/10.3892/mmr.2012.845/abstract

20. Srinivasan A, Thangavel C, Liu Y, Shoyele S, Den RB, Selvakumar P, et al. Quercetin regulates β-catenin signaling and reduces the migration of triple negative breast cancer. Mol Carcinog [Internet]. John Wiley & Sons, Ltd; 2016 [cited 2022 Dec 7];55:743–56. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/mc.22318

21. Zhao X, Wang Q, Yang S, Chen C, Li X, Liu J, et al. Quercetin inhibits angiogenesis by targeting calcineurin in the xenograft model of human breast cancer. Eur J Pharmacol. Elsevier; 2016;781:60–8.

22. Liao W, Chen L, Ma X, Jiao R, Li X, Wang Y. Protective effects of kaempferol against reactive oxygen species-induced hemolysis and its antiproliferative activity on human cancer cells. Eur J Med Chem. Elsevier Masson; 2016;114:24–32.

23. Azevedo C, Correia-Branco A, Araújo JR, Guimarães JT, Keating E, Martel F. The chemopreventive effect of the dietary compound kaempferol on the MCF-7 human breast cancer cell line is dependent on inhibition of glucose cellular uptake. Nutr Cancer [Internet]. Nutr Cancer; 2015 [cited 2022 Dec 4];67:504–13. Available from: https://pubmed.ncbi.nlm.nih.gov/25719685/

24. Kim SH, Hwang KA, Choi KC. Treatment with kaempferol suppresses breast cancer cell growth caused by estrogen and triclosan in cellular and xenograft breast cancer models. J Nutr Biochem. Elsevier; 2016;28:70–82.

25. Li C, Zhao Y, Yang D, Yu Y, Guo H, Zhao Z, et al. Inhibitory effects of kaempferol on the invasion of human breast carcinoma cells by downregulating the expression and activity of matrix metalloproteinase-9. Biochem Cell Biol [Internet]. Canadian Science Publishing; 2015 [cited 2022 Dec 4];93:16–27. Available from: https://cdnsciencepub.com/doi/10.1139/bcb-2014-0067

26. Wang K, Zhu X, Zhang K, Zhu L, Zhou F. Investigation of Gallic Acid Induced Anticancer Effect in Human Breast Carcinoma MCF-7 Cells. J Biochem Mol Toxicol [Internet]. John Wiley & Sons, Ltd; 2014 [cited 2022 Dec 4];28:387–93. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jbt.21575