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FLAVONOID AS A FUNCTIONAL INGREDIENT IN THE NUTRITION MANAGEMENT OF ENDOMETRIOSIS: A REVIEW

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ABSTRACT

Endometriosis is a chronic gynecological disease that often causes chronic pain, dysmenorrhea, and infertility. Hormonal treatment as definitive therapy for endometriosis can disrupt and lead to recurrent pain. Flavonoids are natural bioactive compounds found in various fruits, vegetables, and bee products, and their function as antioxidants to suppress the proliferation of pathological cells, which can also contribute to the improvement of clinical signs and symptoms. The aim of this literature review is to investigate the potential of flavonoids as a functional ingredients in nutrition management of endometriosis. The review was conducted using search engines including PubMed, ScienceDirect, and Cochrane. The inclusion criteria were: (1) The study design could be a randomized clinical trial (RCT), a case-control study, or an in vivo study, (2) the literature has to be published in the last ten years from 2013 to 2023, (3) using English or Indonesian subjects, and (4) literature can be accessed online. The exclusion criteria were irrelevant articles and incomplete texts, such as only abstracts. The triggering factors for the development of endometriosis are still unknown, but oxidative stress is one of the factors that has been strongly associated with endometriosis. The administration of natural antioxidants is a promising adjuvant nutritional therapy option to support primary endometriosis treatment. Flavonoids are bioactive compounds that possess strong antioxidant activity. They are abundantly found in vegetables, fruits, bee products, and have been shown to have anti-inflammatory and anti-proliferative effects on endometriosis, both at the cellular and clinical levels.

Keywords: flavonoids, endometriosis, antioxidants

ABSTRAK

Endometriosis merupakan penyakit ginekologi kronis yang sering menyebabkan nyeri kronis, dismenore dan infertilitas. Pengobatan hormonal sebagai terapi definitif endometriosis dapat mengganggu dan dapat menyebabkan nyeri berulang. Flavonoid merupakan bahan bioaktif alami yang terdapat pada berbagai jenis buah, sayuran, dan produk lebah serta berfungsi sebagai antioksidan untuk menekan proliferasi sel patologis yang juga akan berpengaruh pada perbaikan tanda dan gejala klinis. Studi literatur ini bertujuan untuk memberikan ulasan mengenai flavonoid sebagai zat fungsional yang berpotensi memberikan dampak dalam manajemen gizi pada endometriosis. Tinjauan dilakukan dengan menggunakan mesin pencari yang terdiri dari PubMed, ScienceDirect, dan Cochrane dengan kriteria inklusi berupa: (1) desain studi yaitu uji klinis acak, studi case-*control* atau studi *in-vivo* (2) literatur harus diterbitkan dalam sepuluh tahun terakhir dari tahun 2013 hingga 2023, (3) menggunakan bahasa Inggris atau bahasa Indonesia, dan (4) literatur dapat diakses secara online. Kriteria eksklusi adalah artikel tidak relevan dan teks tidak lengkap; hanya abstrak. Faktor pencetus timbulnya endometriosis masih belum diketahui, stres oksidatif merupakan salah satu faktor yang banyak terbukti berhubungan dengan endometriosis. Pemberian antioksidan alami merupakan salah satu pilihan terapi nutrisi tambahan yang menjanjikan untuk mendukung terapi utama endometriosis. Flavonoid merupakan salah satu senyawa bioaktif yang memiliki aktivitas antioksidan kuat dan banyak terkandung dalam sayuran, buah-buahan dan produk lebah dan memiliki efek anti-inflamasi serta anti proliferasi terhadap kondisi endometriosis secara seluler maupun tanda klinis.

Kata kunci: flavonoid, endometriosis, antioksidan

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INTRODUCTION

Endometriosis is the growth of endometrial tissue outside the uterus, specifically in the peritoneal cavity. It is a benign condition that often causes dysmenorrhea and infertility in women.[1] Approximately 10 percent of the female population, including adolescent girls, worldwide are at risk of developing endometriosis.[2] Previous studies have found that endometriosis is present in 30-50 percent of women with infertility.[2] The Indonesian Association of Obstetrics and Gynecology states that dysmenorrhea can still recur even after operative therapy for endometriosis.[3] However, the exact triggering factors for endometriosis are still unknown, although oxidative stress is now recognized as a risk factor for the development of endometriotic lesions.[4,5] Endometriosis not only affects physiological function but also the quality of life for women. Women with symptomatic endometriosis are prone to experience depression, anxiety, and other mood disorders that impact their daily activities, due to hormonal imbalance, especially estrogen.[6] The signs and symptoms are not specific and may include menstrual pain (dysmenorrhea), pain during intercourse (dyspareunia), pain during urination (dysuria), and deep pelvic pain during bowel movements (dyschezia). Additionally, infertility can occur due to the infiltration of endometriotic lesions in specific areas, which is a concern for scientists regarding these ectopic endometriotic lesions.[8] Not all cases of endometriosis are accompanied by symptoms, but according to the Indonesian Society of Obstetrics and Gynecology (ISOG) consensus in 2017, 62 percent of endometriosis patients experience menstrual pain (dysmenorrhea) and chronic pelvic pain. The nature and frequency of the perceived pain are subjective to each individual with endometriosis.[3]

The mechanisms involved in endometriosis are still theoretical, as the underlying inflammation is not yet fully understood and may be caused by genetic and epigenetic factors resulting in an increased imbalance of estrogen compared to progesterone. Hormonal imbalance leads to pain occurring outside the menstrual cycle as well as fertility disorders. Anatomic factors, estrogen hormonal dysregulation, and exogenous factors such as immune status and hormonal imbalances, especially increased estrogen, may also contribute to endometriosis[7]. These factors result in prolonged oxidation without a proper balance of antioxidants and pro-oxidants. As a result, oxidative stress occurs, leading to inflammatory reactions and compensatory responses from other organs, ultimately leading to the development of hyperproliferative lesions and impacting the physiological function.[8] The goals of managing endometriosis are to reduce clinical symptoms, prevent fertility disorders, minimize surgical interventions, and prevent postoperative recurrence. Endometriosis therapy involves the use of pain-relieving medications such as NSAIDs and continuous hormonal therapy with regular monthly evaluations.[3]

Flavonoids are a group of phenolic compounds that have been extensively studied for their competence as antioxidants. They are abundantly found in natural food sources such as green leafy vegetables, grapes, olives, apples, and bee products, which have been identified to have higher flavonoid content compared to other food sources.[9] Several studies on flavonoids have demonstrated their antioxidant effects in reducing oxidative processes through intracellular pathways, such as the natural factor kappa beta (NF-κβ) pathway, and by binding circulating reactive oxygen species (ROS) both extracellularly and intracellularly.[10,11,12]

Flavonoids are also known as phytoestrogen which were synthesized by plants through UV radiation. The estrogens naturally formed by various types of plants that can bind to estrogen receptors 1 and 2 (ESR1 and ESR2) in human's body.[11] It predominantly works on ESR2 in the endometrium, while acting as antagonists to ESR1, reducing estrogen activation by ESR1 which is located in almost all organs but dominantly in brain and adipose tissue.[11,12] Flavonoids also stimulate the production of incretin hormones, such as glucose-dependent insulinotropic polypeptide (GIP), which increases insulin secretion and glucose uptake into cells, resulting in decreased plasma blood sugar levels. Glucagon-like

peptide (GLP-1) is a hormone activated by flavonoids during the digestion process in the small intestine. GLP-1 prolongs gastric emptying time, reduces gastric acid secretion, improves absorption processes, and reduces appetite.[13,14] The role of flavonoid has been shown can help regulate metabolism under conditions of oxidative stress, especially in chronic diseases. The role of flavonoids in endometriosis has been systematically explained by previous studies. A review article by Bartiromo,et al.,[15] demonstrates the potential of flavonoids as phytoestrogens that can improve endometriosis lesions based on animal studies conducted in several studies. Although not all groups of flavonoids show significant changes in endometriosis lesions compared to the control group, certain flavonoids, such as resveratrol found in berries, chrysin found in bee products, and daidzein found in soybeans and their derivatives, have shown promising effects. In line with the review article by Wardani et al.,[16] which provides an overview of the role of flavonoids in modulating TNF-alpha levels in endometriosis conditions in animal and in vivo studies, this article comprehensively examines the role of flavonoids in endometriosis. The emphasis is placed on studies involving human subjects rather than animal or in vivo studies, providing a more direct understanding of the potential improvement of endometriosis's symptoms through flavonoid administration. The development of targeted nutritional interventions and further research in this area are needed to better understand the potential benefits of antioxidants and flavonoids in managing endometriosis. The aim of this study is to investigate the potential of flavonoids as a functional ingredients in nutrition management of endometriosis.

METHOD

This study used a literature study or literature review using three databases, PubMed, Cochrane, and Science Direct with the keywords "Flavonoids", "endometriosis" and "antioxidant". The inclusion criteria in this literature study were: (1) The study design could be a randomized clinical trial (RCT), a case-control study, or an in vivo study, (2) the literature has to be published in the last ten years from 2013 to 2023, (3) using English or Indonesian subjects, and (4) literature can be accessed online.The exclusion criteria are irrelevant articles and incomplete texts, such as only abstracts.

Literature search was conducted using Boolean Search techniques with the keywords: Flavonoid OR phytoestrogen AND Endometriosis OR Endometriosis-related pain. The identified references will be reviewed first and used if they can address several research questions, such as "what is flavonoid?," "how can flavonoids affect endometriosis improvement?," and "what are the outcomes of orally administered flavonoid-rich foods in endometriosis?". Articles with plant subjects and in vitro designs are considered irrelevant and excluded. Additionally, articles that do not specifically focus on inflammation and the improvement of endometriosis cells are also included in the exclusion criteria due to different outcomes. The PRISMA diagram of literature search process is presented in Figure 1.

RESULTS

In this literature, there are 9 articles consisting of 6 clinical studies articles while 3 other are laboratory experimental studies. Many animal and in-vitro studies investigating the role of flavonoids in improving endometriosis have been designs, demonstrating the antioxidant effects of flavonoids in supporting clinical and cellular improvements in endometriosis. Meanwhile, human studies regarding this issue are still limited. A summary of this literature search results for this study is shown in table 1.

DISCUSSION

Based on the results of literature search, eight articles met the inclusion criteria: two articles discussed flavonoid compound on improving pain scale, five articles discussed about improving lesion and inflammation[7,18,21,22,26,27,], and one article discussed flavonoid reduce the risk of endometriosis.[21]

The Effect Flavonoid on Endometriosis Lesion

Five articles were reviewed and indicated the positive effect of flavonoid compound on endometriosis lesion. The emergence of clinical symptoms in endometriosis is based on the proliferation of abnormal endometrial layers as a consequence of inflammation due to oxidative stress in the uterus. Tumor necrotizing factor alpha (TNFα) levels increase in chronic inflammation, providing a proliferation signal to cells through the nuclear factor kappa beta (NF-kβ) pathway, which is one of the pathways involved in tumorigenesis by triggering the production of vascular endothelial growth factor (VEGF) and aromatase enzyme production by the Golgi apparatus.[17] Clinical study conducted by Mirzaei et al.[18] on female subjects with endometriosis using silymarin (a group of flavonoids) compared with placebo-showed a significant reduction in endometriotic lesion size by 25 mm^3 in the silymarin group. Silymarin is one of the active ingredients found in milk thistle (*Silybum marianum*), which is known as a class of flavonoids.[19]

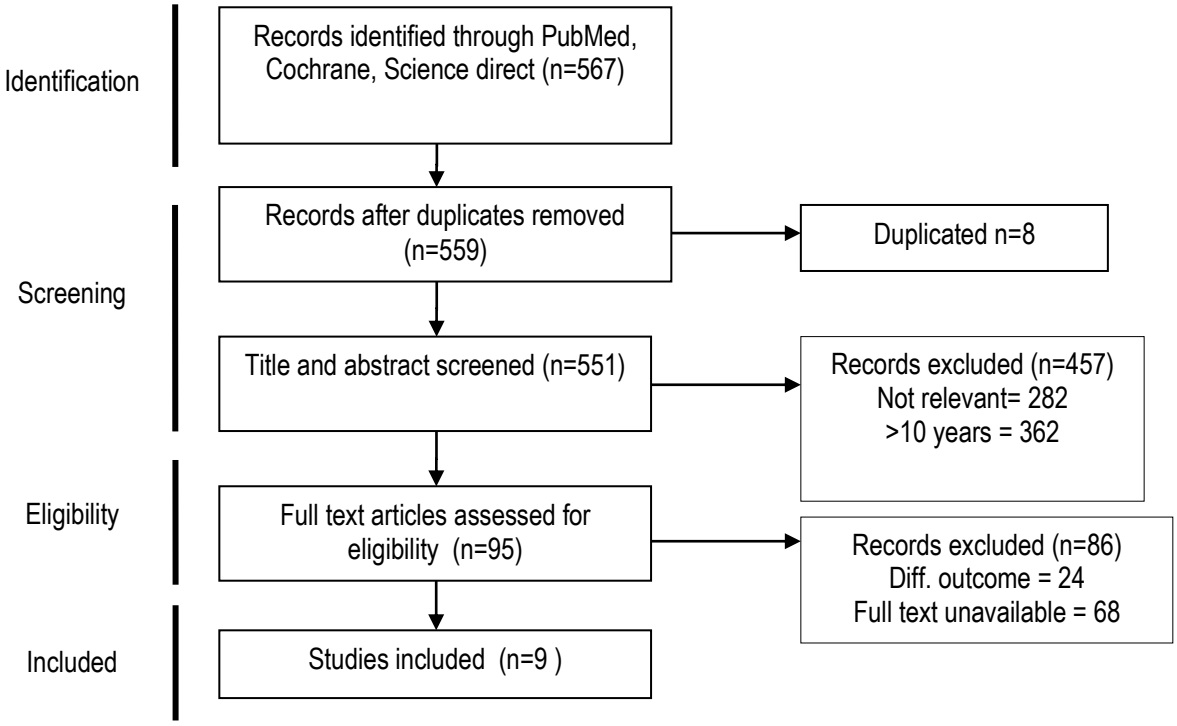

Figure 1.

Literature search proces

Table 1

Summary of articles findings

Author	Subject	Title	Design	Dosage of flavonoid	Duration	Results
Giannini et al, 2015	30 women with endometriosis	Effects of Preoperative and Perioperative administration of Wobenzym Vital, an enzyme-flavonoids combination supplement with antiinflammatory activity, as supportive treatment on Minimal-Mild stage of Endometriosis	Randomized-controlled trial	Each tablet of Wobenzym contains 9 mg chymotrypsin (flavonoid compound), two times a day	60 days	Wobenzym group has lower visual analogue scale (VAS) scores before surgery and perioperatively,in compare with placebo group. Inflammatory and several growth factors were higher than intervention group in perioperative period, significantly (P<0.05)
Da Silva et al, 2017	44 women with endometriosis	The use of Resveratrol as an adjuvant treatment of pain in endometriosis: A randomized clinical trial	Randomized-controlled trial	each resveratrol capsule contains 40 mg resveratrol, 2 times a day	42 days	After treatment, pain values were decreased in both group. Pain values of resveratrol group was lower than placebo group (P<0,005)
Mirzaei et al, 2020	70 women with endometriosis	A randomized trial assessing the eficacy of Silymarin on endometrioma‐related manifestations	Randomized-controlled trial	140 mg of silymarin (flavonoid compound), 2 times a day	12 weeks	The volume of endometrioma in right ovary was reduced significantly (p=0,04) after 12 weeks in silymarin group and IL-6 level in silymarin group was reduced significantly as well (p=0,002). (The Quality of Life (QoL) and female sexual function did not improve substantially in the two groups.

Author	Origin	Title	Design	Subject	Results
Hendarto et al, 2018	Indonesia	Curcumin improves growth factors expression of bovine cumulus-oocyte complexes cultured in peritoneal fluid of women with endometriosis	In vitro study	21 peritoneal fluid from infertile women with endometriosis	Growth Differentiation Factor 9 (GDF-9) produced by oocyte, which is useful for granulosa cell proliferation and differentiation, and Kit Ligand (KitL) secreted by granulosa cells, which induces oocyte maturation were increased significantly (p<0,001) in samples with curcumin, meanwhile TNFα expression in peritoneal fluids added curcumin were reduced compared to those cultured without curcumin (p<0,001)
Youseflu et al, 2020	Iran	Dietary Phytoestrogen Intake and The Risk of Endometriosis in Iranian Women: A Case-Control Study	Case-control study	78 women with laparoscopically confirmed endometriosis and 78 normal pelvis women	Among food groups, intake of total isoflavones, one of flavonoid compound was higher (P-tren=0,002) than others. It was related to reduced endometriosis risk. (OR=0,38)
Jehanara et al, 2018	Indonesia	Effect of Genistein on Decreased Levels of Vascular Endothelial Growth Factor-A in Endometriosis Cell Culture	In-Vitro study	Human endometriosis cell	Concentration of VEGF-A between the control group and genistein group were significantly different at the 24^{th} and 48^{th} hour of incubation period. The lowest VEGF-A concentration was found at the genistein group of 50µm/L with 48 hours of incubation ($p < 0.05$).

Author	Subject	Title	Design	Dosage of Flavonoid	Duration	Results
Jouhari et al, 2018	Rats	Effects of silymarin, cabergoline and letrozole on rat model of Endometriosis	In-vivo study	100 mg/kgBW/day of silymarin	3 weeks	Volume of the endometriosis implants decreased significantly in silymarin, letrozole, and cabergoline compared to the control.
Maharani et al, 2019	Rats	Phytochemical characteristics from *Phaleria macrocarpa* and its activity on the peritoneal damage of endometriosis	In-vivo study	3,75 mg, 7,5 mg, 11,25 mg of flavonoid isolates from P.*macrocarpa* extract	14 days	There was an increase in granulomas, proliferation, and apoptosis in the peritoneal tissues of the endometriosis model (EMT)
Ilhan et al, 2020	Rats	The regression of endometriosis with glycosylated flavonoids isolated from *Melilotus officinalis*(L.) Pall. in an endometriosis rat model	In-Vivo study	100 mg/kgBW/day of glycosylated flavonoid fractions from *Melilotus officinalis*(L.) Pall MeOH extract	4 weeks	The application of the MeOH extract on the top of endometriotic implant significantly decreased the volumes from 81.9 to 54.4 mm^3

This is consistent with the concept of increased inflammatory mediators as activators of cell proliferation leading to hyperplasia and the formation of endometriotic lesions.[20] Endometriotic lesions undergo thickening of the endometrial lining, triggering increased aromatase enzyme production. Aromatase enzyme is required for the catalysis process of androstenedione into estrogen. Increased estrogen levels without a balance in progesterone production can cause vasodilation of blood vessels and angiogenesis in the endometrium, leading to pain as one of the signs of ongoing inflammation. Furthermore, impaired maturation of ovarian eggs and increased mucus production can interfere with the penetration of sperm during fertilization.

Comparisons between flavonoid, lignans, and other phytoestrogen compound were also studied by Youseflu et al.[21] on women with confirmed endometriosis and those with a normal pelvis. By observing the intake of phytoestrogens, specifically flavonoids, lignans, and other flavonoids / coumestrol, showed that a high intake of flavonoids is significantly associated with a lower risk of endometriosis (OR: 0.38; 95% CI: 0.33-0.83; P-trend=0.002). Some studies discussed about the role of flavonoids in the growth factor signaling pathway. Genistein, one of the flavonoid compounds found in soy, is known to inhibit the activity of tyrosine kinase enzymes.[22] Tyrosine kinases are known to be involved in cell proliferation. Inhibiting tyrosine kinase enzymes in cancer conditions can be beneficial in reducing cancer cell proliferation.[24]

Anti-inflammatory Activity

The inflammation that occur in endometriosis lead to sensitization of the endometrium to increased estrogen levels, leading to myometrial contractions and arteriolar vasoconstriction, resulting in ischemia. Ischemia causes an inflammatory response, including the release of prostaglandins that stimulate afferent nerves and result in pain. Several human studies have shown that flavonoids play a role in reducing pain in endometriosis.[25,27]

A study by Da Silva et al.[25] on 44 women confirmed with endometriosis who received combination oral contraceptive therapy divided the participants into an intervention group and a placebo group. The intervention group received oral resveratrol, a group of flavonoids found in many dietary sources such as grapes, wine, peanuts, soy and berries.[26] 40 mg of resveratrol has given to subject in resveratrol group, twice daily for 42 days. Pain measured using visual analogue scale (VAS), during menstruation (dysmenorrhea) and/or pelvic pain was assessed. The results of this study showed pain improvement in both groups within 42 days, with a better VAS score in the intervention group (mean baseline score: 5.4, mean final score: 3.2) compared to the placebo group (mean baseline score: 5.7, mean final score: 3.9). Although no significant difference was found between resveratrol and placebo group, the pain improvement observed in the resveratrol group suggesting the need for further investigation in larger populations or with higher doses.

In vitro study conducted by Hendarto et al.[27] which used peritoneal fluid from 44 infertile women with endometriosis. 0.2 ml of dissolved curcuminwas added on 21 peritoneal fluid and 21 other samples were not given curcumin. Curcumin, a plant-derived polyphenolic compound, naturally present in turmeric (*Curcuma longa*).[27] Growth Differentiation Factor 9 (GDF-9) produced by oocyte, which is useful for granulosa cell proliferation and differentiation, and Kit Ligand (KitL) secreted by granulosa cells, which induces oocyte maturation were increased significantly ($p<0,001$) in samples with curcumin, meanwhile TNFα expression in peritoneal fluids with curcumin were reduced compared to those cultured without curcumin ($p<0,001$). This indicates the presence of other flavonoid compounds, including curcumin, which has a significant positive impact on the improvement of endometriosis compared to the control group. The decrease in TNF-alpha and the increase in growth differentiation factor 9 (GDF9) in peritoneal fluid treated with curcumin suggest the role of curcumin as an anti-inflammatory agent and its ability to improve the regulation of oocyte maturation. Consistent with previous studies, two important points can be highlighted regarding the improvement of endometriosis. First, the significant role of aromatase enzyme

in the proliferation of lesions, as the administration of aromatase inhibitors leads to a reduction in the size of endometriotic lesions. Second, antioxidants have an anti-proliferative effect, such as aromatase inhibitors, and increase the levels of antioxidants involved in inhibiting NF-kβ signaling, thus reducing the formation of tumor-initiating inflammatory mediators such as TNFα.

Consistent with animal study conducted by Jouhari et al.[28] divided 32 female rats induced with endometriosis into four groups: (1) letrozole group, a non-steroidal aromatase inhibitor at a dose of 0.18 mg/kg body weight/day; (2) cabergoline group, a dopamine agonist involved in VEGF receptor endocytosis, resulting in a reduction in VEGF-receptor binding. Cabergoline was administered at a dose of 0.5 mg/kg body weight/day; (3) silymarin group, at a dose of 100 mg/kg body weight/day; and (4) control group, receiving no intervention. The three intervention groups received subcutaneous injections for 21 days. The results of the study showed that the letrozole group had a greater reduction in endometriotic lesion mass by 4.35 mm^3 compared to the other two intervention groups. Additionally, the silymarin group showed significantly higher antioxidant capacity compared to the control group. The higher antioxidant value in the silymarin group is also consistent with a significant decrease in TNFα levels compared to the control group. The improvement in levels of pro-inflammatory mediator such as TNFα and growth factors affects the perceived quality of pain, leading to a better experience. The antioxidant effects of flavonoids also work effectively on several neurotransmitter receptors associated with neuropathic pain.[29]

Potential application of flavonoid in the management of endometriosis

Globally, the use of supplementary nutrition therapy in the management of endometriosis has not been determined. Based on a study by Hujis et al.[30], the intake of fatty acids, antioxidants, and a combination of vitamins and minerals has been found to help improve endometriosis, particularly the clinical symptoms experienced. Vegetables and fruits are among the recommended nutritious ingredients in supplementary nutrition therapy for endometriosis patients. The effective dosage range of flavonoids has not yet been determined, but based on a study by Ortiz-Andrade et al.[31] in animal experiments, an intake of more than 2000 mg of flavonoids per day may pose a risk of liver disorders because flavonoids have the potential to weakly inhibit the metabolism of metabolites through the CYP450 pathway. Several studies have reported that the average flavonoid consumption in Asian populations ranges from 50-200 mg/day, while in European populations, it ranges from 200-500 mg/day, with tea being one of the most frequently consumed food items. Tea is a rich source of flavonoids, followed by oranges and grapes. In Indonesia, the median flavonoid intake, according to a study by Sefrina et al.[32], is approximately 25.02 mg/day. Recommendations to increase the consumption of vegetables, fruits, and bee products can be applied as a supportive therapy.

CONCLUSION

In this review, we discuss potential of flavonoids in improving endometriotic lesions and clinical symptoms. Flavonoids have been shown to reduce inflammation, which is a cause of pain and abnormal lesion growth, by inhibiting the signaling of the NF-kB pathway, which is a key pathway involved in tumorigenesis, as well as through the activation of antioxidant enzymes. Flavonoids, as a group of phytonutrients, hold promise as an additional nutritional therapy for conditions involving chronic pain and abnormal lesion growth, such as endometriosis. Food sources rich in flavonoids can be a favorable option as supplementary nutrition for endometriosis patients, both with or without medical therapy. Flavonoids are abundantly found in natural food sources that are easily accessible and can be consumed in daily life. A limitation of our study is that some of our references were studies conducted on animals. The dosage of drugs or supplements used in animal testing is often higher, making it inappropriate to directly reference those dosages for human use. Furthermore, due to the limited number of

articles reviewed in this study, a definitive conclusion regarding the role of flavonoids in endometriosis cannot be drawn. Evidently, there are still many gaps to explore potential of flavonoids in human's health and also metabolic dysfunction. Further clinical trials, particularly involving human subjects with endometriosis or even other chronic diseases , are needed to validate these positive findings from previous studies as well as to detect possible adverse effects that may arise when administered in the form of supplementation.

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REFERENCES

1. Ezzat, L. Endometriosis and Quality of Life: an Implication on Psychological Well-Being. *Int. J. Gynecol. Obstet*, 2019::2;2:30-34.
2. Coccia ME, Nardone L, Rizzello F. Endometriosis and Infertility: A Long-Life Approach to Preserve Reproductive Integrity. *Int. J. Environ. Res. Public Health* 2022;19;1162. doi:10.3390/ijerph19106162
3. Perkumpulan Obstetri dan Ginekologi Indonesia. Konsensus Tata Laksana Nyeri Endometriosis Revisi Pertama [Internet]. 2017 [cited 2023 May 5]. Available from: https://pogi.or.id/publish/download/pnpk-dan-ppk/
4. Dunselman GAJ, Vermeulen N, Becker C, Calhaz-Jorge C, Hooghe TD, De Bie B, et al. ESHRE Guideline: Management of Women with Endometriosis. *Hum. Reprod*. 2014;29(3);400-412. doi: 10.1093/humrep/det457
5. Sourial S, Tempest N, Hapangama DK. Review Article: Theories on the Pathogenesis of Endometriosis. *Int.J.Reprod.Med,* 2014. doi: 10.1155/2014/179515
6. Parasar P, Ozcan P, Terry LK. Endometriosis: Epidemiology, Diagnosis, and Clinical Management. Curr Obstet Gynecol Rep.2017;6;34-41. doi: 10.1007/s13669-017-0187-1
7. Giannini A, Palla G, Goglia L, Genazzani AR, Genazzani A, Simoncini T. Effects of Preoperative and Perioperative Administration of Wobenzym Vital on Minimal-Mild Endometriosis. J Endometr Pelvic Pain Disord.2015;7(2):71-77. doi: 10.5301/je.5000215
8. Lagana AS, Garzon S, Gotte M, Vigano P, Franchi M, Ghezzi F, et al. The Pathogenesis of Endometriosis: Molecular and Cell Biology Insights. Int J Mol Sci.2019;20;2615Estevez M, Xiong Y. Intake of Oxidized Proteins and Amino Acids and Causative Oxidative Stress and Disease: Recent Scientific Evidences and Hypotheses. J.Food Sci.2019;84:3. doi: 10.3390/ijms20225615
9. Ridwan A, Putra RE, Sari AN. The Potency of Trigona's Propolis Extract as Reactive Oxygen Species Inhibitor in Diabetic Mice. J.Math.Fund.Sci.2015;47;3. doi: 10.5614/j.math.fund.sci.2015.47.3.4
10. Sungkar A, Doewes M, Purwanto B, Wasita B. The Effect of Indonesian Propolis Dosage on Vascularization of Skin Graft in Skin Wound of White Rat's Skin Graft Model: Molecular Studies of Malondialdehyde (MDA), Nuclear Factor-Kappa Beta (NF-κB), Interleukin-6, Vascular Endothelial Growth Factor (VEGF), Caspase-3, and Microvessels Density (MVD).Bali.Med.J.2021;10;2. doi: 10.15562/bmj.v10i2.2339
11. Situmorang H, Hestiantoro A, Purbadi S, Flamandita D. IN SILICO Dynamic Analysis of Sulawesi Propolis as Anti-Endometriosis Drug: Interaction Study with TNF Alpha Receptor, NF-κB, Estrogen Receptor, Progesterone Receptor, and Prostaglandin Receptor.Ann.Med.2021;67. doi: 10.1016/j.amsu.2021.102459
12. Reis FM, Coutinho LM, Vannuccini S, Batteux F, Chapron C, Petraglia F. Progesterone Receptor Ligands for the Treatment of Endometriosis: the Mechanisms Behind Therapeutic Success and Failure. Hum.Reprod.Update. 2020;26;4. doi: 10.1093/humupd/dmaa009

13. Yan B, Chen ZS, Hu Y.Yong Q. Insight in the Recent Application of Polyphenols from Biomass. Front. Bioeng. Biotechnol. 2021.9:753898. doi: 10.3389/fbioe.2021.753898
14. Quintao NLM, Antonialli CS, da Silva GF, Rocha LW, de Souza MM, Malheiros A, et al. Aleurites moluccan and its main active ingredient, the flavonoid 2"-O-rhamnosylswertisin, have promising antinociceptive effects in experimental models of hypersensitivity in mice. Pharmacol Biochem Behav. 2012;102;302-311. doi: 10.1016/j.pbb.2012.05.005
15. Bartiromo L, Schimberni M, Villanacci R, Ottolina J, Dolci C, Salmeri N, et al. Enddometriosis and Phytoestrogens: Friends or Foes? A Systematic Review.Nutrients.2021;13:2532. doi: 10.3390/nu13082532
16. Wardani PK, Gunarti DW, Wulandari Y. Peran Flavonoid terhadap TNF Alfa pada Endometriosis.Jurnal Darma Agung.2023;31(3):241-249. doi: 10.46930/ojsuda.v31i3.3454
17. Bulun SE, Monsavais D, Pavone ME, Dysone M, Qing Xue, Attar E, et al. Role of Estrogen Receptor-β in Endometriosis.Semin Reprod Med. 2012;30(1):39-45. doi: 10.1055/s-0031-1299596
18. Mirzaei N, Sadatmahalleh SJ, Rouholamin S, Nasiri M. A Randomized Trial Assessing the Efficacy of Silymarin on Endometrioma-related Manifestasions. Scientific Reports.2022;;12:17549. doi: 10.1038/s41598-022-22073-8
19. Kshrisagar A, Ingawale D, Ashok P, Vyawahare N. Silymarin: A Comprehensive Review. Phcog Rev. 2009;3(5):126-134.
20. Maharani, Lajuna L. Yuniwati C, Sabrida O, Sutrisno. Phytochemcial Characteristics from Phaleria Macrocarpa and its Activity on the Pertoneal Damage of Endometriosis. J-AIM. 2021;12:229-233. doi: 10.1016/j.jaim.2020.06.002
21. Youseflu S, Sadatmahalleh SJ, Mottaghi A, Kazemnejad A. Dietary Phytoestrogen Intake and The Risk of Endometriosis in Iranian Women: A Case-Control Study. Int J Fertil Steril.2020;13(4):296-300. doi: 10.22074/ijfs.2020.5806
22. Jehanara, Sutrisno, Santoso S. Pengaruh Genistein terhadap Penurunan Kadar Vascular Endothelial Growth Factor-A pada Kultur Sel Endometriosis. Majalah Obstet. Ginekol. Indones. 2014;22(2):94-100.
23. Ilhan M, Ali Z, Khan IA, Tastan H, Akkol EK. The Regression of Endometriosis with Glycosylated Flavonoids Isolated from Melilotus officinalis (L) Pall. in An Endometriosis Rat Model. Taiwan J Obstet Gynecol.2020;59:211-219. doi: 10.1016/j.tjog.2020.01.008
24. Wu Y, Zhou BP. TNF-α/NF-κβ/Snail Pathway in Cancer Cell Migration and Invasion.Br J Cancer.2010;102:639-644. doi: 10.1038/sj.bjc.6605530
25. Da Silva DM, Gross LA, de Paula Guedes Neto E, Lessey BA, Savaris RF. The Use of Resveratrol as An Adjuvant Treatment of Pain in Endometriosis: A Randomized Clinical Trial.J Endocr Soc.2017;1:359-369. doi: 10.1210/js.2017-00053
26. Dull AM, Moga AM, Dimienescu OG, Sechel G, Burtea V, Anastasiu V. Therapeutic Approaches of Resveratrol and Endometriosis via Anti-Inflammatory and Anti-Angiogenic Pathways. Molecules. 2019;24:667. doi: 10.3390/molecules24040667
27. Hendarto H, Widyanugraha MYA, Widjiati W. Curcumin Improves Growth Factors Expression of Bovine Cumulus-Oocyte Complexes Cultured in Peritoneal Fluid of Women with Endometriosis. Int. J. Reprod. BioMed.2018;16(12). doi: 10.18502/ijrm.v16i12.3683
28. Jouhari S, Mohammadzadeh A, Soltanghoraee H, Mohammadi Z, Khazali S, Mirzadegan E. Effects of Silymarine, Cabergoline, and Letrozole in Rat Model of Endometriosis.Taiwan J Obstet Gynecol.2018;57:830-835. doi: 10.1016/j.tjog.2018.10.011
29. Uddin MS, Mamun AA,Rahman MA, Kabir MT, Alkahtani S, Alanazi IS, et al. Exploring the Promise of Flavonoids to Combat Neuropathic Pain: From Molecular Mechanisms to Therapeutic

Implications.Front. Neurosci.2020;14:478. doi: 10.3389/fnins.2020.00478
30. Hujis E, Nap A. The Effects of Nutrients on Symptoms in Women with Endometriosis: A Systemic Review. Reprod Biomed Online.2020;41:2. doi: 10.1016/j.rbmo.2020.04.014
31. Ortiz-Andrade R, Araujo-Leon JA, Sanchez-Recillas A, Navarette-Vazquez G, Gonzalez-Sanchez AA, Hidalgo-Figueroa S, et al. Toxicological Screening of Four Bioactive Citroflavonoids: In Vitro, In Vivo, and In Silico Approaches. Molecules, 2020;25:5959. doi: 10.3390/molecules25245959
32. Sefrina LR, Briawan D, Sinaga T, Permaesih D. Flavonoid Database Based on Indonesian Foods. J Nutr Sci Vitaminol. 2020;66:251–5. doi: 10.3177/jnsv.66.S251