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Literature Review

The Role of Herbal Medicine as An Alternative Treatment Option for Endometriosis: A Literature Review

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ABSTRACT

Introduction: Endometriosis is a benign gynecological disorder characterized by ectopic growth of endometrial tissue. This condition may deteriorate patient's quality of life due to pain as its main manifestation and its complications, including impaired fertility and risk of ovarian cancer. Current standard endometriosis treatment still yields numerous side effects and controversy. Thus, herbal medicine is hoped to be the safer alternative treatment with excellent efficacy for endometriosis.

Methods: The search of literature published in English or Bahasa Indonesia was performed by incorporating the search queries "endometriosis", "herbal therapy", "silymarin", "curcumin", "Viburnum opulus", "Pueraria", "Allium sativum", "black garlic", "naringenin" on databases including PubMed, Cochrane, Springer, Science Direct, Nature, and Google Scholar. The studies included were *in vitro* studies, *in vivo* studies, and clinical trials.

Results: Various herbal treatments have been widely studied regarding their anti-inflammatory, antioxidant, neuroprotective, hepatoprotective, cardioprotective, antiallergy, and immunomodulatory capacity. A lot of herbal compounds have the potential to suppress and manage endometriosis through various mechanisms, such as inhibiting the migration and adhesion of endometriosis to other tissues, suppressing inflammatory response in endometriosis pathogenesis, generating antioxidant, inhibiting estrogen activity, and inducing apoptosis of endometriosis cell through a number of signaling pathways.

Conclusion: Herbal medicine has the potential to manage endometriosis through various mechanisms. Further research is needed regarding the efficacy of herbal therapy in managing endometriosis.

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INTRODUCTION

Endometriosis is an estrogen-dependent benign gynecological disorder characterized by the ectopic growth of endometrial tissues. The exact etiology of endometriosis is still unknown, however retrograde menstruation in which endometrial epithelial tissue or stroma is implanted in the peritoneal cavity through the fallopian tube is believed to be the main cause of endometriosis [1]. Endometriosis prevalence ranged from 0.7% to 12.8%, depending on the geographic setting of the epidemiological research, in which the highest prevalence was reported in 35 y.o. to 44 y.o. age group population. [2,3]. In the United States (US), endometriosis prevalence was as high as 6.1% [4]. Meanwhile, in East Asia, the prevalence was approximately 6.8% [5]. Endometriosis typically manifests as menstrual pain, which is generally felt in the lower abdomen and the pain may radiate to the lower back. With time, the pain may worsen and persist even after the menstruation ends. Moreover, as many as 66% of women with endometriosis have complained about the symptoms prior to 20 years of age. This may significantly deteriorate the quality of life of patients due to the pain and impaired fertility [6]. Endometriosis can be dangerous as it is believed to be a risk factor for

various malignancies, especially ovarian cancer, hence the increased mortality and morbidity rate [7–9].

The treatment for endometriosis may be delivered through pharmacological or surgical approaches. Pharmacological treatment includes the administration of non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraception, followed by the consumption of gonadotropin-releasing hormone (GnRH) inhibitors. However the pharmacological treatment is only suppressive therefore if the treatment is stopped, the endometriosis may recur. Moreover, long-term consumption of these medications is associated with prominent side effects. Surgical treatment is the definitive treatment for endometriosis, however, it still has controversial features. While ablation therapy cannot be performed for endometriosis located near critical structures [10,11].

Herbal treatment has been widely studied to be the alternative treatment for endometriosis. Several plants that have been proven to exert beneficial effects in endometriosis include Pueraria flower, black garlic, Uncaria tormentosa, Curcuma spp., Viburnum opulus, Calligonum comosum, etc. [12–14]. Therefore, as a natural herbal product, this treatment is hoped to have better efficacy and reduce side effects related to the conventional endometriosis treatment. This article will discuss the role of various herbal products in managing endometriosis.

METHODS

Literature Search

The authors searched for articles published between 2012 to 2022 using the following keywords: "endometriosis", "herbal therapy", "silymarin", "curcumin", "Viburnum opulus", "Pueraria", "black garlic", "Allium sativum", "naringenin". The literature search was conducted on several online databases such as PubMed, Cochrane, Springer, Science Direct, Nature, and Google Scholar. The literature searched includes articles published in English or in Bahasa Indonesia and include *in vitro* studies, *in vivo* studies, or clinical trials performed in humans (Fig. 1).

Study Selection and Screening

The authors identified a total of 1564 articles by searching the aforementioned keywords through the listed online databases. A total of 829 articles were then removed due to duplication, leaving a total of 735 articles. The authors then screened the remaining articles and found 411 articles that did not address the subject of the role of herbal medicine as an alternative treatment for endometriosis. Of the 324 remaining articles, a total of 276 articles were excluded and 48 articles were included in the review for analysis (Table 1.)

Herbal Treatment

Herbal products have been utilized in treating various diseases since the earliest of civilizations. In the modern age, herbal treatment has been widely studied regarding its efficacy in managing many health disorders since herbal products are believed to contain several benefits such as anti-inflammatory, antioxidant, antitumor, and antihypertensive properties. Recently, various traditional Chinese medicine or western herbal treatment efficacy has been studied in the management of endometriosis [15–17]. There are many types of plants along with their active components which have been studied as an alternative treatment for endometriosis.

Silymarin

Silymarin is an active compound extracted from the plant closely related to the Aster flower and shrubs, with the scientific name *Silybum marianum*. The plant is also well known as 'Marian thistle', 'Mary thistle', 'Saint Mary's thistle', 'Mediterranean milk thistle', or 'Scotch thistle'. In 1959, silymarin was found to contain the flavonoligan as its main active compound, which was about 65% to 80% of all of its contents, which included silybin A, silybin B, isosilybin A, isosilybin B, silychristin, and silydianin. Meanwhile, 20% to 35% of its other components are fatty acids and polyphenols.

These contents work as antioxidants and exert antitumor, cardioprotective, and neuroprotective effects. In the beginning, silymarin was utilized as the standard treatment for hepatic diseases of various etiologies. Following administration, silymarin is rapidly metabolized by the phase 2 enzyme and detected as a foreign substance by the body. Silymarin bioavailability is considered to be low, a study in rats reported a bioavailability of only 0.95%. However, after its administration, silymarin was proven to increase glutathione S transferase (GST, previously known as ligandin) and quinone reductase activity in various organs. Both substances function in aiding detoxification [18,19].

Nahari and Razi (2018) reported that silymarin was proven to reduce the size of the endometrial lesion in adult female Wistar rats. In the study, silymarin was able to reduce the expression of glial cell-derived neurotrophic factor (GDNF), which binds to its coreceptor a (gfrα) [20]. Glial cell-derived neurotrophic factor activation will initiate several signaling cascades such as mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase 1/2 (ERK1/2) which subsequently induces Bcl-6b, a molecule responsible for regulating cell survival and proliferation. Although silymarin was also reported to stimulate ERK1/2 activity, silymarin administration also reduced Bcl-2 expression, exhibiting its specificity to certain cells or mechanisms. Histopathological analysis on Sprague-Dawley rats showed an improvement in

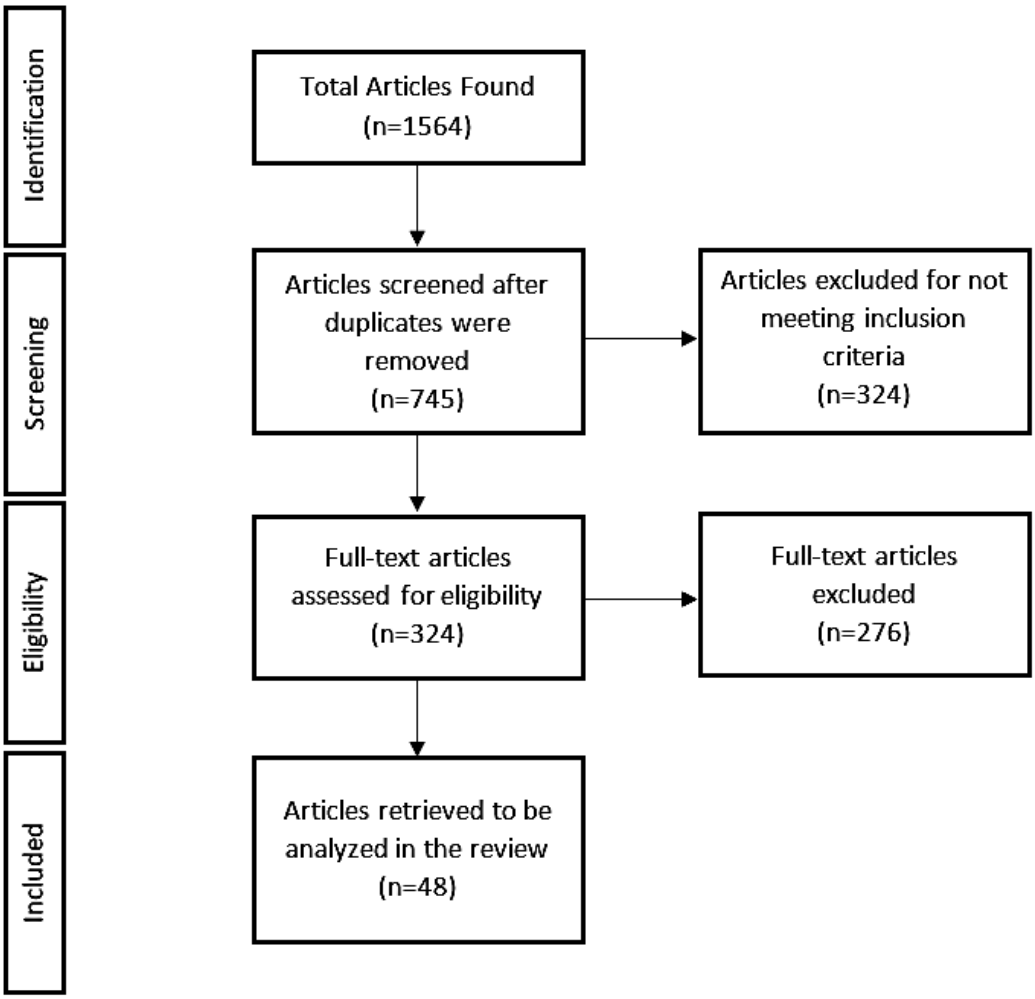

Fig. 1. Flow Diagram

histopathological grading on endometriosis model [21]. In human clinical trial, silymarin was reported to alleviate pain symptom, endometrial lesion size, and interleukin 6 (IL-6) level [22]. Inflammation, despite the lack of detailed information about the exact mechanism, is involved in the development of endometriosis, associated with the high level of inflammatory mediator in various organs of patients with endometriosis.

Curcumin

Curcumin is a compound often referred to as curcuminoid, along with demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC). Curcumin is known by the International Union of Pure and Applied Chemistry (IUPAC) name (1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta1,6-diene-3,5-dione. Other names for curcumin include 1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione or diferuloylmethane. Curcumin is the most abundant content of turmeric or Curcuma longa, which is approximately 3%, followed by DMC (1.4%) and BDMC (1.2%). Turmeric has been used since 4000 years ago in India, as additional seasoning in cuisine and in various religious ceremonies. Furthermore, turmeric has also been used as a component for alternative treatment for many kinds of diseases [23,24].

Based on previous studies, curcumin was reported to have anti-inflammatory, antioxidant, anti-diabetes, hepatoprotective, and neuroprotective properties [25]. However, curcumin bioavailability post-administration is extremely low due to poor absorption and rapid metabolism and excretion [26]. In vitro studies showed that curcumin administration successfully reduced the number and size of endometriosis epithelial and stromal cells, and slowed down endometriosis cell growth by inhibiting estradiol activity (E2) causing the induction of apoptosis. Estradiol is a hormone which is thought to play an important role in endometriosis growth. In the

same study, estradiol level in endometriosis lesions were significantly higher than that of the control [27].

In vivo study in Mus musculus mice showed curcumin activity in suppressing prostaglandin E2 (PGE2) and matrix metalloproteinase 9 (MMP9) in all doses of curcumin [28]. Prostaglandin E2 inhibition is achieved through the suppression of cyclooxygenase 2 (COX-2) and lipoxygenase (LOX) and therefore successfully subsided proinflammatory cytokines production. While MMP9 functions in degradation of extracellular matrix (ECM), a necessary phenomenon in the implantation of endometrial tissue to the peritoneum. In the clinical trial involving 10 women in the age range of 26 y.o. to 39 y.o., curcumin was proven to manage endometriosis by inhibiting inflammation through phosphatidylinositol-3-kinase (PI3K)/Akt and sterol regulatory element-binding protein 1 (SREBP-1). This inhibition subsequently blocks COX-2 and nuclear factor kappa B (NFκB), thus the production of various inflammatory cytokines (tumor necrosis factor α, IL-1, IL-2, IL-6, IL-8) is also impaired [29]. Hypoxia-induced inflammation is thought to be substantial in the development and growth of endometriosis.

Viburnum opulus

Viburnum opulus is a plant resembling a shrub classified in the *Adoxaceae* family or sometimes classified in *Viburnaceae*. The plant is also well-known as 'guelder rose', 'water elder', 'Rose Ebru', 'cherry-wood', 'crampbark', 'snowball tree', and 'gilaburu', and it dwells in Rusia, Europe, North Africa, and North Asia. This plant has been used in various fields, ranging from treatment, decoration, or cuisine (jam, cake, marmalade, tea, or liquor). The main content of the *Viburnum opulus* fruit is water, ranging from 85.7% to 88.3%. However, *Viburnum opulus* also consists of various acids with anti-inflammatory, antimicrobial, anti-obesity, osteogenic, cytoprotective, and cardioprotective traits.

The acid content of *Viburnum opulus* harvested in Rusia is relatively greater compared to the ones harvested in Turkey [30,31]. Saltan *et al*. (2016) reported that administration of the ethyl acetate extract and methanol extract of *Viburnum opulus* into endometriosis model Sprague-Dawley rats significantly reduced the level of TNF-α, vascular endothelial growth factor (VEGF), and IL-6 in the peritoneum. This finding was not observed in the hexane extract of *Viburnum opulus* fruit, although a decreasing trend of the cytokine was observed. This result was similar to the result of the reference group which was intervened using buserelin acetate. The active compounds of *Viburnum opulus* include arbutin, valerianic acid, catechin, epicatechin, and quercetin glycoside [32]. Interestingly, *Viburnum opulus* fruit is also known to contain a high level of chlorogenic acid which has antioxidant properties and is therefore considered to be the source of chlorogenic acid [33].

Pueraria spp.

Pueraria spp. is a Japanese arrowroot also known as 'Kudzu', which is classified in the Leguminsoae family. This plant is commonly found in Asia, North America, and South America. The name *Puearaia spp*. was derived from the Swiss botanist Marc Nicolas Puerari. There are 26 species of plants in the Pueraria genus, such as *Pueraria montana, Pueraria tuberosa, Pueraria lobata, Pueraria thunbergiana*, and *Pueraria candollei*. This plant has been widely used for its efficacy as herbal treatment or as cosmetics. In the ayurvedic treatment, the plant, especially *Pueraria tuberosa*, was classified as 'Rasayana'. Several previous studies stated that the plant Pueraria has anti-obesity, antitumor, hepatoprotective, antioxidant, anti-inflammatory, antimicrobial, cardioprotective, neuroprotective, immunomodulatory, antipyretic, analgesic, and muscle relaxant effects [34,35].

Based on its pharmacokinetic aspect, *Pueraria* plants can pass the blood-brain barrier (BBB) and exert its neuroprotective effect. It is known that the median lethal dose (LD_{50}) of the *Pueraria* plant is 227.5 mg. Some *Pueraria* constituents have been studied in which its active compounds differ depending on the extraction. Jin *et al*. (2012) reported that ethanol extraction of *Pueraria lobata* produces daidzein, genistein, puerarin, and (+)-puerarol B-2-O-glucopyranoside. Buthanol extract consisted of allantoin, 3'-hidroxypuerarin, daidzein 8-C-apiosil-(1→6)-glucoside, puerarin, genistin, 3'-metoxypuerarin, and daidzin. While hexane extraction generates lupenone, lupeol, puerarol, and coumestirol [36].

A study conducted by Kim et al (2017) stated that Pueraria flower extract successfully inhibited endometrial cell (11Z and 12Z) migration and adhesion to the mesothelial cell Met5A. This was supported by the finding that the extract also reduced the expression of MMP2 and MMP9, which is necessary for the invasion, migration, and adhesion of endometrial cells. Matrix metalloproteinase was proven to be at in increased level in the peritoneum of endometriosis models. Besides, *Pueraria* flower extract also increased ERK1/2 activation and inhibited endometrial cell growth in BALB/c mice [37]. Lin *et al*. (2017) reported that *Pueraria mirifica* extract suppressed endometrial cell proliferation induced by 17β-estradiol [38]. However, contrary to the findings of other studies, *Pueraria mirifica* extract was reported to stimulate endometrial mesenchymal cell growth through estrogen receptors. This was also observed in a study by Kakehashi *et al*. (2016) in which *Pueraria mirifica* extract exerted estrogenic activity which may aid in the growth of breast cancer [39].

Table 1. Summary of Herbal Treatment Effect on Endometriosis

Herbal Plant / Extract	Author	Publication Year	Model	Therapy Effect
Silymarin	Nahari and Razi [20]	2018	Adult Wistar rats	Reduction of lesion size GDNF inhibition Increased activation of ERK1/2 Suppression of Bcl-6b and Bcl-2
	Jouhari *et al.* [21]	2018	Sprague-Dawley rats	Reduction of lesion size Improvement of histopathological grading
	Rouholamin *et al.* [22]	2022	Women diagnosed with endometriosis	Symptoms alleviation Reduction of lesion size Reduction of IL-6 level
Curcumin	Zhang *et al.* [27]	2013	Endometriosis cells	Reduction of lesion size Inhibition of proliferation Reduction of E_2 level
	Annas *et al.* [28]	2014	*Mus musculus* mice	Reduction of PGE2 level Reduction of MMP9 level
	Kim *et al.* [29]	2019	Women diagnosed with endometriosis	Suppression of PI3K/Akt signalling pathway Inhibition of SREBP1
Viburnum opulus	Saltan *et al.* [32]	2016	Sprague-Dawley rats	Reduction of TNF-α level VEGF inhibition Reduction of IL-6 level
Pueraria spp.	Kim *et al.* [37]	2017	Endometriosis cell line 11Z and 12Z, BALB/c mice	Endometriosis cell migration and adhesion inhibition Reduction of MMP2 and MMP9 expression Increased activation of ERK1/2
	Lin *et al.* [38]	2017	Human endometrial mesenchymal cell (hEN-MSCs)	Suppression of endometriosis cell growth through 17β-estradiol
Allium sativum	Amirsalari *et al.* [41]	2021	Adult women aged 20-45 y.o. diagnosed with endometriosis	Alleviation of back and pelvic pain, dyspareunia, dan dysmenorrhea
Bawang Putih Hitam	Kim *et al.* [45]	2013	Endometrial stromal cell	ICAM-1 and VCAM-1 suppression
Naringenin	Park *et al.* [46]	2017	Endometrial cell	Apoptosis stimulation by induction of Bax and Bak ROS generation on endometriosis cell Suppression of PI3K/Akt signalling pathway
	Kapoor *et al.* [47]	2018	Rats	Increment of Nrf2, NQO1, and HO1 protein level Inhibition of repressor molecule Keap1
	Kapoor *et al.* [48]	2019	Rats	ROS generation on endometriosis cell Reduction of MMP2 and MMP9 expression

Allium sativum

Garlic (*Allium sativum*) is a plant that has been used for medical purposes since ancient times. The use of garlic has been documented in Zoroastrian documents since 6 centuries BC. Garlic has also been used in the Sumerian and early Egyptian civilizations. In China and India, garlic was used as an alternative treatment for managing leprosy, and parasite infection, and aiding respiratory or digestive functions. The main compound of garlic is allicin which gives a strong flavor and taste. Moreover, garlic also contains 1-propenyl allyl thiosulfonate, allyl methyl thiosulfonate, (E,Z)-4,5,9-trythiadodeca-l,6,11-triene 9-oxide (ajoene), and y-L-glutamyl-S-alkyl-L-cystein. Clinical trials on adult women between the ages of 20 y.o. and 45 y.o. showed that garlic tablet administration was capable of alleviating endometriosis symptoms including back and pelvic pain, dyspareunia, and dysmenorrhea [40]. Four mechanisms contribute to the reduction of symptoms, including reduction of oxidative stress, inhibition of

prostaglandin production, suppression of endometrial cell proliferation, and enhancement of estrogen elimination. This is thought to be caused by N-acetylcysteine activity, an antioxidant contained in garlic [41].

Black Garlic

Black garlic is the product of fermentation of garlic (*Allium sativum L.*) in high temperatures ranging from 60°C to 90°C, in a high level of humidity. The black garlic loses its strong taste and flavor due to the loss of allicin throughout the fermentation process. A difference in the content of pure garlic and black garlic has been noted, in which a proportion of garlic components are converted to Amadori/Heyns compounds during fermentation. Compared to pure garlic, black garlic possesses a health benefit that is believed to be substantially greater, regarding its content of polyphenol, flavonoid, and Maillard reaction intermediate compounds. The benefits include antioxidant, antitumor, anti-obesity, anti-inflammatory, antiallergy, hepatoprotective, and anti-dyslipidemia activities [42–44].

A study conducted by Kim *et al*. (2013) reported that the hexane extract of black garlic inhibited vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) expression in stromal cell induced by TNF-α [45]. Proinflammatory cytokines are believed to play an important role in the pathogenesis of endometriosis, which subsequently activates the signaling pathway of MAPK, which regulates cell proliferation and cell cycle progression.

Naringenin

Naringenin (5,7,4'-trihidroxyflavanone) is a colorless and flavorless flavanone, which is an active compound predominantly found in the fruit of *Citrus* × *paradisi* and *Citrus sinensis,* and also found in many other kinds of fruits and herbs. This compound is considered an immunomodulator, which has the properties to prevent acute or chronic inflammation. Its usage in managing septic shock and hepatitis has been documented previously. Besides, naringenin also exerts a hepatoprotective effect and can improve insulin resistance, which may benefit in preventing diabetes Mellitus, atherosclerosis, and metabolic syndrome. In the field of oncology, naringenin is known to have antiproliferative activity in various cancer cell lines. In vitro study on the endometriosis cell line conducted by Park *et al*. (2017) proved that naringenin inhibits cell proliferation and induces apoptosis of the cells by increasing the expression of Bax and Bak protein. With naringenin administration, eIF2α and IRE1α, GADD153 and GRP78 phosphorylation caused the generation of reactive oxygen species (ROS) on endometriosis cell leading to cell death. Furthermore, naringenin also block the signalling pathway of PI3K/Akt resulting in the inhibition of endometriosis cell proliferation [46].

In a study on rats, naringenin was proven to decrease endometriosis lesion counts and size and improved its histopathological features. Naringenin also block the inflammation process which is a crucial feature of endometriosis pathogenesis, which was proven by the decrease of TNFα level on the specimen. Furthermore, naringenin administration induces the increment of the protein Nrf2, which was subsequently followed by the suppression of repressor molecule Keap-1 [47]. Upon the translocation of the molecule Nrf2, various antioxidants were generated and the molecule NQO1 and HO1 were activated. Downstream molecule of Nrf2 also has cytoprotective capacity. In addition, decreased MMP2 and MMP9 expression was also observed after naringenin administration. The finding regarding reactive oxygen species binding and MMP inhibition was also supported by a study by Kapoor *et al*. (2018) [48].

CONCLUSION

Herbal treatment has exhibited the potentials to be a promising alternative treatment to manage endometriosis due to its anti-inflammatory and antioxidant capacity. Herbal treatment is also considered to be much safer compared to the hormonal therapy and surgical intervention because of its fewer side effects. Herbal treatment has been proven to suppress endometriosis through several mechanisms. However, further research is necessary to confirm the potential of herbal treatment in managing endometriosis.

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CONFLICT OF INTEREST

The author states that there is no factor of interest.

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