

R E V I E W

Dietary supplements for treatment of endometriosis: A review

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Abstract. As search for optimal therapy continues for endometriosis, aid of dietary supplements is gaining attention. Supplements can be used for their anti-inflammatory, anti-oxidant, anti-proliferative and immune modulatory characteristics. We reviewed the literature, evaluated and synthesized effects of vitamin D, zinc, magnesium, omega 3, propolis, quercetin, curcumin, N-acetylcysteine, probiotics, resveratrol, alpha lipoic acid, vitamin C, vitamin E, selenium and epigallocatechin-3-gallate. Based on results of in vitro, animal and human studies, it might be safe to say that dietary supplements can be used as a complementary treatment for endometriosis. (www.actabiomedica.it)

Key words: dietary supplements, complementary therapies, endometriosis

Introduction

Pathogenesis of endometriosis involves the interaction of endocrine, immunologic, proinflammatory, and proangiogenic processes, all discussed in detail throughout the literature (1). There are new theories in endometriosis on these issues, the immune cells, adhesion molecules, extracellular matrix metalloproteinase and pro-inflammatory cytokines activate/alter peritoneal microenvironment, creating the conditions for differentiation, adhesion, proliferation and survival of ectopic endometrial cells (2-5). Whether these factors are causal or merely represent a feature of the pathophysiological process measured years after symptom onset remains uncertain. When choosing treatment for endometriosis, it is crucial to consider the patient's predominant symptoms and preferences, age, the side-effect profile of medications, and outcomes of possible surgery; as well as the extent and location of disease, previous treatment, and cost effectivity (6,7).

Pathophysiology of endometriosis is, even today, not yet clarified, and the search for optimal treatment continues. Non-steroidal anti-inflammatory drugs, combined estrogen-progestin therapy, aromatase inhibitors, progestins, and selective progesterone receptor modulators are the main treatment options in current practice.

Elaborate pathogenetic mechanisms of endometriosis challenge clinicians to address each and every one of them when it comes to treatment. While conventional medical and surgical therapies are essential, the aid of dietary supplements may result in a synergistic effect by their anti-inflammatory, anti-oxidant, anti-proliferative, and immune-modulatory characteristics. Current surgical and medical approaches to endometriosis are inefficient for a sizable proportion of women, besides, treatment can be associated with complications and morbidity (8). Although peritoneal superficial lesions and ovarian endometriomas represent the majority of endometriotic implants within the

pelvis, deep infiltrating endometriosis and extrapelvic endometriosis are the most challenging conditions to face off. Despite sometimes medical therapy is enough to reduce symptoms and signs (9,10), in a large number of patients a complete eradication, with nerve-sparing and vascular sparing approach (11,12) is needed to restore the normal pelvic anatomy and its functions. Considering these, while the search for new treatment options continues, the therapeutic benefits of dietary supplements with or without conventional treatment are being investigated. Different types of supplements can be effective in various ways. In this review, we aimed to evaluate the efficacy of supplement use for the treatment of endometriosis, by compiling the most used and studied supplements.

Vitamin D

Vitamin D is a fat-soluble vitamin that is naturally present in fatty fish (salmon, tuna, and mackerel), liver, egg yolk, and cheese (13). Vitamin D in these foods is primarily in the form of vitamin D3 and its metabolite 25(OH)D3.

1,25-dihydroxyvitamin-D3 (vitamin D) has immune-modulating effects on cell differentiation and proliferation in all cell types. Vitamin D deficiency and endometriosis have long been associated with autoimmune diseases (14). Furthermore, vitamin D receptors and vitamin D metabolizing enzymes are found in the ovaries and endometrium of women with and without endometriosis, in addition to the different immune cells and it is likely that vitamin D acts in a local immunologic environment (15). Vitamin D increases anti-inflammatory cytokines (transforming growth factor (TGF)- β , interleukin (IL)-4) and decreases pro-inflammatory cytokines (tumor necrosis factor (TNF)- β IL-2, IL-6), suggesting that vitamin D may help to improve chronic inflammatory and autoimmune diseases (16).

Though the physiological effects of vitamin D indicate probable relevance in endometriosis treatment, literature is scarce. Studies on experimental animal models showed decreasing IL-6 levels in the peritoneal fluid after vitamin D supplementation (17). A double-blind clinical trial by Almassinokiani et al. found no

significant effect of vitamin D supplementation on dysmenorrhea and/or pelvic pain of patients who had surgical treatment for endometriosis (15). Also, retrospective studies of patients with surgically confirmed endometriosis have shown higher dietary intake of vitamin D is correlated with decreased risk (18). A recent meta-analysis about vitamin D status of patients with endometriosis has shown that women with endometriosis had lower vitamin D levels compared to controls, and a negative relationship between vitamin D levels and severity of endometriosis was observed, however, this study was focused on vitamin D status, not the effects of vitamin D supplementation (19).

Zinc

Zinc is an essential mineral that is naturally present in some foods such as oysters, crab, lobster, red meat, poultry, beans, nuts, and dairy products (20). Excessive accumulation, deficiency, or an imbalance of trace metals might interfere with cell functions, cell degeneration, and apoptosis or resulting in abnormal cell proliferation and malignant transformation (21). Antioxidant enzymes usually need various trace metals for catalysis, so the essential trace metals in the human body play a role in both the immune reactions and the protection against oxidative damage (22). Zinc is an intracellular signaling molecule and an anti-inflammatory agent that has an essential role in oxidative stress and immune functions; inhibits free radical production (23). Zinc deficiency may complicate the clinical features in many diseases, affect the immunological status, increase the generation of inflammatory cytokines, and increase oxidative stress.

These properties of zinc might have some remedial effects. There are no in vitro or animal studies in literature, regarding zinc levels or supplementation in endometriosis. Studies conducted in patients with rheumatoid arthritis have shown that low plasma zinc correlates negatively with levels of TNF- α and IL-1 α (24), a result which also has importance when endometriosis pathophysiology kept in mind. Many studies argued this relation, finding lower zinc levels were seen in women with endometriosis (25,26). In addition, a study suggested that zinc levels in the ovarian

follicular fluid of infertile women with endometriosis were lower, compared to tubal infertility (27). The study also indicated that zinc levels in follicular fluid were higher in women with endometriosis who conceived after in vitro fertilization (IVF).

Although there are no studies on supplementation of zinc and its effects on women with endometriosis to our best knowledge, researchers found that dietary intake of zinc in women without endometriosis was higher compared to women with endometriosis (28). There is also no meta-analysis on zinc supplementation in endometriosis.

Magnesium

Magnesium is one of the most abundant electrolytes in the human body and is well known to be implied in several important functions such as protein and deoxyribonucleic acid (DNA) synthesis, enzyme activity, and neuromuscular excitability. Approximately 99% of the total body magnesium is stored intracellular, predominantly in muscles, bones, and soft tissues (29). Food sources of magnesium include nuts, grains, spinach, legumes, avocado, and potatoes (30).

Magnesium has been used in gynecological practice for ages. Magnesium deficiency was seen in premenstrual syndrome (31). Mathias et al. (32) observed that the fallopian tubes of women with endometriosis contract irregularly and more spasmodically. Magnesium also relaxes smooth muscles (33) and as a result, may affect retrograde menstruation, thought to be the major cause of endometriosis. As a result of these findings, a decreased risk of endometriosis with increasing magnesium intake can be discussed, with the strong association being with oral magnesium intake by food (18).

Hosgorler et al, studied changes of vascular endothelial growth factor (VEGF) in uterine tissue based on magnesium supplementation in an animal model, found that VEGF decreases after magnesium use, therefore concluding it might be useful in gynecologic diseases that have angiogenesis in their pathophysiological process, like endometriosis (34). Human studies on complimentary use of magnesium in endometriosis are rare, indicates a subject to address in future studies.

Omega-3

Polyunsaturated fatty acids (PUFAs) are rich in omega-3 fatty acids (FAs). In recent years, antiproliferative, antiangiogenic, anti-inflammatory, anti-apoptotic effects of omega-3 PUFAs have been demonstrated in several studies (35).

An association between decreased circulating inflammatory cytokines and dietary PUFA intake was first reported by Pischon and colleagues in 2003 (36). Arachidonic acid (AA) is an omega-6 polyunsaturated fatty acid (PUFA) that is synthesized from linoleic acid, found in plant-derived oils. It is a substrate used for the synthesis of prostaglandins (PGE2) and leukotrienes (LTB4), which are thought related to pelvic pain in endometriosis. On the other hand, eicosapentaenoic acid (EPA) is an omega-3 PUFA, found in fish oil, also serves as a substrate for PGE3 and LTB5 production. PGE3 and LTB5 have less potent inflammatory activity in comparison with those synthesized from AA. Also, EPA inhibits the conversion of AA to PGE2 and LTB4 (37). As a result, omega-3 PUFAs, such as EPA and docosahexaenoic acid (DHA) might inhibit inflammation (38). The anti-inflammatory effect of omega-3 PUFA has been proven by studies showing improvement after dietary intake, on diseases like atherosclerosis, rheumatoid arthritis, and asthma (39).

PUFAs are probably the most extensively studied supplement on endometriosis pathogenesis, symptoms, and outcomes. An in vitro study by Gazvani et al have shown that survival of endometrial cells from women with and without endometriosis was significantly reduced in the presence of high omega-3:omega-6 PUFA ratios compared with cells incubated in the absence of fatty acids, in balanced omega-3:omega-6 PUFA ratios, and in high omega-6:omega-3 PUFA ratios (40). Animal studies have reported decreased endometriosis-associated pain after omega 3 supplementation (41). Besides symptom relief, PUFAs have a role in preventing disease pathogenesis (42). Also, adding fish oils to the diet of endometriosis models, decreased the size of the lesions caused by endometriosis (43,44).

Human studies vary between food frequency questionnaires and supplementation trials. A cohort of endometriosis patients was given various supplements

including omega 3, and visual analog scale (VAS) scores were improved compared to controls (45). Fish oil supplemented adolescents with endometriosis were reported to have a 50% drop in VAS scores (46). Women with higher circulating levels of EPA are less likely to have endometriosis (47). Reviews have reported similar results, underlining the heterogeneity and generally experimental nature of studies (48,49).

Propolis

Propolis has a long history of use due to its therapeutic characteristics. In experimental medicine, it was used to treat malignant tumors, local wounds, and ulcers. Propolis compounds include terpenes, flavonoids, phenolic acids as well as sugar, protein, vitamins, and abundant minerals. Flavonoids have an extensive range of biological behavior, including anti-inflammatory, anti-oxidant, anti-bacterial, and anti-viral properties (50).

Chrysin is a natural flavonoid mainly found in plant extracts, propolis, and honey. In vitro studies have shown that chrysin stimulates an increase in apoptosis and a decrease in proliferation in human endometriotic cells; to suppress the phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway related to the proliferation of endometriotic cells (51). To our best knowledge, there are no animal or human studies on the effects of propolis in endometriosis.

Curcumin

Curcumin is the principal polyphenol isolated from turmeric. Anti-inflammatory, anti-metastatic, the anti-oxidant, wound healing, hypoglycemic, anti-angiogenic, anti-microbial, antitumor, anti-mutagenic, and hormonal regulatory properties of curcumin were reported by numerous in vitro and vivo studies (52–54).

Curcumin seemed to improve folliculogenesis in endometriosis, reported an in vitro study (55). Moreover, curcumin leads to reduced estrogen production, thus inhibits endometriosis development (56). An in vivo study on mouse models designed a curcumin delivery system to the peritoneum, and showed a reduction

in endometrial glands and stroma, along with the significant decrease of infiltrating inflammatory cells (57). Many animal studies reported decreased endometriotic implant size or delayed development after curcumin supplementation (58–60). Treatment with curcumin reduces inflammation by decreasing the expression of pro-inflammatory cytokines, also inhibits invasion, attachment, and angiogenesis of endometrial lesions (56,61).

Human studies investigating the effect of curcumin supplementation reported downregulation of vascular endothelial growth factor (VEGF) signaling pathway and decreased serum CA 125 and PGE2 levels (45,62). Thus, it may have potential benefits as a dietary supplement and pharmacological agent for prevention and as part of the treatment of endometriosis (63).

Quercetin

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a major dietary flavonol found in vegetables and fruits such as onion, cauliflower, lettuce, apple skin, and chili pepper. Quercetin inhibits proliferation and induces cell cycle arrest in endometriotic cells. Furthermore, it has been shown to induce apoptosis by causing the production of reactive oxygen species, DNA fragmentation, loss of mitochondrial membrane potential, with in vitro and in vivo studies (64). In an animal study, it was also shown that it has anti-estrogenic and progestogenic effects (65). Hence, quercetin may have a potential role as a natural therapy to improve and treat endometriosis.

N-acetylcysteine

N-acetylcysteine (NAC), is the acetylated form of the amino acid cysteine. It is naturally present in some vegetables like onion and garlic and shows a marked antiproliferative action in vitro on cancer cells of epithelial origin—also the origin of endometrial cells (66). In vitro studies showed that NAC action neither involves induction of cell death nor is due to a specific toxic effect; rather, it builds a differentiation pathway, including activation of specific molecular mechanisms

all converge into proliferation switch, eventually causing decreased cell proliferation and a decrease in cell locomotory behavior, especially relevant in endometriosis (67). In addition, NAC downregulates inflammatory protein activity (67).

Animal studies have shown that NAC causes significant decreases in mean lesion areas, in serum and peritoneal TNF- α levels, in levels of inflammatory cyclooxygenase (COX) -2 enzyme; this could be a possible explanation of the observed reduction in dimensions of endometrioma (68,69). Indeed, decreasing COX-2 expression reduces available estrogen in ectopic endometrial tissue through decreased production of PGE₂—a powerful stimulator of aromatase. Considering NAC action on cell signaling and protein activity, overall causing a deranged proliferation, researchers reported reduced endometrioma size on NAC supplemented women and argued it can effectively help the medical treatment of ovarian endometriosis and prevent recurrence (70). Also combined effect of NAC, alpha-lipoic acid, and bromelain significantly decreased pain in endometriotic women (70).

Probiotics

Probiotics, prebiotics, or synbiotics in the diet are favorable for the intestinal microbiota. These may be consumed in the form of dairy products, raw vegetables, and fruits. Another source may be pharmaceutical formulas and functional food (71). One of the major positive effects of probiotics on human health is improved immunity (72). In 2007, the World Health Organisation (WHO) experts described prebiotics as a nonviable food component that is beneficial when consumed, by modulation of the microbiota (73).

Probiotic microorganisms such as *Lactobacillus Plantarum*, *Lactobacillus reuteri*, *Bifidobacterium adolescentis* and *Bifidobacterium pseudocatenulatum* are natural producers of vitamin B (71). Particularly in patients suffering from endometriosis, probiotics are important in this respect, because vitamin B levels are usually lower than the normal population. They also increase the efficiency of the immune system, enhance the absorption of vitamins and minerals, and stimulate the synthesis of organic acids and amino acids.

Probiotic microorganisms may also be able to produce certain types of enzymes, such as esterase, lipase, and co-enzymes A, Q, NAD, and NADP (71).

Prebiotic use is beneficial in patients with endometriosis, especially in patients with advanced-stage endometriosis, because of the common dysbiosis (72).

Resveratrol

Resveratrol has high levels in foods such as grapes, wine, strawberries, Itadori tea, nuts; and is a natural phytoalexin (trans-3,5,40-trihydroxystilbene) synthesized by plants under the influence of ultraviolet radiation and fungal infections (74,75). There are many studies showing that resveratrol has antineoplastic, anti-inflammatory, antioxidant, antiatherogenic, and antiangiogenic effects (75,76). It is known that the presence of a chronic inflammatory process affects the development of endometriosis (77). Many studies have been conducted on the effect of resveratrol on endometriosis disease, which is known to have antioxidant, anti-inflammatory, and antiangiogenic effects in patients with endometriosis.

In an in vitro study by Taguchi et al, resveratrol has been shown to induce apoptosis by increasing TNF- α -related-apoptosis-inducing ligand (TRAIL) in endometriotic stromal cells (78). In a study on animal models, resveratrol has been shown to reduce, matrix metalloproteinase (MMP)-2 and MMP-9 in patients with endometriosis, and in another study, it has been shown to have anti-inflammatory and antiangiogenic activity, in addition to decreasing vascular endothelial growth factor (VEGF) levels in addition to MMP-2 and MMP-9 (79,80). In an experimental endometriosis model made by Cenksoy et al, the antiangiogenic and anti-inflammatory effect of resveratrol was reported by showing decreased serum VEGF and MCP1 levels and VEGF staining in endometriotic implants (81). In another experimental model of endometriosis, resveratrol has been shown to reduce micro vascularization and cell proliferation by reducing CD 31 positive endometrial cells in endometriotic tissue (82). In contrast, a randomized controlled trial has failed to show resveratrol's superiority in women with pain due to endometriosis (83).

Based on its proapoptotic, anti-inflammatory, antioxidant, and antiangiogenic effects, resveratrol may be a complementary treatment to medical therapy in patients with endometriosis.

Alpha Lipoic Acid

Alpha-lipoic acid (α -LA) is a substance naturally found in spinach, broccoli, and tomatoes, and is also synthesized in the human body. It has two isoforms: oxidized lipoic acid and reduced dihydrolipoic acid. β LA is both hydrophilic and lipophilic. When taken orally, it is absorbed from intestinal villi and reduced to dihydrolipoic acid (DHLA) in hepatocytes. It is a high reductant, a powerful antioxidant. In a study based on the anti-inflammatory and antioxidant effect of β LA in an experimental endometriosis model, the oxidant status and oxidative stress index, endometrial implant volumes, and histopathological scores were shown to be lower in the study group compared to the control group (84). Other in vivo studies have shown that regular use of β LA causes a significant improvement in pain symptoms associated with endometriosis such as dyspareunia, dysmenorrhea, and chronic pelvic pain, as well as decreased quality of life and sexual functions (70,85,86).

In addition to medical treatment, the use of β LA may be a suitable option to decrease symptoms and improve the quality of life, especially in patients predominantly presenting with pain.

Vitamin C

Vitamin C is a water-soluble vitamin that is naturally present in citrus fruits, tomatoes, potatoes, red and green peppers, kiwi, broccoli, and strawberries. Humans, unlike most animals, are unable to synthesize vitamin C endogenously, so it is an essential dietary component.

Formulated as two phenolic hydroxyl groups containing 2-3 endiol-L gluconic acid lactone, vitamin C is a powerful reductive and is one of the most important antioxidants in the human body (87). Antioxidants inhibit lipid peroxidation by inhibiting the peroxidation

chain reaction or by deactivating reactive oxygen species (88,89). It has been argued that intravenous vitamin C treatment may facilitate the prevention of endometriotic implant induction and regression of endometriotic implant volumes, and this was explained by anti-inflammatory and antiangiogenic effects of vitamin C. Vitamin C supplementation was also found to significantly reduce the volume and weight of endometriotic cysts in a dose-dependent manner (90). In an experimental model by Erten et al., endometriotic implant volumes of the group receiving vitamin C were observed to be significantly smaller than the control group (91). Another animal study had reported significantly reduced endometriotic cyst volumes in vitamin C supplemented models in a dose-dependent manner (90). While human studies are rare on the effects of vitamin C on endometriosis, a randomized controlled trial showed that vitamin C supplementation increased vitamin C levels in follicular fluid, however, had no effect on oxidative stress markers (92).

Vitamin C supplementation can be considered due to its anti-inflammatory and antiangiogenic effects in addition to medical treatment to prevent the growth of endometriotic implants, especially to patients with high oxidative stress.

Vitamin E

Vitamin E, which is found in plant-based oils, nuts, seeds, fruits, and vegetables, consists of tocopherols and tocotrienols. Cell membranes and plasma lipoproteins contain alpha-tocopherol. After oral intake, vitamin E is absorbed via intestinal villi and transported to the liver by chylomicrons. Alpha tocopherols bind to specific proteins and transferred to the circulation. Alpha-tocopherol (vitamin E) inhibits lipid peroxidation and inhibits oxidative stress (93). In vivo studies reported vitamin E levels were lower in patients with endometriosis (94,95). Patients with endometriosis seem to have higher lipid peroxidase and lower selenium, superoxide dismutase, and vitamin E levels compared to healthy controls (96). Vitamin E and glutathione levels were lower in patients with moderate-to-severe endometriosis compared to patients with minimal to mild endometriosis; therefore

the reduction of the antioxidant system may be one of the underlying mechanisms and correlate with the severity of the disease (97).

Santanam N et al., found a significant reduction in chronic pelvic pain, dysmenorrhea, dyspareunia, and inflammatory markers in peritoneal fluid (IL-6, MCP-1) in patients with endometriosis who received antioxidant therapy with combined vitamin C (98). In another study, after six-month therapy with combined vitamin C and E, malondialdehyde (MDA) and lipid hydroperoxides (LOOHs) levels were found to be significantly lower as an indicator of oxidative stress in plasma and peritoneal fluid (99).

Vitamin E has an antioxidant effect, especially on lipid peroxidation. For patients with severe endometriosis and associated infertility, supplementation might be useful as a complementary treatment. However, it may be more appropriate to use combined vitamin E and vitamin C supplements for pain management.

Selenium

Selenium is an essential trace element with nutritional and pharmacological properties (100). Whole grains and dairy products, some fruits and vegetables, white and red meat, seafood, and eggs are good sources of selenium.

In vitro and in vivo studies show that selenium modulates the functions of many regulatory proteins in signal transduction, conferring benefits in inflammatory diseases (101). Decreased selenium levels have been noted in acute and chronic inflammatory states. In a study conducted on patients with endometriosis, when vitamin E, C, selenium, and zinc were given simultaneously, there was an inverse correlation with the intensity of the disease. With the less oral intake of antioxidant nutrients, the more severe disease was observed. There seems to be a positive association between pathological development and lipoperoxidation status (102).

Epigallocatechin-3-gallate (EGCG)

EGCG is a plant-based compound, especially found in green tea. EGCG was found to suppress

estrogen-related activation, proliferation, and VEGF expression of endometrial cells in vitro (103,104). It also significantly reduced the mean number and the volume of endometriotic implants, inhibited cell proliferation, reduced vascularization, and increased apoptosis (105). Prevention of fibrosis was another finding of in vitro studies (106).

An in vivo study conducted on mice endometriosis models showed that EGCG significantly decreased the growth of endometrial implants, decreased the lesion size and weight, inhibited angiogenesis, and caused lesion apoptosis (107). Another animal study reported EGCG leads to downregulation of VEGF signaling pathway and decreased VEGF expression, thereby inhibiting angiogenesis in endometriotic implants (108). There are no human studies about EGCG effects on endometriosis.

Conclusion

As in many diseases and conditions, the positive effects of dietary supplements have been shown in endometriosis. Certain types of supplements can be given as a complementary treatment for symptoms, and some are beneficial in preventing the disease.

After a careful review of the literature, we can confidently report that lower levels of vitamin D, zinc, and vitamin E, carry a greater risk for endometriosis. Magnesium, curcumin, resveratrol, and EGCG were beneficial in animal studies due to their antiangiogenic effects. Omega 3 and alpha-lipoic acid improved endometriosis-associated pain in human studies. Curcumin, omega 3, NAC, vitamin C, and EGCG supplementation decreased endometriotic lesion size in animal and human studies. Curcumin, omega 3, and NAC were found to prevent disease pathogenesis or recurrence in animal studies. Conducted studies are summarized in Table 1.

It is important to note that studies on this issue often have limitations, such as low sample size and experimental study design. Moreover, one should keep in mind that food resources and pharmacological formulas of supplements may have different mechanisms of actions, also there is not a consensus on dosing and recommendation guidelines. However, as more clinicians

Table 1. Summary of study types on supplement use for endometriosis

Supplement	In vitro study	Animal study	Human study
Vitamin D	+	+	+
Zinc	-	-	+
Magnesium	+	+	-
Omega 3	+	+	+
Propolis	+	-	-
Curcumin	+	+	+
Quercetin	+	+	-
N-acetylcysteine	+	+	+
Probiotics	-	-	+
Resveratrol	+	+	+
Alpha Lipoic Acid	-	+	+
Vitamin C	+	+	+
Vitamin E	+	+	+
Selenium	+	+	+
Epigallocatechin-3-gallate	+	+	-

become aware of the beneficial effects of supplements in dealing with endometriosis, more studies on supplement use concomitant with surgery or medical treatment will follow, and therefore treatment, surveillance, and counseling of patients may improve.

Ethics Approval: Due to the nature of our study, Ethics approval was not required.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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