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# Novel dietary supplement association reduces symptoms in endometriosis patients

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Endometriosis is characterized by disabling symptoms that afflict young women with severe physical discomfort, difficulty in relationship life, and infertility; however, the currently available therapeutic strategies are unsatisfactory. Goal of this research was to identify a new combination of natural active ingredients that, administered as dietary supplements, could have the effect of reducing inflammatory response in endometriosis patients, decreasing the symptoms the disease produces and its harmful effects on affected organs. A cohort of endometriosis patient was treated for 3 months with a composition including quercitin, curcumin, parthenium, nicotinamide, 5-methyltetrahydrofolate, and omega 3/6. Using a VAS scale, we demonstrated a significant reduction of the symptoms in endometriosis patients treated with the dietary composition respect to the controls. Moreover, we demonstrated also a significant reduction in the serum levels of PGE2 and CA-125. Further study are required to compare the effect of this combination of molecules with standard therapies and to evaluate if the use of these dietary supplements in combination with standard therapies may lead to the improvement of the regular medical treatment for endometriosis.

**KEYWORDS**
5-methyltetrahydrofolate, curcumin, nicotinamide, nutraceutical, omega 3/6, quercitin

## 1 | INTRODUCTION

Endometriosis is a chronic estrogen-dependent condition characterized by the occurrence of endometrium-like structure outside the uterine cavity. Endometriosis is an illness afflicting over 150,000,000 women in the Western world, and a chronic disease for which there are currently no medical therapies designed to significantly reduce or eliminate it (Baldi, Campioni, & Signorile, 2008; Signorile, Campioni, Vincenzi, D'Avino, & Baldi, 2009). Pathogenesis of endometriosis is still not completely understood. Actually, retrograde menstruation and coelomic metaplasia are the most acknowledged hypotheses (Benagiano & Brosens, 2006; Bulun, 2009). Recent works from our research group indicate that endometriosis is already present in the foetal life and it is caused by small defects during the development of the female genital system (Crispi et al., 2013; Signorile & Baldi, 2010; Signorile, Baldi, et al., 2009; Signorile, Baldi et al., 2010; Signorile, Spugnini, et al., 2010; Signorile et al., 2012). Evidences in vitro and in vivo suggest that molecular perturbations of the oestrogen pathway during embryogenesis are responsible of these alterations of the fine-tuning of the development of the female genital system (Boccellino et al., 2012; Signorile & Baldi, 2015a).

Endometriosis is characterized by disabling symptoms that afflict young women with severe physical discomfort, difficulty in relationship life, and infertility (Leite Ferreira, Moura Bessa, Drezett, & de Abreu, 2016). These symptoms are due to the inflammatory process determined by the development of the disease most frequently in the

**Abbreviations:** PG, prostaglandin; TNF, tumor necrosis factor; VAS, visual analog scale.

  

pelvis, genital organs, intestine and bladder, as well in their support structures (Gao et al., 2006). These symptoms have a direct impact on the quality of lives of women. Moreover, pain has a cyclic nature and is able to interfere with women's health from a holistic point of view. Finally, the absence of a reliable non-invasive diagnostic test considerably contributes to the long interval between onset of the symptoms and definitive diagnosis of endometriosis (Signorile & Baldi, 2014, 2015b, 2015c, 2016).

It is well known that estrogen reduction favors a lesser activity of the disease with a lower immune response of the host, which results in less acute and chronic inflammation (Liang & Yao, 2016). Moreover, estrogens exert neuro-modulatory effects on endometriosic lesions, favoring the imbalance in sympathetic and sensory innervation, and in stimulating macrophage-nerve interaction. In turn, this abnormal innervation is fundamental in the generation of pain (Liang & Yao, 2016). In fact, endometriosis is now considered an estrogen-dependent neuro-inflammatory disorder. There are numerous factors altered in acute and chronic inflammatory processes. A reduction in these factors diminishes the inflammatory process in endometriosis and, therefore, the accompanying symptoms (acute and chronic pelvic pain, dyspareunia, dysmenorrhea, and infertility). Among the different factors involved in this inflammatory process, there are prostaglandins PGE2, tumor necrosis factor (TNF) alpha, metalloproteinases, VEGF (Sacco, Portelli, Pollacco, Shembri-Wismayer, & Calleja-Agius, 2012).

Endometriosis is treated by a surgical approach, excising peritoneal implants, deep nodules, and ovarian cysts. Although this procedure is able to enhance the fertility potential of the patients, the real benefit on reproductive performance is moderate (Fuldeore et al., 2011). Nevertheless, surgical removal of ectopic lesions still represent the first line of intervention for the treatment of endometriosis even if it is characterized by a significant percentage of recurrences (Porpora et al., 2010). From the clinical point of view, the most widely accepted procedure consists in the administration of medical hormonal therapies, all aimed to reduce the levels of circulating estrogens (Kennedy et al., 2005). Unfortunately, these drugs are often inadequate; moreover, they cannot be given to the patients over long periods, because they can cause severe adverse effects (Soares, Martínez-Varea, Hidalgo-Mora, & Pellicer, 2012). Therefore, new and value-added therapeutic strategies that can efficiently reduce lesions and symptoms for the patients with few side effects and no interference with the patient's fertility are urgently required.

Goal of this research was to identify a new combination of natural active ingredients that could have the effect of reducing inflammatory response in endometriosis patients, decreasing the symptoms the disease produces, and its harmful effects on affected organs. In particular, a number of substances were used at concentrations compatible with those of a dietary supplement.

The composition included an extract of plants of turmeric species, in particular belonging to the curcuma longa species. Curcuma causes a reduction in the amount of estrogen, inhibition of metalloproteinase, accelerates cellular apoptosis, reduces immune mediator TNF alpha, reduces interleukin mediators, inhibits angiogenesis by reducing VEGF (Schaffer, Schaffer, & Bar-Sela, 2015). The composition also included an extract of plants belonging to the species *Tanacetum parthenium*. Parthenium inhibits PGE2, and TNF alpha, stops fibroblast proliferation, has anti-migraine action, and an inflammatory process reduction action (Pareek, Suthar, Rathore, & Bansal, 2011). Furthermore, the composition comprised nicotinamide and 5-methyltetrahydrofolate calcium salt. 5-methyltetyrate calcium salt reduces homocysteine (thromboembolic factor), while Nicotinamide (Vitamin B3) performs an anti-angiogenetic action (Wang & Hartnett, 2017). Finally, the composition of the invention also included quercetin. Quercetin, reduces local estrogen by reducing FSH and LH (animal model studies), and reduces VEGF (Massi et al., 2017). Moreover, it has recently been demonstrated that quercetin decreases the incidence of hyperalgesia in mice with experimental adenomyosis through the reduction of central sensitization and this could be a promising treatment for adenomyosis (Nie & Liu, 2017).

## 2 | MATERIALS AND METHODS

### 2.1 | Dietary supplement composition

The composition of the dietary supplement included the following substances: 1002 mg linoleic acid (omega 3), 432 mg alpha linolenic acid (omega 3), 172.8 mg linoleic acid (omega 6), 200 mg quercetin, 20 mg nicotinamide, 400 mcg 5-methyltetrahydrofolate calcium salt, 20 mg titrated turmeric, 19.5 mg titrated parthenium. Moreover, all three group started a dietetic regimen for the 3 months of the study in order to increase about 20/30% the fibers, and to increase food containing Omega 3. Briefly, in this regimen the patients had a reduction (at least 30%) of milk and derivatives, reduction (at least 50%) of meat, gluten food, caffeine, alcohol, chocolate, saturated fat, butter, and margarine. Finally, the consumption of soy, aloe, and oats for all the observation was forbidden.

### 2.2 | Patient selection

The study participants were recruited by the Centro Italiano Endometriosi under a research project of Italian Endometriosis Foundation. The study was approved by the ethical committee of the Italian Endometriosis Foundation. Written informed consent was obtained from all the subjects before inclusion in the study. Patients with endometriosis were selected using a diagnostic protocol consisting of vaginal and rectal bimanual examination, positive serum CA125, positive pelvic Nuclear Magnetic Resonance Imaging. Nevertheless, the clinical diagnosis of endometriosis was confirmed in all patients by histologic diagnosis at the end of the study following surgery and diagnostic laparoscopy. Moreover, the stage of endometriosis was categorized according to the Revised American Society for Reproductive Medicine classification of endometriosis (Revised American Society for Reproductive Medicine classification of endometriosis, 1997). All the patients enrolled in the study were defined as stage IV, according to this classification.

## 2.3 | Clinical study

Ninety patients with endometriosis were identified, and divided into three groups of 30 patients each. The first group of 30 patients was treated with the above-mentioned composition comprising all the active ingredients. The second group of 30 patients was treated with a composition comprising only linseed oil and 5-methyltetrahydrofolate calcium salt. The third group of 30 patients with endometriosis took placebo for the same duration of the first two groups and thus had the function of control group. All the patients took two doses a day, every 12 hr, for 3 months.

For the effects of the treatment on symptomatology, the intensity of headache, cystitis, muscular pain or fibromyalgia, irritable colon, dysmenorrhea, dyspareunia, chronic pelvic pain, were measured using the visual analog scale (VAS). This is a psychometric response scale which can be used in internet-based questionnaires (Reips & Funke, 2008). The pain VAS is a continuous scale comprised of a horizontal or vertical line 10 cm in length, anchored by two verbal descriptors, one for each symptom extreme ("no pain" with a score of 0 and "pain as bad as it could be" with a score of 100) (Scott & Huskisson, 1979). The VAS was administered as a paper and pencil measure to the patients at the beginning and at the end of the treatment. Based on the distribution of pain VAS scores in endometriosis patients, the two following cut points on the pain VAS have been considered: no pain (0 cm on the line), moderate pain (5 cm on the line), and severe pain (over 10 cm on the line). In Figure 1 the VAS scale adopted in the study is depicted. The patients were divided in two groups: patients with a VAS ≤5 and patient with a VAS >5. All the results have been expressed as median values of all the patients of each group.

The laboratory parameters analyzed in all patients at the beginning and at the end of treatment were as follows: serum dosage of 17 Beta Estradiol, serum dosage of PGE2, serum dosage of CA-125, all at the day 21 of the cycle. The results have been expressed as median values of all the patients of each group.

## 3 | RESULTS

The mean ages of the three different groups of patients, as described in the method section, were respectively 34.0, 34.8, and 35.2 years. In Tables 1 and 2 the results on the variation of several symptoms and serologic data related to endometriosis in the three different groups of patients are depicted. In detail, the cohort of patients treated with the dietary supplements for 3 months, displayed a significant reduction of the symptoms at the end of the treatment: headache from 14% to 4%; cystitis from 12% to 2%; muscle aches from 4% to 1%; irritable colon from 15% to 6%; dysmenorrhea from 62% to 18%; dyspareunia from 30% to 15%; chronic pelvic pain from 62% to 18%. Concerning the laboratory parameters, a significant reduction in the absolute values was also observed: serum dosage of PGE2 from 3404 ± 346 ng/L to 1377 ± 326 ng/L; serum dosage of CA 125 from 61.4 U/ml to 38 U/ml. The serum dosage of 17 Beta Estradiol on day 21 of the cycle declined from 184 pg/ml to 171 pg/ml. Interestingly the control group did not display significant reduction in any of the parameters analyzed, while the group of patients treated with a composition comprising only linseed oil and 5-methyltetrahydrofolate calcium salt displayed a consistent reduction of PGE2 levels, but not enough to have effects on the symptoms of the patients.

**TABLE 1** Analysis of variations in symptoms after the treatment with dietary supplements in the three different groups of endometriosis patients

| Before treatment/after treatment | (%)/(%) |
|---|---|
| Group 1 | |
| Headache | 14/4 |
| Cystitis | 12/2 |
| Muscular pain | 4/1 |
| Irritable colon | 15/6 |
| Dismenorrhoea | 62/18 |
| Dispareunia | 30/15 |
| Chronic pelvic pain | 62/18 |
| Group 2 | |
| Headache | 15/12 |
| Cystitis | 11/8 |
| Muscular pain | 4/4 |
| Irritable colon | 14/12 |
| Dismenorrhoea | 65/41 |
| Dispareunia | 32/37 |
| Chronic pelvic pain | 60/45 |
| Group 3 | |
| Headache | 14/13 |
| Cystitis | 10/12 |
| Muscular pain | 3/4 |
| Irritable colon | 12/15 |
| Dismenorrhoea | 66/62 |
| Dispareunia | 30/30 |
| Chronic pelvic pain | 62/60 |

Intensity of symptoms were evaluated with the VAS scale and the data presented as percentage of patients with high VAS score (see method section).

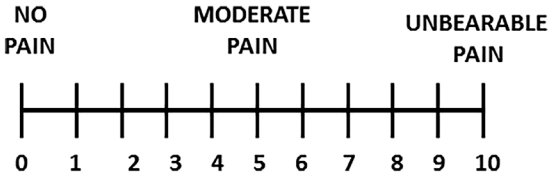


**FIGURE 1** Zero to ten VAS numeric pain distress scale

## 4 | DISCUSSION

Most recent guidelines for the treatment of endometriosis-associated symptoms show the surgical removal of endometriosis lesions as an

**TABLE 2** Analysis of variations in serologic parameters after the treatment with dietary supplements in the three different groups of endometriosis patients

| Before treatment versus after treatment | | |
|---|---|---|
| **17 Beta estradiol** | **PGE2** | **CA-125** |
| Group 1 | | |
| 184 pg/ml versus 171 pg/ml | 3404 ± 346 ng/L versus 1377 ± 326 ng/L | 61.4 U/ml versus 38 U/ml |
| Group 2 | | |
| 176 pg/ml versus 168 pg/ml | 3305 ± 396 ng/L versus 2605 ± 396 ng/l | 61.8 U/ml versus 61.4 U/ml |
| Group 3 | | |
| 164 pg/ml versus 154 pg/ml | 3481 ± 462 ng/L versus 3469 ± 451 ng/L | 61.4 U/ml versus 62 U/ml |

efficacious treatment for decreasing endometriosis-associated pain, especially for those in whom medical therapy was unsuccessful (Dunselman et al., 2014). Medical treatments for endometriosis have as final effect the induction of endometrial differentiation with progestins and/or the reduction of the production of endogenous estrogens. First-line agents for the treatment of pain associated with endometriosis are oral contraceptive drugs and/or non-steroidal anti-inflammatory drugs, because these agents display few side effects and are not very expensive. Only in patients where these drugs have failed to provide a satisfactory degree of relief, it is possible to administrate second-line agents, such as GnRH agonists, danazol or progestational agents, and recently, aromatase inhibitors. These agents represent standard therapies for endometriosis but are associated with long-term side effects (Gao et al., 2006). Nevertheless, it must be underlined the fact that all these currently available medical therapies, even if are effective for pain relief, are not curative per se. Thus, there is an urgent need for new treatments with higher efficacy and fewer side effects. Several different molecules have been tested in in vitro and in vivo models of endometriosis due to their capacity of affecting chief pathophysiologic pathways of the disease, such as cell proliferation, migration, adhesion and invasion, angiogenesis and inflammatory response. Unfortunately, most of these drugs were efficacious in preclinical models, but did not reach the clinical setting, because of the high risk of adverse effects (Soares et al., 2012).

An alternative approach for treatment of symptoms of endometriosis could be the use of compounds as dietary supplements able to interfere with the key pathophysiologic events responsible for pain (Onalan, Gulumser, Mulayim, Dagdeviren, & Zeyneloglu, 2014). Indeed, a connection between dietary factors and endometriosis has become a topic of interest, especially considering the fact that physiological and pathological processes of the disease can be influenced by diet. Several article have been published reviewing this topic, but the results are still equivocal (Parazzini, Viganò, Candiani, & Fedele, 2013; Pattanittum et al., 2016). In this study, the administration of a specific group of compounds as dietary supplements, was indeed able in a cohort of endometriosis patients to significantly reduce the symptoms associated with the disease. The variations in the intensity of pain was measured in the patients by the VAS scale. The VAS is widely used due to its simplicity and adaptability to a broad range of populations and settings. Indeed, VAS is actually considered the most reliable pain scale for quantification of endometriosis-related pain and skin graft donor site-related pain (Bourdel et al., 2014). Analysis of the data produced, clearly proved a significant effect in reduction of the pain in the patients treated with these dietary supplements respect to the other two groups of endometriosis patients.

Concerning the serum data, it was registered a significant decrease of the PGE2. These data clearly indicate an anti-inflammatory action of the compounds, that, in this way, mimic the pharmacological action of the most common used drugs for the therapy of endometriosis. Concerning the serum level of Beta Estradiol, the reduction displayed in the treated patients was not significant when contrasted with the levels found in the other two groups of control. Even more interesting, the serologic data indicate that this symptomatic activity in reducing pain was, at least in part, due to the ability of these compounds to decrease the size of the endometriosis foci, as suggested by the reduction in the value of CA125 serum levels in the treated patients at the end of the protocol. It must be underlined the fact that the beneficial effects were obtained at relatively low doses of the individual components, remaining in the specifications of the dietary supplements tables. The lack of effects on the symptoms in the group treated only with linseed oil and 5-methyltetrahydrofolate calcium salt and in the control group treated with a placebo, confirms the specificity of the data and the synergic activity of all compounds, when administered together. It must be underlined, however, that the composition of linseed oil and 5-methyltetrahydrofolate calcium salt was still able to decrease PGE2 levels at the end of the treatment, but without having significant effects on the symptoms of these patients.

Based on the data from the literature, we can hypothesize that in our patients, the decrease in PGE2 causes a reduction of aromatase activity (Karck, Reister, Schafer, Zahradnik, & Breckwoldt, 1996; Noble et al., 1997). This enzyme is one of the most important molecular effectors in endometriosis cells responsible of the growth of the endometriosis lesions and of the establishment of an inflammatory condition through a positive feedback cycle between PGE2, COX-2, aromatase, and 17 Beta Estradiol (Bulun et al., 1999). Indeed, it has been demonstrated that the inflammatory process in endometriotic tissues giving rise to increased production of cytokines (e.g., IL-1β, tumor necrosis factor α) by monocytes and macrophages stimulate PGE2 production in this tissue. Therefore, the ability of this

combination of dietary supplements to decrease PGE2 levels could justify the clinical effects seen in the patients at the end of the treatment. Nevertheless, it must be also considered the recent observation that treatment with quercetin improves the generalized hyperalgesia in an animal model of adenomyosis (Nie & Liu, 2017).

It would be interesting in a further study to compare the effect of this combination of molecules with standard therapies and to evaluate if the use of these dietary supplements in combination with standard therapies may lead to the improvement of the regular medical treatment for endometriosis.

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