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# The Use of Green Tea in the Treatment of Symptomatic Uterine Fibroids

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**Abstract**---Background: Green tea is a natural product, commonly used by women for multiple purposes. Epigallocatechin gallate (EGCG), the major catechin in green tea, exhibits several useful biological effects, including anti-inflammatory, antiproliferative, and antioxidant effects. A study conducted by the US Department of Agriculture reported that green tea has potent anticancer effects against a wide range of human cancer cells. Green tea's polyphenols are considered responsible for these positive effects, and most notably EGCG has been shown to inhibit key pathways of tumor growth. Objective: Aim of the work was to study the effects of epigallocatechin gallate (EGCG), an extract of green tea on human leiomyoma and quality of life in women with symptomatic uterine fibroids. Patients and methods: A Prospective, sealed envelopes, randomized control trial was conducted including 75 reproductive-age women with symptomatic uterine fibroids (UF) were recruited for this study. All subjects had at least one fibroid lesion  $\geq 2 \text{ cm}^3$ , as confirmed by transvaginal ultrasonography. The subjects had been randomized by SNOSE (Sequentially Numbered Opaque Sealed Envelopes); to oral daily treatment with either 900 mg of green tea extract or only symptomatic treatment for 4 months. The duration of study was about 3 years. Results: There was statistically significant difference ( $P < 0.001$ ) in the mean UFV after three month treatment between groups (Study group =  $178.6 \pm 21.9 \text{ cm}^3$  vs. symptomatic treatment group =

195.9 ± 23.5 cm<sup>3</sup>). Also, there was statistically significant difference ( $p < 0.001$ ) in the mean UFV after four month treatment between groups (Study group = 157.3 ± 26.2 cm<sup>3</sup> vs. symptomatic treatment group = 203.9 ± 23.1 cm<sup>3</sup>). There was statistically insignificant difference ( $p = 0.830$ ) in the mean SS after four months of treatment between groups (Study group = 47% ± 7% vs. symptomatic treatment group = 46% ± 5%). Conclusions: Green tea extract (EGCG) has a significant positive effect on the reduction of UF burden, and shrinkage in total fibroid volume. Thus, green tea extract could possibly be an effective oral treatment for UF.

**Keywords**---Green Tea, Symptomatic Uterine Fibroids.

## Introduction

Tea is one of the most popular beverages consumed worldwide. Based on the manufacturing process, green, black and oolong tea are the three major commercial types of tea. Green tea, without fermentation, is processed to prevent the oxidation of green leaf polyphenols, while majority of polyphenols are oxidized in black tea or oolong tea during fermentation production [1]. Green tea is a natural product, commonly used by women for multiple purposes. Epigallocatechin gallate (EGCG), the major catechin in green tea, exhibits several useful biological effects, including anti-inflammatory, antiproliferative, and antioxidant effects [2].

Fermentation of green tea converts catechin to theaflavins and thearubigins, consequently decreasing the catechin content. The polyphenols present in green tea are flavonols, commonly known as catechins, which contains 5 major subtypes: catechin, epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate (EGCG) [3]. These natural compounds show diverse chemical and biological activities and are nontoxic under daily dose [4]. In recent years, the evidences from epidemiological and animal studies have emerged, showing chemopreventive and anticancer potential of dietary polyphenols [5].

Several studies have suggested positive correlations between human consumption of green tea and a lower incidence of gastric, esophageal, ovarian, pancreatic, and colorectal cancers [6]. EGCG, the major polyphenol in green tea, was found in animal studies to effectively and broadly inhibit carcinogenesis in various organs such as esophagus, stomach, duodenum [7].

Uterine leiomyoma (fibroids) are the most common tumors of the reproductive tract in women of reproductive age [8]. Wide ranges were reported in both uterine fibroid (UF) incidence and prevalence depending on study populations and diagnostic methods, black race as a risk factor increases UF incidence by two to three folds [9].

Although, uterine fibroids (UF) are benign tumors and often asymptomatic, they may cause debilitating symptoms: such as abnormal uterine bleeding, abdominal pain and in some cases infertility. Pregnancy complications attributed to uterine

fibroids include miscarriage, preterm labor and postpartum hemorrhage. Approaches available for the treatment of uterine fibroids include pharmacologic option, surgical approaches, and uterine artery embolization [10]. We have recently reported on the utility of gene therapy approach as a potential alternative treatment for uterine leiomyoma [11]. However, approaches that are minimally invasive, easy to perform, preserve fertility would be preferable and cost effective. A dietary agent, such as green tea, if proven effective against uterine fibroids, would be a welcome addition since it is safe, inexpensive, well tolerated and readily available [12].

A uterine fibroid is seen typically on ultrasound as a well-defined round lesion within the myometrium or attached to it, often showing shadows at the edge of the lesion and/or internal fan-shaped shadowing. The echogenicity varies and some hyperechogenicity may be present internally. On color- or power-Doppler imaging, circumferential flow around the lesion is often visible. However, some fibroids do not exhibit such typical features. We suggest that such fibroids are labeled as sonographically atypical fibroids [13].

The MUSA (Morphological Uterus Sonographic Assessment) statement is a consensus statement on terms, definitions and measurements that may be used to describe and report the sonographic features of the myometrium using gray-scale sonography, color/power Doppler and three-dimensional ultrasound imaging. The terms and definitions described may form the basis for prospective studies to predict the risk of different myometrial pathologies, based on their ultrasound appearance, and thus should be relevant for the clinician in daily practice and for clinical research. The sonographic features and use of terminology for describing the most common myometrial lesions; fibroid [14]. Aim of the work was to study the effects of epigallocatechin gallate (EGCG), an extract of green tea on human leiomyoma and quality of life in women with symptomatic uterine fibroids.

### **Patients and Methods**

The current study was non-blinded randomized clinical trial (RCT), conducted including 75 reproductive-age women attended the Obstetrics and Gynecology outpatient clinic, Aswan University Hospital, complained from uterine fibroid-related symptoms were considered for enrollment. In the period from September 2015 to September 2018. Eligible women were selected from the outpatient clinic.

### **Inclusion criteria:**

1. Age of women from 18 to 50 years old, willing and able to give informed consent.
2. Premenopausal with follicle-stimulating hormone (FSH) level less than 10 mIU/L.
3. Have at least moderate uterine fibroid-related symptoms (score of 24 or higher according to UFS-QOL questionnaire).
4. All types of myomas with total uterine volume of  $>160 \text{ cm}^3$  by vaginal and/or abdominal ultrasound and at least one UF that was  $\geq 2 \text{ cm}^3$ .

5. Agreed to use non-hormonal methods of contraception during the course of the trial.

**Exclusion criteria:**

1. Pregnancy.
2. Breastfeeding.
3. Had major medical morbidity or anemia with hemoglobin level less than 8.0 mg/dL, elevated liver enzymes more than 1.5 times the upper limit of normal.
4. Reported current or recent (within the past 3 months) use of the following medications: oral or systemic corticosteroids, hormones (estrogen, progestin, and oral contraceptives), herbal or botanical supplements with possible hormonal or EGCG effects, use of GnRH analogues or Depo-Provera within the past 6 months.
5. Presence of adnexal masses or tenderness indicating the need for further evaluation or surgery.
6. Mental health disorder.

**Consent:** Eligible women were counseled and offered to join the study after obtaining a written informed consent and completed discussion with woman and explanation of the study purpose, interventions, outcomes, and adverse events.

**The study includes two treatment groups: Group I** “green tea extract” they received green tea tablets, and **Group II** “symptomatic treatment” they received diosmin tablets and/or oral nonsteroidal anti-inflammatory (ibuprofen tablets).

**Screening and base line assessment:**

Patients enrollment were done in obstetrics and gynecology outpatient clinic, Aswan University Hospital. Baseline assessment included history-taking, examination, review of the prior investigations; hormonal profile, Hemoglobin level, transabdominal and Transvaginal-US reports. Followed by counseling of the eligible patients to obtain consent, filling UFS-QOL questionnaire which is a disease specific questionnaire that assesses symptoms severity and health related quality of life (HRQL) in patients with uterine fibroids.

**Randomization:**

At the start randomization was done with the use of sequentially numbered opaque envelopes that had been prepared based on a computer-generated list. They were randomized into Group I (green tea extract) and Group II (symptomatic treatment). Through the study period, 110 women were examined. 35 were excluded (not meeting inclusion criteria (n=8) presence of exclusion criteria (n=12)- refused to participate (n=15)). 75 women were randomized, 35 women Allocated to Group I who received green tea extract, 40 women Allocated to Group II who received symptomatic treatment. 15 women lost to follow up through the study period.

**Sonographic examination:**

Before sonographic examination, women were asked to empty the bladder and to lie supine. Sonographic examinations were performed using GE Veloson S8 (General Electric Co) trans abdominal route probe using average frequency 4 MHz, trans-vaginal route, probe using an average frequency of 7 MHz.

Evaluation of the uterus using ultrasound measuring uterine volume, number of fibroids > 2cm in diameter and calculating the total fibroids volume, using the color Doppler to measure the uterine artery resistant index (RI) and calculating the mean of 3 readings. All women in both groups were appointed a sonographic examination post menstruation. And followed up by repeated sonographic examination once every month for the next four months.

**Blinding:**

Blinding of the study methods was not possible, as the tablets color, size and regimen in the two groups was different. None of the enrolling participants, ultrasound personnel and clinicians were blinded to the type of protocol used.

**Interventions:**

**The women participants were randomly assigned to the two arms of this 4 months study:**

**Group I “green tea extract”**

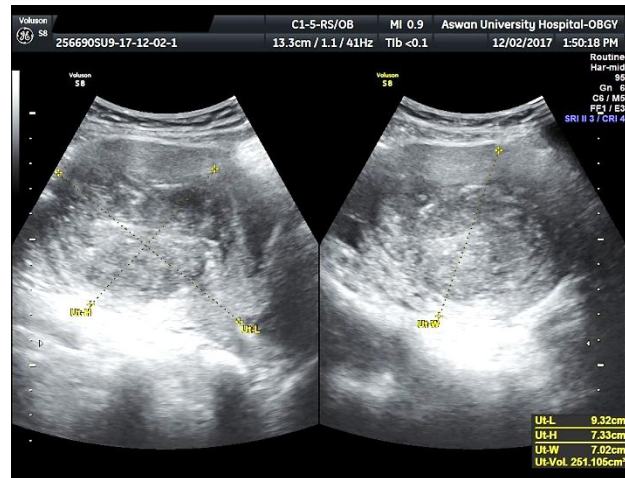
Daily dosage of three tablets of green tea extract of Mepaco Green Tea film coated tablets produced by Arab Company for Pharmaceuticals & Medical Plants MEPACO – MEDIFOOD (this company did not fund the study) (3×300 mg/day) TID for 4 months, tablets were taken after meals to avoid possible irritation to stomach mucosa.

**Group II “symptomatic treatment”**

Follow up for 4 months with symptomatic treatment in the form of diosmin 500 mg tablets of Daflon®500 manufactured by SERVIER Egypt Industries Limited twice or 3 times daily in cases of abnormal uterine bleeding according to severity and/or ibuprofen 400 mg tablets Brufen®400 manufactured by Kahira Pharmaceutical & Chemical Industries Company once or twice a day–after meals–in case of lower abdominal or pelvic pain.

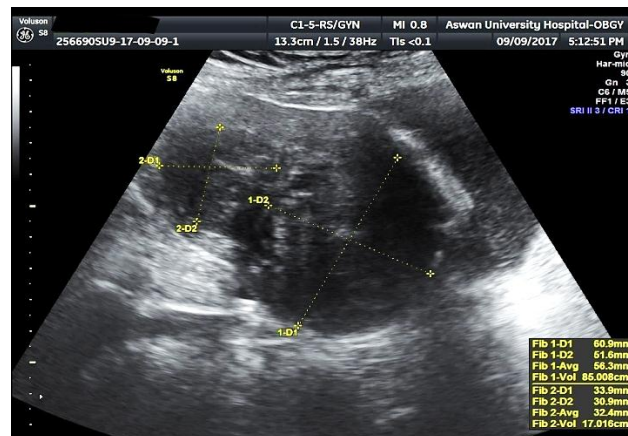
**At baseline visit (visit No 1);** procedures consisted of a brief history and physical examination, including biometric measurement, also assessed UFS-QOL which has two scales: the first assesses symptoms severity (SS) , with a scale range from 8 to 40, where high values were indicative of greater symptom severity, The second scale is the health related quality of life (HRQL) questionnaire, which measures perceived impact of leiomyoma on activities of daily living, general concern and worry, energy, mood, sense of self-control, self-consciousness, and sexual functioning of the participants. The scale for this second questionnaire ranges from 29 to 145; the higher the scores, the better the quality of life. Using

U/S software formula to calculate uterine volume by measuring the uterus in three planes (Figure 1).



**Figure (1):** Uterine volume measurement

All visible UF were identified, numbered, we calculated the volume for each fibroid using the ultrasound device software formula by measuring length, width, and height (Figure 2), then the results summed (total uterine fibroids volume UFV).



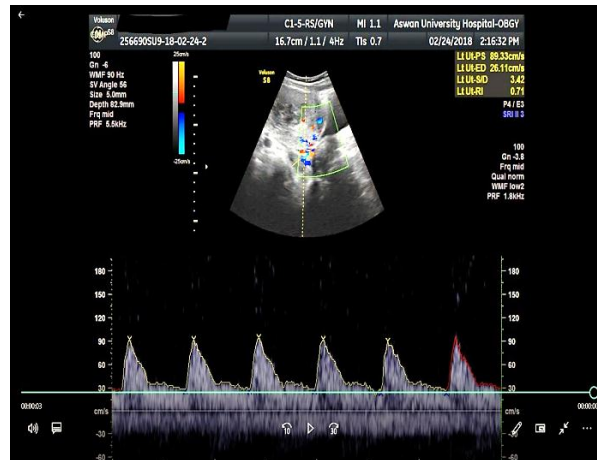
**Figure (2):** Fibroids volume measurement

Uterine vascularization was analysed using uterine artery color Doppler waveform study using the resistive index (RI) as a measuring parameter. To minimize intra-observer variation, the uterine artery Doppler signal was always obtained from near its origin from the internal iliac artery. Scanning was performed with a trans-abdominal and/or trans-vaginal probe of GE Veloson S8 (General Electric Co) Ultrasound System by the same sonographer. Calculated the mean of 3 uterine artery RI readings (Figure 3).

**At follow up monthly visits (visit No 2,3,4 and 5);** the same uterine measurement, calculate total volume and identified , numbered and calculated all

visible UFs was done also assessed Each of these questionnaires monthly. Monthly monitoring included hemoglobin levels, liver- and kidney-function tests, and pregnancy testing. In the last visit the mean changes in fibroid-specific health-related quality of life (UFS-QOL) was measured.

Protocol adherence was determined from monthly logs and counts of returned tablets. To follow up on possible adverse events, a monthly data safety-monitoring meetings were held to review the lab results and monitor the study participants' compliance and adverse effects.



**Figure (3):** Uterine artery resistance index measurement.

### **Outcome:**

**The primary outcome measures:** Uterine leiomyoma volume, which was assessed by transvaginal and/or transabdominal ultrasonography. Symptoms severity and quality of life in women with symptomatic UF assessed by filling the questionnaire of UFS-QOL.

**The secondary outcome measures:** Hemoglobin levels assessed by monthly complete blood count throughout the study period. Body mass index by measuring height and follow up body weight during the study period

### **Data collection:**

A sheet was designed for data collection. In Brief, it included the patient study number, personal, medical, menstrual and obstetric history, BMI, FSH, Hemoglobin (Hb) level, calculated score of UFS-QOL and Also, it included a description of the abdominal and/or transvaginal ultrasound report measuring the volume of uterus and fibroids. UF will be followed monthly till the end of the study by abdominal and/or transvaginal ultrasonography to measure the fibroids volume also the changes in the Doppler of uterine artery RI. Four Months follow up data included Hb level, ultrasound findings and the fibroid-specific symptom severity and HRQL of these UF patients will be scored at each monthly visit, using the symptom severity and quality-of-life questionnaires.

### Sample size calculation:

Sample size calculation was carried out using G\*Power 3 software [15]. A calculated minimum sample of 60 women with uterine fibroid-related symptoms were needed and randomly assigned into one of two groups (**Group I: Study group** (n=30): Green tea extract tablets were used for treatment, and **group II: symptomatic treatment group** (n=30): Diosmin tablets and/or oral nonsteroidal anti-inflammatory (Ibuprofen) were used for treatment to detect an effect size of 0.3 [2]. In the mean uterine leiomyoma volume/ml as an indicator of improvement with an error probability of 0.05 and 80% power on a two-tailed test.

### Ethical considerations:

**Confidentiality:** The confidentiality of all patients admitted to the study was protected. The study participants were not be identified by name in any report or publication resulting from data collected in the study.

**Research statement:** Ethical aspects whether substantial or procedural was implicated in this study. The participant must agree that she understood the investigational nature of this study and keep her rights to terminate participation in the study at any time. Women refusal for participation in the study were not affect by any means the quality of care she was received in our service. This study was approved by the Institutional Research Board (IRB) committee of the Aswan Medical Faculty (IRB No. 28/11/15).

### Statistical analysis:

Data was collected, verified and processed by the principle researcher. IBM-SPSS version 25 used for analysis. Data was expressed as mean, standard deviation, median and range for numerical data. The qualitative variables were expressed as frequencies and percentage. Chi-square/Fisher's exact test and Odds ratio (OR) with a confidence interval (CI) of 95% were used for comparison of frequencies. Normality of numerical data was tested by Shapiro-Wilk test. For continuous variables, one way ANOVA was carried out to compare the means of normally distributed data. For continuous variables with more than two categories on repeated measures; two-way repeated measure ANOVA (RM-ANOVA) test was calculated to test the mean differences of the data that follow normal distribution and had repeated measures (between groups, within groups and overall difference. Significance was considered when it is < 0.05).

### Results

**Table (1):** Baseline characteristics of the studied sample

Variable	Category	n = 60
Age in years	Mean ± SD	38.23 ± 4.2
	Range	29 – 47
BMI	Mean ± SD	30.17 ± 3.1
	Range	25 – 35
Gravidity	0	7 (11.7%)



	<b>1</b>	17 (28.3%)
	<b>≥ 2</b>	36 (60%)
<b>Parity</b>	<b>0</b>	19 (31.7%)
	<b>1</b>	19 (31.7%)
	<b>2</b>	22 (36.6%)
<b>FSH (IU/L)</b>	<b>Mean ± SD</b>	6.82 ± 1.7
	<b>Median (Range)</b>	6.7 (2 – 9.9)

**Table (1)** showed the baseline characteristics of the studied cohort. Regarding age, mean patients' age was  $38.2 \pm 4.2$  years with a range of (29 - 47). Moreover, the BMI of the respondent ranged between 25 and 35 with a mean of  $30.2 \pm 3.1$ . Furthermore, distribution of the studied sample according to parity was as follows; 31.7% was nulliparous, 31.7% had one child and 36.6% had two, the median parity number was 1 (0-2). For the level of FSH, the mean level was  $6.8 \pm 1.7$  IU/L with a median of 6.7 and a range of 2-9.9 IU/L.

**Table (2):** Relationship between baseline socio-demographics and treatment group

<b>Variable</b>	<b>Group I (n = 30) (Mean ± SD)</b>	<b>Group II (n = 30) (Mean ± SD)</b>	<b>P-value</b>
<b>Age/year</b>	38.07 ± 4.2	38.40 ± 4.3	= 0.762
<b>Parity</b>	0.97 ± 0.2	0.88 ± 0.1	= 0.308
<b>Gravidity</b>	1.72 ± 0.2	1.73 ± 0.1	= 0.981
<b>BMI</b>	30.37 ± 2.9	30.17 ± 3.3	= 0.809
<b>FSH</b>	6.84 ± 1.5	6.79 ± 1.6	= 0.905

**Student t-test was used to compare the mean difference between groups**

**Table (2)** showed the differences in the baseline characteristics of the two studied groups. Regarding age, symptomatic treatment group patients were insignificantly older ( $38.4 \pm 4.3$  years) compared with group I ( $38.1 \pm 4.2$  years). The difference in the mean ages was statistically insignificant ( $p = 0.762$ ). Likewise, group II patients had insignificantly less parity number ( $0.88 \pm 0.1$ ) compared with group I ( $0.97 \pm 0.2$ ) ( $p = 0.308$ ). Also, group II patients had insignificantly higher mean gravidity number ( $1.73 \pm 0.1$ ) compared with group I ( $1.72 \pm 0.2$ ) ( $p = 0.981$ ). Additionally, the green tea group patients had insignificantly higher mean BMI ( $30.4 \pm 2.9$ ) compared with the symptomatic treatment group ( $30.2 \pm 3.3$ ) ( $p = 0.809$ ). Also, group II patients had insignificantly lower mean FSH level ( $6.79 \pm 1.6$  IU/L) compared with group I ( $6.84 \pm 1.5$  IU/L) ( $p = 0.905$ ).

**Table (3):** Comparison of uterine fibroid symptom severity score between groups over time

Variable	Group I (n=30) (Mean ± SD)	Group II (n=30) (Mean ± SD)	P-value*
Baseline	81% ± 16%	80% ± 18%	= 0.815
4-months	47% ± 7%	46% ± 5%	= 0.830
P-value*	< 0.001	< 0.001	P = 0.714**

\*Mean differences between Group Comparison and Mean differences within Group Comparison

\*\*Two-way Repeated Measure ANOVA was used to compare the mean differences over time

**Table (3)** treated the effect of different treatment Modalities on the uterine fibroids symptom severity score (SS). Initially, the two groups were matched ( $p = 0.815$ ) for the mean SS before treatment (Study group =  $81\% \pm 16\%$  vs. symptomatic treatment group =  $80\% \pm 18\%$ ). Likely, there was statistically insignificant difference ( $p = 0.830$ ) in the mean SS after four months of treatment between groups (Study group =  $47\% \pm 7\%$  vs. symptomatic treatment group =  $46\% \pm 5\%$ ). For repeated measures in each group, there was significant decrease in the mean SS score in the two groups ( $p < 0.001$ ). For the interaction between group and time, green tea group had non-significantly ( $p = 0.714$ ) reduction in the mean SS ( $81\%$  vs.  $47\%$ ) compared with the symptomatic treatment group ( $80\%$  vs.  $46\%$ ).

**Table (4):** Comparison of health related quality of life score between groups over time

Variable	Group I (n=30) (Mean ± SD)	Group II (n=30) (Mean ± SD)	P-value*
Baseline	20% ± 3%	22.5% ± 3%	= 0.561
4-months	44% ± 4%	50% ± 4%	= 0.321
P-value*	< 0.001	< 0.001	P = 0.933**

\*Mean differences between Group Comparison and Mean differences within Group Comparison

\*\*Two-way Repeated Measure ANOVA was used to compare the mean differences over time

**Table (4)** demonstrated the effect of different treatment Modalities on the health related quality of life score (HRQL). Initially, the two groups were matched ( $P = 0.561$ ) for the mean HRQL before treatment (Study group =  $20\% \pm 3\%$  vs. symptomatic treatment group =  $22.5\% \pm 3\%$ ). likely, there was statistically insignificant difference ( $P = 0.321$ ) in the mean HRQL after four months of treatment between groups (Study group =  $44\% \pm 4\%$  vs. symptomatic treatment group =  $50\% \pm 4\%$ ). For repeated measures in each group, there was significant increase in the mean HRQL in the two groups ( $P < 0.001$ ). For the interaction between group and time, green tea group had non-significantly ( $P = 0.933$ ) increase in the mean HRQL ( $20\%$  vs.  $44\%$ ) compared with the symptomatic treatment group ( $22.5\%$  vs.  $50\%$ ).

**Table (5):** Comparison of uterine fibroids volume between groups over time

Variable	Group I (n=30) (Mean ± SD) cm <sup>3</sup>	Group II (n=30) (Mean ± SD)cm <sup>3</sup>	P-value*
Baseline	210.16 ± 23.7	199.58 ± 23.6	= 0.104
1-months	201.05 ± 27.1	215.20 ± 32.1	= 0.070
2-months	197.40 ± 26.6	190.36 ± 24.1	= 0.287
3-months	178.62 ± 21.9	195.98 ± 23.5	= <b>0.005</b>
4-months	157.34 ± 26.2	203.88 ± 23.1	< <b>0.001</b>
P-value*	< <b>0.001</b>	= 0.127	<b>P &lt; 0.001**</b>

\*Mean differences between group comparison and mean differences within group comparison

\*\*Two-way repeated measure ANOVA was used to compare the mean differences over time

**Table (5)** depicted the effect of different treatment Modalities on the uterine fibroids volume (UFV). Initially, the two groups were matched ( $P = 0.104$ ) for the mean UFV before treatment (Study group =  $210.2 \pm 23.7$  cm<sup>3</sup> vs. symptomatic treatment group =  $199.6 \pm 23.6$  cm<sup>3</sup>). Unlike, there was statistically significant difference ( $P = 0.005$ ) in the mean UFV after three month treatment between groups (Study group =  $178.6 \pm 21.9$  cm<sup>3</sup> vs. symptomatic treatment group =  $195.9 \pm 23.5$  cm<sup>3</sup>). Also, there was statistically significant difference ( $P < 0.001$ ) in the mean UFV after four months treatment between groups (Study group =  $157.3 \pm 26.2$  cm<sup>3</sup> vs. symptomatic treatment group =  $203.9 \pm 23.1$  cm<sup>3</sup>). For measures at 1 and 2 months there was non-significant difference in the mean UFV in the two groups ( $P > 0.05$ ). For repeated measures in each group, although there was significant decrease in the mean UFV in the study groups ( $P < 0.001$ ), non-significant change was observed for the symptomatic treatment group ( $P = 0.127$ ). For the interaction between group and time, green tea group had significantly ( $P < 0.001$ ) higher reduction in the mean UFV ( $210.2$  vs  $157$  cm<sup>3</sup>) compared with the symptomatic treatment group ( $199.6$  vs.  $203$  cm<sup>3</sup>).

**Table (6):** Comparison of mean uterine artery resistance index between groups over time

	Group I (n=30) (Mean ± SD)	Group II (n=30) (Mean ± SD)	P-value*
Baseline	0.757 ± 0.1	0.749 ± 0.1	= 0.581
1-months	0.756 ± 0.1	0.748 ± 0.1	= 0.647
2-months	0.756 ± 0.1	0.748 ± 0.1	= 0.636
3-months	0.756 ± 0.1	0.747 ± 0.1	= 0.581
4-months	0.752 ± 0.1	0.737 ± 0.1	= 0.479
P-value*	= 0.589	= 0.391	P = 0.322**

\*Mean differences between group comparison and mean differences within group comparison

\*\*Two-way repeated measure ANOVA was used to compare the mean differences over time

**Table (6)** illustrated the effect of different treatment Modalities on the uterine artery resistant index (UA-RI). Initially, the two groups were matched ( $P = 0.581$ ) for the mean UA-RI before treatment (Study group =  $0.76 \pm 0.1$  vs. symptomatic treatment group =  $0.75 \pm 0.1$ ). Also, there was non-statistically significant difference ( $P = 0.479$ ) in the mean UA-RI after four months of treatment (Study group =  $0.75 \pm 0.1$  vs. symptomatic treatment group =  $0.74 \pm 0.1$ ). For measures at 1, 2 and 3 months there was non-significant difference in the mean UA-RI in the two groups ( $P > 0.05$ ). For repeated measures in each group, there was non-significant decrease in the mean UA-RI in the two groups ( $P = 0.589$  and  $P = 0.391$ ). For the interaction between groups and time, green tea group had non-significant ( $P = 0.322$ ) reduction in the mean UA-RI ( $0.757$  vs.  $0.752$ ) compared with the symptomatic treatment group ( $0.749$  vs.  $0.737$ ).

**Table (7):** Comparison of body mass index between groups over time

Variable	Group I (n=30) (Mean $\pm$ SD)	Group II (n=30) (Mean $\pm$ SD)	P-value*
Baseline	30.37 $\pm$ 2.9	30.17 $\pm$ 3.3	= 0.809
4-months	28.91 $\pm$ 3.2	29.29 $\pm$ 3.1	= 0.856
P-value*	= <b>0.002</b>	= 0.206	P = 0.670**

\*Mean differences between group comparison and mean differences within group comparison

\*\*Two-way repeated measure ANOVA was used to compare the mean differences over time

**Table (7)** illustrated the effect of different treatment Modalities on the BMI. Initially, the two groups were matched ( $P = 0.809$ ) for the mean BMI before treatment (Study group =  $30.4 \pm 2.9$  vs. symptomatic treatment group =  $30.2 \pm 3.3$ ). Likely, there was statistically insignificant difference ( $P = 0.856$ ) in the mean BMI after four months of treatment between groups (group I =  $28.9 \pm 3.2$  vs. group II =  $29.3 \pm 3.1$ ). For repeated measures in each group, there was significant decrease in the mean BMI score in the study groups ( $P = 0.002$ ) while nonsignificant BMI reduction was observed in the conservative group ( $P = 0.206$ ). For the interaction between group and time, the two groups showed insignificant result ( $P = 0.670$ ).

**Table (8):** Comparison of hemoglobin level between groups over time

Variable	Group I (n=30) (Mean $\pm$ SD) mg/dl	Group II (n=30) (Mean $\pm$ SD) mg/dl	P-value*
Baseline	10.42 $\pm$ 1.0	10.57 $\pm$ 1.1	= 0.243
1-month	10.41 $\pm$ 1.0	10.75 $\pm$ 1.1	= 0.234
2-months	11.17 $\pm$ 0.6	11.42 $\pm$ 0.7	= 0.171
3-months	11.57 $\pm$ 0.6	11.78 $\pm$ 0.7	= 0.225
4-months	11.86 $\pm$ 0.7	12.03 $\pm$ 0.6	= 0.355
P-value*	< <b>0.001</b>	< <b>0.001</b>	P = 177**

\*Mean differences between group comparison and mean differences within group comparison

**\*\*Two-way repeated measure ANOVA was used to compare the mean differences over time**

**Table (8)** presented the effect of different treatment Modalities on the level of hemoglobin (Hb). The two groups were matched ( $P = 0.243$ ) for the mean Hb level at baseline (Study group =  $10.4 \pm 1.0$  mg/dl vs. symptomatic treatment group =  $10.6 \pm 1.1$  mg/dl). For measures after treatment at 1, 2, 3 and 4 months there was non-significant difference in the mean Hb level in the two groups ( $P > 0.05$ ). For repeated measures in each group, there was significant increase in the mean Hb Level in the two groups ( $P < 0.001$ ). In group I, the mean Hb showed steady increase from baseline till the study end (10.4, 10.4, 11.2, 11.6 and 11.9 mg/dl, respectively). Likewise, in group II, the mean Hb showed steady increase from baseline till the study end (10.6, 10.8, 11.4, 11.8 and 12.1 mg/dl, respectively). For the interaction between group and time, green tea group had nonsignificantly ( $P < 0.177$ ) increase in the mean Hb Level (10.4 vs. 11.9 mg/dl) compared with the symptomatic treatment group (10.6 vs. 12.1 mg/dl).

## Discussion

This study included homogenous population of women complaining of uterine fibroid symptoms, their age ranged from 29-47 years old, mean age (year) was ( $38.23 \pm 4.2$ ) years 60% of them showed gravidity  $\geq 2$  in while parity was  $< 2$  in 63.4% of them. Their mean BMI was ( $30.17 \pm 3.1$ )  $\text{kg/m}^2$  and mean FSH level ( $6.82 \pm 1.7$ ) IU/L. Our mean included study population were in agreement with study of **Miriello et al.** [16] as they reported that the mean of their participants age (year) was ( $37.78 \pm 2.1$ ) and their mean BMI ( $\text{kg/m}^2$ ) ( $23.58 \pm 2.9$ ) was lower than our study as they excluded obese women with BMI  $> 30$   $\text{kg/m}^2$  from their study.

Our results are supported by study of **Roshdy et al.** [2] the base line characteristics of the study population age was ranged from 25-50 years old with mean ( $41.5 \pm 5.9$ ) and mean of BMI were ( $33 \pm 6.9$ )  $\text{kg/m}^2$  also they reported that the mean of parity of their cases was 1.04 with range 0-5 and the mean of gravidity of them was 1.7 with rang 0-7.

Many studies in the literature reported variable effects of medical treatment for uterine fibroids few of them report the effect of green tea with uterine fibroids. These results are comparable to that reported in this study.

As regard the mean uterine fibroids volume we found reduction in the volume of studied green tea group throughout the 4 months treatment from ( $210 \pm 23.7$ )  $\text{cm}^3$  before to ( $157 \pm 26.2$ )  $\text{cm}^3$  after and this reduction was statistically significant compared to symptomatic treatment group ( $199.58 \pm 23.6$ )  $\text{cm}^3$  before and after 4 months ( $203.88 \pm 23.1$ )  $\text{cm}^3$  ( $P < 0.001$ ) the volume reduction became significant started after first 3 months treatment ( $P < 0.005$ ). The mean difference of UFV within the green tea group over time was significant  $P < 0.001$ .

Regarding UFV our results were supported by study of **Roshdy et al.** [2] conducted at Sohag, Egypt from November 2010 to August 2011 on 33 women randomly assigned to two arms of 4-months study into green tea extract group  $n=22$  and placebo group  $n=11$  The participants were had daily dosage of green tea

(800 mg/day) or placebo. As they reported that the overall UFs volumes were compared at baseline and at the end of the 4-month treatment period. The overall percentage reduction in mean total fibroid volume due to EGCG treatment was highly significant compared to placebo treatment. Interestingly, while the placebo group showed increase in total fibroid volume, none of the participants in the EGCG treatment group showed any increase in fibroid volume. Only one showed no change, and all others showed shrinkage in fibroid volume. Such a volume increase in the placebo group is consistent also with other longitudinal observation studies conducted by **Mavrelos et al.** [17] and **Bukulmez et al.** [18] of the natural history of uterine leiomyomata.

In our study the overall uterine fibroids volume decreased by 25.13% after 4 months EGCG treatment compared to an increase by 2.1% in the symptomatic treatment group  $P < 0.001$ . The same results obtained by **Grandi et al.** [19] use small dose of EGCG 300 mg with Vitamin B6 10 mg and Vitamin D 50  $\mu\text{g}/\text{day}$  for 90 days significant decrease in UFs size (-17.8%,  $p = .03$ ). This range of changes in uterine fibroids volume is fairly similar to results obtained using ulipristal, goserelin, and leuprolide studies carried out by **Donnez et al.** [20] and **Friedman et al.** [21]. The **Carbonell Esteve et al.** [22] study the effect of mifepristone in different doses on fibroids, however, did not show significant decrease in uterine volume in either treatment groups.

Green tea is processed in a manner to prevent the oxidation of green tea-leaf polyphenols, which contain five major catechins, including catechin, epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate (EGCG). These compounds show diverse chemical and biological activities and regulate the expression of a number of cyclins, oncogenes and tumor suppressor genes. EGCG comprises >40% of the total polyphenolic mixture of green tea catechins and possesses antioxidant, anti-inflammation and antitumor capacity [23].

According to **Zhang et al.** [24], EGCG-treated WT-HuLM (wildtype human leiomyoma) cells showed significantly decreased COMT (catechol- o - methyltransferase ) expression ( $p < 0.001$ ) and enzyme activity ( $p < 0.05$ ) The antiproliferative and gene-modulating effects of EGCG on HuLM cells are mediated, at least partially, via its effect on COMT expression and enzyme activity.

In vitro study done by **Zhang et al.** [25] to investigate the effect of epigallocatechin gallate (EGCG) on rat leiomyoma cells EGCG treatment dramatically reduced the volume and weight of tumors at 4 and 8 weeks after the treatment ( $P < .05$ ). EGCG effectively inhibits proliferation and induces apoptosis in rat uterine leiomyoma cells in vitro and in vivo.

In the study in our hands there was a significant decline in the severity of symptoms (SS) for repeated measures in the EGCG group after 4 months treatment from ( $81\% \pm 16\%$ ) to ( $47\% \pm 7$ )  $P < 0.001$ . Measuring the effects of different treatment Modalities on the HRQL score there was statistically insignificant improvement ( $p = 0.321$ ) in HRQL after four months of treatment between groups. For repeated measures in each group, there was significant increase in the mean HRQL score in the two groups ( $p < 0.001$ ). These results

were similar to study conducted by **Roshdy et al.** [2]. The mean SS percentile score dramatically decreased in patients with 4 months use of green tea extract (EGCG) while the mean SS percentile score increased in patients randomized to the placebo group. The mean change in SS score for the EGCG-treated group was  $-25.28(\pm 17.38)$  and significantly low ( $t = 5.22, P < 0.0001$ ) compared to the placebo group, for which mean change in SS score was  $= 7.1(\pm 15.5)$ . Unlike our study we found significant decrease in SS during repeated measures in symptomatic treatment group from  $(80\% \pm 18\%)$  to  $(46\% \pm 5\%)$  after 4 months treatment  $P < 0.001$  meaning that treated women with diosmin and/or ibuprofen give the same better SS results.

Another similar results found by **Pérez-López** [26]; 4 courses of oral ulipristal acetate (UPA) treatment (10 mg/day); treated women reported a high rate of bleeding control, and improved quality of life, pain anxiety and depression. While adverse events were mild or moderate throughout the several courses of treatment. Cost assessment of UPA treatment for uterine fibroids is to be considered, Furthermore, long-term UPA treatment should include endometrial, cardiocirculatory and neurological assessment.

**Roshdy et al.** [2] they observed a significant increase in the leiomyoma-specific HRQL (health-related quality-of-life) measures in the EGCG treatment group compared to the placebo group. However, SS (symptom-severity) worsened in the placebo group, while there was no significant change in their leiomyoma-specific quality of life at the end of the study, with only a 2% improvement, possibly due to the placebo effect or participant's subjective bias. The only dropouts were from the placebo group. It is very plausible that they were not relieved of symptoms and opted to seek other modalities of treatment.

The improvement in HRQL and decline in SS in response to EGCG treatment was comparable to different modalities of fibroids treatment ; a study conducted by **Millo et al.** [27] found that Changes in uterine and fibroid volumes did not correlate with changes in symptom severity or HRQL after UAE ( $P > 0.05$ ). Residual fibroid vascularity was a negative predictor of reduction in uterine and fibroid volume ( $P < 0.05$ ), but did not affect changes in symptom severity or HRQL.

Furthermore, **Goodwin et al.** [28] studied uterine artery embolization for treatment of leiomyomata found that mean symptom scores improved 41.41 points ( $P < .001$ ), and the quality of life scores improved 41.47 points ( $P < .001$ ), both moving into the normal range for this questionnaire.

Throughout our 4 months study repeated measures of mean Hb level in green tea group showed steady monthly increase from baseline till the study end (10.4, 10.4, 11.2, 11.6 and 11.9, respectively) and this increase was statistically significant  $P < 0.001$ . The same results were with **Roshdy et al.** [2] limited subject population was observed to have borderline anemia, with an average hemoglobin level at 11.7 g/dL, and using iron supplements was not an exclusion criterion for their study. However, there was a significant rise ( $P = 0.02$ ) from (12.1 to 15.1) g/dL from baseline to the end of the study period within the treatment group and a significant difference when compared to the change in placebo group ( $P = 0.05$ ).

This objective biomarker also appropriately validates the subjects' reporting of decreased SS in the HRQL questionnaire. In our study measuring Hb level after treatment at 1, 2, 3 and 4 months showed no significant difference in the mean Hb level between the two groups ( $P > 0.05$ ). But we found significant increase in the mean Hb Level by repeated measures in the symptomatic treatment groups ( $P < 0.001$ ). Likewise group I; the mean Hb in group II, showed steady increase from baseline till the study end (10.6, 10.8, 11.4, 11.8 and 12.1, respectively) as patients in group II also received medical treatment to control vaginal bleeding which also improved SS in this group. Regarding the increase in Hb level in both groups versus time, green tea group had nonsignificantly ( $P < 0.177$ ) increase in the mean Hb level (10.4 vs. 11.9 mg/dl) compared with the symptomatic treatment group (10.6 vs. 12.1 mg/dl).

Fibroid tumorigenesis is associated with myometrial vascular abnormalities including venular ectasia/increased venous plexus, arterial dilatation, localized expansion of myometrial vasculature, and abnormal vascular organization in the perifibroid region [29]. A study was done in Nigeria by **Idowu et al.** [30] found a significant increased blood perfusion of leiomyomatous uteri that is most likely due to uterine enlargement.

Doppler sonography of fibroid arteries has been found useful in monitoring leiomyoma response to medical therapy, differentiating leiomyomas from adenomyosis, and assessment of tumor size changes in response to uterine artery embolization (UAE). Furthermore, the degree of vascularity is said to reflect the likely growth pattern of the tumor and the risk of increased bleeding at surgery [31].

Unlike our study by comparing uterine artery resistant index value in both groups of our study there was insignificant difference ( $P = 0.479$ ) in the mean UA-RI after four months of treatment (Study group =  $0.75 \pm 0.1$  vs. symptomatic treatment group =  $0.74 \pm 0.1$ ). Also for repeated measures in each group, there was non-significant decrease in the mean UA-RI in the two groups ( $P = 0.589$  and  $P = 0.391$ ). The same was found for the interaction between groups and time, green tea group had non-significant ( $P = 0.322$ ) reduction in the mean UA-RI (0.757 vs. 0.752) compared with the symptomatic treatment group (0.749 vs. 0.737).

In a study by **Naguib et al.** [32] on 38 patients who underwent uterine artery embolization for leiomyoma, they determined the predictive value of Doppler ultrasonography indices (including peak systolic velocity (PSV), end-diastolic (EDV) velocities, and RI) in relation to embolizing material needed and leiomyoma tumor volume at follow-up after 3 months. They reported that the uterine artery PSV and EDV values decreased significantly when compared to pre-embolization values.

The advantage of this oral intervention, however, would be the avoidance of possible side effects of uterine artery embolization as UAE was associated with a higher rate of minor complications and 15% to 32% of them requiring surgical re-intervention within two to five years of the initial procedure This increase in the surgical re-intervention rate may balance out any initial cost advantage of UAE [33].



Furthermore, **Kanelopoulos et al.** [34] measured uterine artery RI as a predictor of uterine fibroid response to GnRH therapy they found an increase from  $0.73 \pm 0.16$  to  $1.05 \pm 0.27$  at the 3rd month of GnRH therapy ( $P < 0.001$ ). **Idowu et al.** [30] reported that the mean PI, resistivity index (RI), systolic/diastolic ratio (SDR) of uterine artery in fibroids women were significantly lower than those of the controls  $P < 0.001$  for all values.

Repeated measures of BMI in each group of our study found significant decrease in the green tea group ( $30.4 \pm 2.9$  Kg/m<sup>2</sup> to  $28.9 \pm 3.2$  Kg/m<sup>2</sup> ( $P=0.002$ ). The same results found by **Chen et al.**[35] when examined the effect and safety of high-dose green tea extract (EGCG) at a daily dosage of 856.8 mg on weight reduction they found significant weight loss, from  $76.8 \pm 11.3$  kg to  $75.7 \pm 11.5$  kg ( $P = 0.025$ ), as well as decreases in BMI ( $P = 0.018$ ) in the treatment group after 12 weeks of high-dose EGCG treatment.

### Conclusion

- Green tea extract (EGCG) has a significant positive effect on the reduction of UF burden. Our data demonstrate that patients who used green tea extracts experienced significant shrinkage in their total fibroid volume.
- No statistical significant improvement **between the two groups** as regard symptoms severity, health related quality of life, body mass index and hemoglobin level.
- In **each group** there was statistical significant improvement throughout the study as regards symptoms severity, health related quality of life, body mass index and hemoglobin level.
- Administration of green tea extract could possibly be an effective oral treatment for UF. Our data suggest a promising alternative in which the burden of this disease could be reduced by making green tea extract available to women who have UF.

### Recommendations

- Wide use of this novel noninvasive intervention is recommended for all women with fibroid related symptoms especially obese patients.
- More studies are required for the use of green tea extract to reduce the fibroid volume prior to myomectomy.
- More studies are required to compare the usage of green tea extracts with other modalities of fibroid treatment.
- Larger multicenter trials are required to prove a positive therapeutic and possibly preventive option for leiomyoma.

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