Dietary Natural Compounds and Vitamins Impact Uterine Fibroids

Subjects: Allergy

Contributor: Iwona Szydłowska

Within the past 20 year-span concerning risks of uterine fibroids (UFs) occurrence and dietary factors was carried out. A link between Vitamin D deficiency and UFs formation is strongly indicated, making it a potent compound in leiomyoma therapy. Analogs of the 25-hydroxyvitamin D3, not susceptible to degradation by tissue 24-hydroxylase, appear to be especially promising and tend to show better therapeutic results. Although research on the role of Vitamin A in the formation of fibroids is contradictory, Vitamin A-enriched diet, as well as synthetic retinoid analogues, may be preventative or limit the growth of fibroids. Unambiguous conclusions cannot be drawn regarding Vitamin E and C supplementation, except for alpha-tocopherol. Alpha-tocopherol as a phytoestrogen taking part in the modulation of estrogen receptors (ERs) involved in UF etiology, should be particularly avoided in therapy. A diet enriched in fruits and vegetables, as sources of carotenoids, polyphenols, quercetin, and indole-3-carbinol, constitutes an easily modifiable lifestyle element with beneficial results in patients with UFs. Other natural substances, such as curcumin, can reduce the oxidative stress and protect against inflammation in leiomyoma. Although the exact effect of probiotics on uterine fibroids has not yet been thoroughly evaluated at this point, the protective role of dairy products, i.e., yogurt consumption, has been indicated. Trace elements such as selenium can also contribute to antioxidative and anti-inflammatory properties of a recommended diet.

Keywords: uterine fibroids ; diet ; Vitamins

1. Vitamin A. Retinoids

A 2020 study by Wise et al. found no association of UF incidence with dietary Vitamin A intake (i.e., salad greens, carrots, spinach, sweet potatoes, eggs, cheese, and cereal products) [1]. These results were generated within a particular racial group of women and as such might be worth exploring in the remaining population. Previously, in 2011, Wise et al. observed an inverse correlation between dietary intake of Vitamin A and the risk of UFs. They noted that it was predominantly conditioned by preformed Vitamin A derived from animal sources (i.e., liver and milk), but not by provitamin A from fruit and vegetable sources (i.e., carrots, sweet potatoes/yams, and collard greens) [2]. These findings may complement the molecular study of Heinonen et al. who showed that levels of vitamin A were specifically reduced in leiomyomas of the *MED12* subtype [3], yet appeared to be contradictory to conclusions drawn by Martin et al. who noted positive, statistically significant, and dose-dependent association between vitamin A and uterine fibroid risk, except for the population of Hispanic women [4].

A possible explanation for the positive association between Vitamin A and the risk of UFs is that exposure to high levels of Vitamin A can activate peroxisome proliferator-activated receptors (PPARs). These nuclear receptors, in combination with retinoid X receptors, can activate gene expression, and thus simultaneously increase the risk of UFs in some women [4]. Retinoids are small molecule derivatives of Vitamin A. Studies have shown that the retinoid pathway is significantly altered in fibroids compared to normal myometrium. Retinol requires conversion to retinoic acid (RA), which requires the activity of specific enzymes. In fibroid fibroblasts, aldehyde dehydrogenase (ALDH1) has been specifically identified as one of them. Studies concluded that alterations in the retinoid pathway could lead to abnormal RA production and signaling, which might be important in fibroid development [5][6][7][8]. Zaitseva reports that transcription factor II (known as NR2F2) and CTNNB1(b-catenin) genes are potentially causal factors in the development of UFs [9]. According to her research, the combination of RA and progesterone regulates NR2F2 expression and thus affects fibroid growth. This suggests that retinoids, by causing these molecular alternations, may be useful in the treatment of UFs. In their in vitro studies, Ben-Sasson et al. and Malik et al. demonstrated decreased cell proliferation, ECM formation, RA metabolism, transforming growth factor beta (TGF- β) regulation, and increased apoptosis in human leiomyoma treated with retinoic acid (ATRA-all-trans-retinoic acid) [10][11]. Broaddus et al. showed, again in vitro, that treatment with 4-(N-hydroxyphenyl)-retinamide (4-HPR) or a-difluoromethylornithine (DFMO) resulted in growth inhibition of primary cultures of human uterine leiomyoma

[12]. 4-HPR is a synthetic retinoid analog that, in comparison to other retinoids, has a reduced toxicity potential. It promotes apoptosis and induces growth inhibition through induction of p53, p21, and p16, and modulation of extracellular matrix in human uterine leiomyomas. It was noted that the mechanisms of growth inhibition and apoptosis induction could be independent of binding to nuclear retinoid receptors [12].

The above results suggest that a diet rich in Vitamin A and retinoids can prevent fibroids and inhibit tumor growth. Synthetic retinoid analogues can also be effective.

2. Vitamin E

Vitamin E is a potent antioxidant that acts by scavenging lipid hydroperoxyl radicals and so can protect cells from the effects of free radicals [13]. Food sources of Vitamin E include canola oil, olive oil, almonds and peanuts, meat, dairy, leafy greens, and fortified cereals. It is also available in oral supplements. Little data is available on Vitamin E and its effects on UFs. Wise et al. found no associated risks with consumption of diet-derived Vitamin E [2]. Martin et al. highlighted a positive, dose-dependent link between vitamin E and the incidence of UFs; the findings were, however, not statistically significant [4]. Ciebiera et al. showed higher serum concentration levels of α-tocopherol (the most common form of vitamin E) in Caucasian women, which may be an important factor in fibroid development [14].

Vitamin E, despite its antioxidant properties, appears not to demonstrate proven beneficial effects in terms of leiomyoma prevention and management.

3. Vitamin D

Vitamin D is obtained mainly from sun exposure (skin synthesis), food (oily fish such as trout, salmon, tuna, mackerel, and fish liver oils), and vitamin supplements. Prohormonal forms of vitamin D require hydroxylation in the liver to 25-hydroxyvitamin D (25(OH)D) and in the kidney to their active form, that is 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$). Vitamin D_3 exerts its biological functions by interacting with and activating the nuclear vitamin D receptor (VDR). In vitro studies point toward uterine myoma cells exhibiting lower levels of VDR expression [15][16]. In addition, a negative correlation between decreased levels of vitamin D receptor (VDR) and increased levels of estrogen and progesterone receptors (ER-α, PR-A, PR-B) was observed in myoma tumors [17]. It is estimated that Vitamin D deficiency affects 25–50% (possibly more) of patients [18]. Several studies found that insubstantial levels of Vitamin D can contribute to the development of UFs in African American, Caucasian, and Asian women alike [19][20][21][22][23][24][25][26][27]. Vitamin D_3 deficiency activates fibroid cell growth, exacerbates DNA damage, and reduces DNA repairability; it promotes uncontrolled proliferation and fibrosis, and increases chronic inflammation. In combination, these processes are highly tumorogenic [28][29]. Othman et al. demonstrated that, in comparison to normal myometrium, myoma tissue contains significantly lower concentrations of $1,25(OH)_2D_3$. Additionally, an overexpression of 24-hydroxylase was found in myoma, which may further suppress the anti-tumor effect of $1,25(OH)_2D_3$ and exacerbate vitamin D deficiency in the tissue [30]. A recent study by Ciebiera et al. revealed an inverse correlation between lower 25(OH)D serum concentrations and increased serum transforming growth factor β3 (TGF-β3) concentrations in women affected by fibroids [31]. This growth factor can be associated with increased fibrosis and ECM accumulation in myoma [32][33]. Findings on inverse correlation between serum levels of 25(OH)D and fibroid volume vary, ranging from significant to insignificant association [19][34][35]. No correlation was however observed between 25(OH)D serum levels and number of fibroids [34]. Some data suggest that Vitamin D supplementation reduces leiomyoma cell proliferation and thus prevents leiomyoma growth [23][36][37][38]. A significant downregulation of ER-α, PR-A, PR-B, and steroid receptor coactivators in human myoma cells may be one of the mechanisms—an effect similar to that observed during the course of hormone therapy with GnRH analogues and ulipristal acetate (UPA) [17][39][40]. Halder et al. and Li et al. point to the antifibrotic activity of Vitamin D [41][42]. Vitamin D_3 inhibited TGF-β3-induced protein expression and all TGF-β3-mediated effects involved in the fibrotic processes in leiomyoma. Other studies indicate that increasing Vitamin D levels by one unit can reduce the risk of developing UFs by 4–8% [26][31]. Hajhashemi et al. confirmed a significant decrease in leiomyoma size after 10 weeks of vitamin D administration [43]. A slight, statistically insignificant reduction in fibroid volume after a short-term Vitamin D supplementation was observed by Arjeh et al. [44], Davari Tanha et al. [45], and Suneja et al. [46] in patients with hypovitaminosis D (12, 16, and 8 weeks, respectively). Ciavattini et al. reported a similar effect after 12 months of Vitamin D_3 supplementation [34]. Vitamin D_3 supplementation may inhibit the growth of UFs, reduce fibroid-related symptoms, and reduce the need for surgical or medical treatment for progression of fibroids [34][45][46]. Especially, a long-term course of treatment can have antiproliferative, antifibrotic, and proapoptotic effects in leiomyoma, as demonstrated by Corachán et al. [47], a finding consistent with other studies in vitro [28][41][42]. Beside apoptosis induction, Vitamin D suppresses catechol-O-methyltransferase (COMT) expression and activity in myoma cells—an enzyme that plays a vital role in myoma formation [41]. In fact, physiological concentrations of vitamin D can effectively inhibit the growth of myoma cells [28]. $1,25(OH)_2D_3$ can significantly reduce the expression of ECM-

associated proteins and structural actin fibers in human leiomyoma cells, as observed by Halder et al. [15]. This effect was a consequence of previous significant induction of nuclear vitamin D receptor (VDR) expression by 1,25$(OH)_2D_3$ in a concentration-dependent manner. In another study, Halder et al. observed a significant reduction in MMP-2 and MMP-9 mRNA levels, as well as a reduction in MMP-2 and MMP-9 protein levels in uterine fibroid cells in a concentration-dependent manner and concluded that through this mechanism, 1,25$(OH)_2D_3$ might limit fibroid growth and ECM deposition [48]. Al-Hendy et al. observed that 1,25$(OH)_2D_3$ spontaneously induced its own VDR, while significantly downregulating the expression of sex steroid receptors (ERs and PRs) and receptor coactivators, which affected myoma formation and growth; hence, 1,25$(OH)_2D_3$ suppressed estrogen-induced proliferation in leiomyoma cells [17]. Cell proliferation and extracellular matrix production in myoma tumors can be affected by Vitamin D as it can suppress tumor-promoting Wnt4/β-catenin expression and reduce activation of mTOR signaling in human UF cells [49]. As observed by Corachán et al., Vitamin D inhibits the Wnt/β-catenin and TGFβ pathways, reducing proliferation and extracellular matrix formation, in different molecular subtypes of uterine myomas (MED12-mutated and wild-type human tumors) [50]. Ali et al. hypothesized that myoma tumor progression might be inhibited by recovering the damaged DNA repair system [51]. They showed in vitro that vitamin D_3 treatment significantly reduces DNA damage, restores the normal DNA damage response, and is accompanied by induction of VDR in fibroid cells [51]. DNA repair in cells exposed to classic DNA damage inducers in UF pathogenesis (endocrine-disrupting chemicals -EDCs) was achieved by a 1,25$(OH)_2D_3$ treatment of myoma cells in animal models [52]. Clinical trials show promising results in patients with UFs and hypovitaminosis D treated with Vitamin D_3 supplementation, revealing a significant decrease in tumor size and numbers [43][53]. At the time of the review, search results pointed to a randomized trial (RCT) being conducted in women at reproductive age affected with uterine myoma, aiming to evaluate whether supplementation with Vitamin D_3 could reduce the risk and inhibit the growth of fibroids [54]. Results of the evaluation of Vitamin D_3 effects in this particular group of women can be of value in everyday gynecological practice.

Paricalcitol, an analog of 1,25$(OH)_2D_3$, has less calcemic activity and, therefore, appears to be safer in long-term use than 1,25$(OH)_2D_3$. Halder et al. study indicates that treatment with paricalcitol has an inhibitory effect on uterine fibroid cell proliferation [36]. On a murine model, both paricalcitol and 1,25$(OH)_2D_3$ significantly reduced fibroid size, but paricalcitol was more potent. Porcaro et al. observed a significant reduction in myoma volume and overall improvement in quality of life in patients treated with a combination of Vitamin D, EGCG, and vitamin B6 [55]. This combined supplementation treatment presents as quite an innovative approach to treating leiomyoma with oral supplementation. Shen et al., on the other hand, arrived at contrary conclusions. In their study, Vitamin D supplementation had no effects on the risk of UFs [56].

A study by Güleç et al. determined the association between Vitamin D receptor polymorphisms and the occurrence of uterine myomas [57]. It shows that among the fok1 polymorphisms of the vitamin D receptor, the presence of the CC fok1 genotype may be a risk-reducing factor, and the T allele may increase the risk of uterine myomas. A recent study by Fazeli et al. evaluated CYP24A1 gene expression in uterine myoma tissue [58]. CYP24A1 is a mitochondrial enzyme that catalyzes the degradation of 1,25$(OH)_2D_3$ to its less active 25-D3 form and regulates the amount of active Vitamin D in tissues. The expression of CYP24A1 in leiomyoma suggests that local degradation of 1,25$(OH)_2D_3$ may also have a role in fibroma development.

Overall, Vitamin D_3 may be a promising option in prevention and treatment of UFs. The majority of presented studies consider treatment with Vitamin D_3 as safe and effective.

4. The Active Compounds from Plants

4.1. Green Tea—Polyphenols

Green tea is widely known for its antioxidant activity and is extensively consumed, especially in Asian countries. Compared to other beverages, it has a much higher catechin content. Components of green tea include polyphenols (epigallocatechin-3-gallate—EGCG, epigallocatechin—EGC, epicatechin-3-gallate—ECG, epicatechin—EC), flavones, and flavanols (kaempferol, myricetin, quercetin). The average daily intake of EGCG from green tea consumption in the EU ranges from 90 to 300 mg/day, while high-level consumers intake even up to 860 mg EGCG/day. In vitro studies showed that EGCG, consumed in the form of a green tea extract, inhibited proliferation and growth and promoted apoptosis in cultures of human uterine leiomyoma cells in a dose-dependent manner [59][60]. Antiproliferative and gene-modulating effects of EGCG were partially mediated through the effect on catechol-O-methyltransferase (COMT) enzyme activity. Similar EGCG action effects were observed in vivo in animal models [61][62]. Ozercan et al. observed that EGCG extract decreased tumor necrosis factor α (TNFα) levels, a cytokine associated with leiomyoma pathophysiology [62]. It appears that EGCG supplementation, by modulating multiple cellular signaling pathways, reduces tumor size and may be an

alternative therapeutic option in treatment of UFs. Roshdy et al. evaluated green tea extract (EGCG) taken orally as safe and effective treatment for symptomatic UFs [63]. EGCG intake at a dose of 800 mg/day resulted not only in a significant reduction in tumor volume but also in a reduction of fibroid-specific symptoms, and many treated patients experienced improved health-related quality of life. However, the European Food Safety Authority (EFSA) notes the potential adverse hepatotoxic effects of green tea catechins at intakes ≥ 800 mg EGCG/day taken as a dietary supplement [64]. Grandi et al. observed that EGCG at a daily dose of 300 mg, when vitamin B6 and vitamin D were added, significantly reduced the volume of intramural (mainly) and subserosal UFs [65]. The 90-day treatment resulted in a significant reduction in the length of menstrual bleeding, but not significant changes in health-related quality of life or an improved comfort of sex-life. Grandi et al. suggest EGCG supplementation as an alternative method of treatment for women in late reproductive age, when hormone therapy is not optional. Similar results were observed by Porcaro et al. for a dose of 150 mg EGCG with 25 µg vitamin D and 5 mg vitamin B6 intake in women at reproductive age with symptomatic myomas [55]. Young women at childbearing age can also benefit from EGCG supplementation. Miriello et al. noted that combined daily supplementation of EGCG (300 mg), vitamin D (50 µg), and vitamin B6 (10 mg) can, with no side effects, reduce myoma volume and related symptoms and improve patients' quality of life [66].

EGCG under normal, physiological conditions is characterized by low stability, poor bioavailability, and high metabolic changes. Therefore, methods are being sought to improve the stability of EGCG as a drug. Ahmed et al. studied the biological properties of pro-drug EGCG analogs (pro-EGCG analogs) in human leiomyoma cell lines [67]. They found that these drugs, with improved stability, bioavailability, and biological activity, exhibited potent antiproliferative, antiangiogenic, proapoptotic, and antifibrotic activities in UFs. Pro-drugs EGCG analogs share the same molecular targets as natural EGCG in inhibiting enzymatic activity and could potentially be more effective than natural EGCG therapeutic agent in a long-term use in women with symptomatic UFs. Contrary results were reported in an observational study by Biro et al. [68]. They found that consumption of green tea extract (GTE) capsules resulted only in a significant improvement in physical quality of life (QoL) score. No changes were observed in myoma size or myoma-related complaints or in global QoL score after GTE supplementation. Shen et al. arrived at the same conclusion: that drinking green tea had no effect on the risk of leiomyoma [56].

To sum up, the effects of UFs treatment with polyphenols can depend on dose, duration of treatment, and patient selection.

4.2. Curcumin/Turmeric

Curcumin is one of the three major curcuminoids in turmeric plant (*Curcuma longa*). Numerous studies have highlighted its antioxidant, anti-inflammatory, anti-carcinogenic and immunoregulatory activity at the molecular level [69][70][71]. By suppressing anti-apoptotic proteins, curcumin can protect against the formation and growth of tumors, including uterine myomas.

Malik et al. demonstrated in vitro that curcumin inhibited the proliferation of uterine leiomyoma cells [72]. The curcumin compound caused upregulation of the apoptotic pathway and inhibited fibronectin production, a component of ECM [72]. Tsuiji et al. noted the effect of curcumin on peroxisome proliferator-activated receptor-gamma (PPARγ) activation [73]. Feng et al. demonstrated in an animal model that Rhizoma Curcumae (RC) and Rhizoma Sparganii (RS), used in traditional Chinese medicine, were effective in preventing and treating UFs in rats [74]. The combination of RC and RS effectively reduced the expression of extracellular matrix component collagen, fibroblast activating protein, and transforming growth factor beta (TGF-β), simultaneously decreasing the expression level of signaling factors (AKT, ERK and MEK) in cell proliferation [74]. Similar effects were observed by Yu et al. [75]. They noted that RC/RS herbs regulated key pathways in UF cell proliferation and ECM formation, such as MAPK, PPAR, Notch, and TGF-β/Smad. Curcumin can thus reduce the oxidative stress and protect against inflammation. This activity is expressed through modulation of proinflammatory cytokines and signaling pathways, including beforementioned peroxisome proliferator-activated receptor gamma (PPAR-γ) [70].

In conclusion, turmeric appears to be a desirable dietary component for women at risk of developing uterine myomas and those already affected by this disease.

4.3. Quercetin and Indole-3-Carbinol

Indole-3-carbinol (I3C) and quercetin, as plant- derived components, were also of interest in a potential treatment of UFs. The former one can be sourced mainly from cruciferous vegetables, the latter is an active compound of onion. A recent in-vitro study revealed anti-fibrotic and anti-migratory effects of quercetin and I3C for uterine leiomyomas, but with no impact on myoma cell proliferation [76].

References

1. Wise, L.A.; Wesselink, A.K.; Bethea, T.N.; Brasky, T.M.; Wegienka, G.; Harmon, Q.; Block, T.; Baird, D.D. Intake of Lycopene and other Carotenoids and Incidence of Uterine Leiomyomata: A Prospective Ultrasound Study. J. Acad. Nutr. Diet. 2021, 121, 92–104.
2. Wise, L.A.; Radin, R.G.; Palmer, J.R.; Kumanyika, S.K.; Boggs, D.A.; Rosenberg, L. Intake of fruit, vegetables, and carotenoids in relation to risk of uterine leiomyomata. Am. J. Clin. Nutr. 2011, 94, 1620–1631.
3. Heinonen, H.-R.; Mehine, M.; Mäkinen, N.; Pasanen, A.; Pitkänen, E.; Karhu, A.; Sarvilinna, N.S.; Sjöberg, J.; Heikinheimo, O.; Bützow, R.; et al. Global metabolomic profiling of uterine leiomyomas. Br. J. Cancer 2017, 117, 1855–1864.
4. Martin, C.L.; Huber, L.R.B.; Thompson, M.E.; Racine, E.F. Serum Micronutrient Concentrations and Risk of Uterine Fibroids. J. Women's Health 2011, 20, 915–922.
5. Zaitseva, M.; Vollenhoven, B.J.; Rogers, P.A. Retinoids regulate genes involved in retinoic acid synthesis and transport in human myometrial and fibroid smooth muscle cells. Hum. Reprod. 2008, 23, 1076–1086.
6. Lattuada, D.; Vigano, P.; Mangioni, S.; Sassone, J.; Di Francesco, S.; Vignali, M.; Di Blasio, A.M. Accumulation of Retinoid X Receptor-α in Uterine Leiomyomas Is Associated with a Delayed Ligand-Dependent Proteasome-Mediated Degradation and an Alteration of Its Transcriptional Activity. Mol. Endocrinol. 2007, 21, 602–612.
7. Zaitseva, M.; Vollenhoven, B.J.; Rogers, P.A.W. Retinoic acid pathway genes show significantly altered expression in uterine fibroids when compared with normal myometrium. Mol. Hum. Reprod. 2007, 13, 577–585.
8. Catherino, W.H.; Malik, M. Uterine leiomyomas express a molecular pattern that lowers retinoic acid exposure. Fertil. Steril. 2007, 87, 1388–1398.
9. Zaitseva, M.; Holdsworth-Carson, S.J.; Waldrip, L.; Nevzorova, J.; Martelotto, L.; Vollenhoven, B.J.; Rogers, P.A.W. Aberrant expression and regulation of NR2F2 and CTNNB1 in uterine fibroids. Reproduction 2013, 146, 91–102.
10. Ben-Sasson, H.; Ben-Meir, A.; Shushan, A.; Karra, L.; Rojansky, N.; Klein, B.Y.; Levitzki, R.; Ben-Bassat, H. All-trans-retinoic acid mediates changes in PI3K and retinoic acid signaling proteins of leiomyomas. Fertil. Steril. 2011, 95, 2080–2086.
11. Malik, M.; Webb, J.; Catherino, W.H. Retinoic acid treatment of human leiomyoma cells transformed the cell phenotype to one strongly resembling myometrial cells. Clin. Endocrinol. 2008, 69, 462–470.
12. Broaddus, R.R.; Xie, S.; Hsu, C.-J.; Wang, J.; Zhang, S.; Zou, C. The chemopreventive agents 4-HPR and DFMO inhibit growth and induce apoptosis in uterine leiomyomas. Am. J. Obstet. Gynecol. 2004, 190, 686–692.
13. Traber, M.G.; Stevens, J.F. Vitamins C and E: Beneficial effects from a mechanistic perspective. Free Radic. Biol. Med. 2011, 51, 1000–1013.
14. Ciebiera, M.; Szymańska-Majchrzak, J.; Sentkowska, A.; Kilian, K.; Rogulski, Z.; Nowicka, G.; Jakiel, G.; Tomaszewski, P.; Włodarczyk, M. Alpha-Tocopherol Serum Levels Are Increased in Caucasian Women with Uterine Fibroids: A Pilot Study. BioMed Res. Int. 2018, 2018, 6793726.
15. Halder, S.K.; Osteen, K.G.; Al-Hendy, A. 1,25-Dihydroxyvitamin D3 Reduces Extracellular Matrix-Associated Protein Expression in Human Uterine Fibroid Cells. Biol. Reprod. 2013, 89, 150.
16. Lima, M.S.O.; da Silva, B.B.; de Medeiros, M.L.; dos Santos, A.R.; Brazil, E.D.D.N.; Filho, W.M.N.E.; Ibiapina, J.O.; Brito, A.G.A.; Costa, P.V.L. Evaluation of vitamin D receptor expression in uterine leiomyoma and nonneoplastic myometrial tissue: A cross-sectional controlled study. Reprod. Biol. Endocrinol. 2021, 19, 67.
17. Al-Hendy, A.; Diamond, M.P.; El-Sohemy, A.; Halder, S.K. 1,25-dihydroxyvitamin D3 regulates expression of sex steroid receptors in human uterine fibroid cells. J. Clin. Endocrinol. Metab. 2015, 100, E572–E582.
18. Kennel, K.A.; Drake, M.T.; Hurley, D.L. Vitamin D Deficiency in Adults: When to Test and How to Treat. Mayo Clin. Proc. 2010, 85, 752–758.
19. Al-Hendy, A.; Halder, S.K.; Allah, A.S.A.; Roshdy, E.; Rajaratnam, V.; Sabry, M. Serum vitamin D3 level inversely correlates with uterine fibroid volume in different ethnic groups: A cross-sectional observational study. Int. J. Women's Health 2013, 5, 93–100.
20. Baird, D.D.; Hill, M.C.; Schectman, J.M.; Hollis, B.W. Vitamin D and the Risk of Uterine Fibroids. Epidemiology 2013, 24, 447–453.
21. Paffoni, A.; Somigliana, E.; Vigano, P.; Benaglia, L.; Cardellicchio, L.; Pagliardini, L.; Papaleo, E.; Candiani, M.; Fedele, L. Vitamin D Status in Women With Uterine Leiomyomas. J. Clin. Endocrinol. Metab. 2013, 98, E1374–E1378.

22. Li, S.; Chen, B.; Sheng, B.; Wang, J.; Zhu, X. The associations between serum vitamin D, calcium and uterine fibroids in Chinese women: A case-controlled study. J. Int. Med Res. 2020, 48, 300060520923492.

23. Brakta, S.; Diamond, J.S.; Al-Hendy, A.; Diamond, M.; Halder, S.K. Role of vitamin D in uterine fibroid biology. Fertil. Steril. 2015, 104, 698–706.

24. Wise, L.A.; Ruiz-Narváez, E.A.; Haddad, S.A.; Rosenberg, L.; Palmer, J.R. Polymorphisms in vitamin D–related genes and risk of uterine leiomyomata. Fertil. Steril. 2014, 102, 503–510.e1.

25. Singh, V.; Barik, A.; Imam, N. Vitamin D3 Level in Women with Uterine Fibroid: An Observational Study in Eastern Indian Population. J. Obstet. Gynecol. India 2019, 69, 161–165.

26. Tunau, K.A.; Garba, J.A.; Panti, A.A.; Shehu, C.E.; Adamu, A.N.; AbdulRahman, M.B.; Ahmad, M.K. Low plasma vitamin D as a predictor of uterine fibroids in a nigerian population. Niger. Postgrad. Med J. 2021, 28, 181–186.

27. Xu, F.; Li, F.; Li, L.; Lin, D.; Hu, H.; Shi, Q. Vitamin D as a risk factor for the presence of asymptomatic uterine fibroids in premenopausal Han Chinese women. Fertil. Steril. 2021, 115, 1288–1293.

28. Bläuer, M.; Rovio, P.H.; Ylikomi, T.; Heinonen, P.K. Vitamin D inhibits myometrial and leiomyoma cell proliferation in vitro. Fertil. Steril. 2009, 91, 1919–1925.

29. ElHusseini, H.; Elkafas, H.; Abdelaziz, M.; Halder, S.; Atabiekov, I.; Eziba, N.; Ismail, N.; El Andaloussi, A.; Al-Hendy, A. Diet-induced vitamin D deficiency triggers inflammation and DNA damage profile in murine myometrium. Int. J. Women's Health 2018, 10, 503–514.

30. Othman, E.R.; Ahmed, E.; Sayed, A.A.; Hussein, M.; Abdelaal, I.I.; Fetih, A.N.; Abou-Taleb, H.A.; Yousef, A.-E.A. Human uterine leiomyoma contains low levels of 1, 25 dihdroxyvitamin D3, and shows dysregulated expression of vitamin D metabolizing enzymes. Eur. J. Obstet. Gynecol. Reprod. Biol. 2018, 229, 117–122.

31. Ciebiera, M.; Włodarczyk, M.; Słabuszewska-Jóźwiak, A.; Nowicka, G.; Jakiel, G. Influence of vitamin D and transforming growth factor β3 serum concentrations, obesity, and family history on the risk for uterine fibroids. Fertil. Steril. 2016, 106, 1787–1792.

32. Islam, S.; Ciavattini, A.; Petraglia, F.; Castellucci, M.; Ciarmela, P. Extracellular matrix in uterine leiomyoma pathogenesis: A potential target for future therapeutics. Hum. Reprod. Updat. 2018, 24, 59–85.

33. Arici, A.; Sozen, I. Transforming growth factor-β3 is expressed at high levels in leiomyoma where it stimulates fibronectin expression and cell proliferation. Fertil. Steril. 2000, 73, 1006–1011.

34. Ciavattini, A.; Carpini, G.D.; Serri, M.; Vignini, A.; Sabbatinelli, J.; Tozzi, A.; Aggiusti, A.; Clemente, N. Hypovitaminosis D and "small burden" uterine fibroids: Opportunity for a vitamin D supplementation. Medicine 2016, 95, e5698.

35. Kaplan, Z.A.O.; Taşçi, Y.; Topçu, H.O.; Erkaya, S. 25-Hydroxy vitamin D levels in premenopausal Turkish women with uterine leiomyoma. Gynecol. Endocrinol. 2018, 34, 261–264.

36. Halder, S.K.; Sharan, C.; Al-Hendy, O.; Al-Hendy, A. Paricalcitol, a Vitamin D Receptor Activator, Inhibits Tumor Formation in a Murine Model of Uterine Fibroids. Reprod. Sci. 2014, 21, 1108–1119.

37. Halder, S.K.; Sharan, C.; Al-Hendy, A. 1,25-Dihydroxyvitamin D3 Treatment Shrinks Uterine Leiomyoma Tumors in the Eker Rat Model1. Biol. Reprod. 2012, 86, 116.

38. Corachán, A.; Ferrero, H.; Aguilar, A.; Garcia, N.; Monleon, J.; Faus, A.; Cervelló, I.; Pellicer, A. Inhibition of tumor cell proliferation in human uterine leiomyomas by vitamin D via Wnt/β-catenin pathway. Fertil. Steril. 2019, 111, 397–407.

39. Khan, K.N.; Fujishita, A.; Koshiba, A.; Ogawa, K.; Mori, T.; Ogi, H.; Itoh, K.; Teramukai, S.; Kitawaki, J. Expression profiles of E/P receptors and fibrosis in GnRHa-treated and -untreated women with different uterine leiomyomas. PLoS ONE 2020, 15, e0242246.

40. Szydłowska, I.; Grabowska, M.; Nawrocka-Rutkowska, J.; Piasecka, M.; Starczewski, A. Markers of Cellular Proliferation, Apoptosis, Estrogen/Progesterone Receptor Expression and Fibrosis in Selective Progesterone Receptor Modulator (Ulipristal Acetate)-Treated Uterine Fibroids. J. Clin. Med. 2021, 10, 562.

41. Sharan, C.; Halder, S.K.; Thota, C.; Jaleel, T.; Nair, S.; Al-Hendy, A. Vitamin D inhibits proliferation of human uterine leiomyoma cells via catechol-O-methyltransferase. Fertil. Steril. 2011, 95, 247–253.

42. Halder, S.K.; Goodwin, J.S.; Al-Hendy, A. 1,25-Dihydroxyvitamin D3 Reduces TGF-β3-Induced Fibrosis-Related Gene Expression in Human Uterine Leiomyoma Cells. J. Clin. Endocrinol. Metab. 2011, 96, E754–E762.

43. Hajhashemi, M.; Ansari, M.; Haghollahi, F.; Eslami, B. The effect of vitamin D supplementation on the size of uterine leiomyoma in women with vitamin D deficiency. Casp. J. Intern. Med. 2019, 10, 125–131.

44. Arjeh, S.; Darsareh, F.; Asl, Z.A.; Kutenaei, M.A. Effect of oral consumption of vitamin D on uterine fibroids: A randomized clinical trial. Complement. Ther. Clin. Pr. 2020, 39, 101159.

45. Tanha, F.D.; Feizabad, E.; Farahani, M.V.; Amuzegar, H.; Moradi, B.; Sadeh, S.S. The Effect of Vitamin D Deficiency on Overgrowth of Uterine Fibroids: A Blinded Randomized Clinical Tria. Int. J. Fertil. Steril. 2021, 15, 95–100.

46. Suneja, A.; Faridi, F.; Bhatt, S.; Guleria, K.; Mehndiratta, M.; Sharma, R. Effect of Vitamin D3 supplementation on symptomatic uterine leiomyoma in women with Hypovitaminosis D. J. Midlife Health 2021, 12, 53–60.

47. Corachán, A.; Ferrero, H.; Escrig, J.; Monleon, J.; Faus, A.; Cervelló, I.; Pellicer, A. Long-term vitamin D treatment decreases human uterine leiomyoma size in a xenograft animal model. Fertil. Steril. 2020, 113, 205–216.e4.

48. Halder, S.K.; Osteen, K.G.; Al-Hendy, A. Vitamin D3 inhibits expression and activities of matrix metalloproteinase-2 and -9 in human uterine fibroid cells. Hum. Reprod. 2013, 28, 2407–2416.

49. Al-Hendy, A.; Diamond, M.P.; Boyer, T.G.; Halder, S.K. Vitamin D3 Inhibits Wnt/β-Catenin and mTOR Signaling Pathways in Human Uterine Fibroid Cells. J. Clin. Endocrinol. Metab. 2016, 101, 1542–1551.

50. Corachán, A.; Trejo, M.G.; Carbajo-García, M.C.; Monleón, J.; Escrig, J.; Faus, A.; Pellicer, A.; Cervelló, I.; Ferrero, H. Vitamin D as an effective treatment in human uterine leiomyomas independent of mediator complex subunit 12 mutation. Fertil. Steril. 2021, 115, 512–521.

51. Ali, M.; Shahin, S.M.; Sabri, N.A.; Al-Hendy, A.; Yang, Q. Hypovitaminosis D exacerbates the DNA damage load in human uterine fibroids, which is ameliorated by vitamin D3 treatment. Acta Pharmacol. Sin. 2019, 40, 957–970.

52. Elkafas, H.; Ali, M.; Elmorsy, E.; Kamel, R.; Thompson, W.E.; Badary, O.; Al-Hendy, A.; Yang, Q.; Yang, Q. Vitamin D3 Ameliorates DNA Damage Caused by Developmental Exposure to Endocrine Disruptors in the Uterine Myometrial Stem Cells of Eker Rats. Cells 2020, 9, 1459.

53. Xess, S.; Sahu, J. A study to correlate association between vitamin D with fibroid and its supplementation in the progression of the disease. Int. J. Reprod. Contracept. Obstet. Gynecol. 2020, 9, 1477–1481.

54. Sheng, B.; Song, Y.; Liu, Y.; Jiang, C.; Zhu, X. Association between vitamin D and uterine fibroids: A study protocol of an open-label, randomised controlled trial. BMJ Open 2020, 10, e038709.

55. Porcaro, G.; Santamaria, A.; Giordano, D.; Angelozzi, P. Vitamin D plus epigallocatechin gallate: A novel promising approach for uterine myomas. Eur. Rev. Med. Pharmacol. Sci. 2020, 24, 3344–3351.

56. Shen, Y.; Wu, Y.; Lu, Q.; Ren, M. Vegetarian diet and reduced uterine fibroids risk: A case-control study in Nanjing, China. J. Obstet. Gynaecol. Res. 2016, 42, 87–94.

57. Yılmaz, S.G.; Gul, T.; Attar, R.; Yıldırım, G.; Isbir, T. Association between fok1 polymorphism of vitamin D receptor gene with uterine leiomyoma in Turkish populations. J. Turk. Ger. Gynecol. Assoc. 2018, 19, 128–131.

58. Fazeli, E.; Piltan, S.; Gholami, M.; Akbari, M.; Falahati, Z.; Yassaee, F.; Sadeghi, H.; Mirfakhraie, R. CYP24A1 expression analysis in uterine leiomyoma regarding MED12 mutation profile. Arch. Gynecol. Obstet. 2021, 303, 787–792.

59. Zhang, D.; Al-Hendy, M.; Richard-Davis, G.; Montgomery-Rice, V.; Rajaratnam, V.; Al-Hendy, A. Antiproliferative and proapoptotic effects of epigallocatechin gallate on human leiomyoma cells. Fertil. Steril. 2010, 94, 1887–1893.

60. Zhang, N.; Rajaratnam, V.; Al-Hendy, O.; Halder, S.; Al-Hendy, A. Green Tea Extract Inhibition of Human Leiomyoma Cell Proliferation Is Mediated via Catechol- O -Methyltransferase. Gynecol. Obstet. Investig. 2014, 78, 109–118.

61. Zhang, D.; Al-Hendy, M.; Richard-Davis, G.; Montgomery-Rice, V.; Sharan, C.; Rajaratnam, V.; Khurana, A.; Al-Hendy, A. Green tea extract inhibits proliferation of uterine leiomyoma cells in vitro and in nude mice. Am. J. Obstet. Gynecol. 2010, 202, 289.e1–289.e9.

62. Ozercan, I.H.; Sahin, N.; Akdemir, F.; Onderci, M.; Seren, S.; Sahin, K.; Kucuk, O. Chemoprevention of fibroid tumors by -epigallocatechin-3-gallate in quail. Nutr. Res. 2008, 28, 92–97.

63. Al-Hendy, A.; Roshdy, E.; Rajaratnam, V.; Maitra, S.; Sabry, M.; Allah, A.S.A. Treatment of symptomatic uterine fibroids with green tea extract: A pilot randomized controlled clinical study. Int. J. Women's Health 2013, 5, 477–486.

64. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS); Younes, M.; Aggett, P.; Aguilar, F.; Crebelli, R.; Dusemund, B.; Filipič, M.; Frutos, M.J.; Galtier, P.; Gott, D.; et al. Scientific opinion on the safety of green tea catechins. EFSA J. 2018, 16, e05239.

65. Grandi, G.; Del Savio, M.C.; Melotti, C.; Feliciello, L.; Facchinetti, F. Vitamin D and green tea extracts for the treatment of uterine fibroids in late reproductive life: A pilot, prospective, daily-diary based study. Gynecol. Endocrinol. 2021, 38, 63–67.

66. Miriello, D.; Galanti, F.; Cignini, P.; Antonaci, D.; Schiavi, M.C.; Rago, R. Uterine fibroids treatment: Do we have new valid alternative? Experiencing the combination of vitamin D plus epigallocatechin gallate in childbearing age affected women. Eur. Rev. Med. Pharmacol. Sci. 2021, 25, 2843–2851.

67. Ahmed, R.S.I.; Liu, G.; Renzetti, A.; Farshi, P.; Yang, H.; Soave, C.; Saed, G.; El-Ghoneimy, A.A.; El Banna, H.; Foldes, R.; et al. Biological and Mechanistic Characterization of Novel Prodrugs of Green Tea Polyphenol Epigallocatechin Gallate Analogs in Human Leiomyoma Cell Lines. J. Cell. Biochem. 2016, 117, 2357–2369.
68. Biro, R.; Richter, R.; Ortiz, M.; Sehouli, J.; David, M. Effects of epigallocatechin gallate-enriched green tea extract capsules in uterine myomas: Results of an observational study. Arch. Gynecol. Obstet. 2021, 303, 1235–1243.
69. Hewlings, S.J.; Kalman, D.S. Curcumin: A Review of Its Effects on Human Health. Foods 2017, 6, 92.
70. Xu, X.-Y.; Meng, X.; Li, S.; Gan, R.-Y.; Li, Y.; Li, H.-B. Bioactivity, Health Benefits, and Related Molecular Mechanisms of Curcumin: Current Progress, Challenges, and Perspectives. Nutrients 2018, 10, 1553.
71. McCubrey, J.A.; Lertpiriyapong, K.; Steelman, L.S.; Abrams, S.L.; Yang, L.V.; Murata, R.M.; Rosalen, P.L.; Scalisi, A.; Neri, L.M.; Cocco, L.; et al. Effects of resveratrol, curcumin, berberine and other nutraceuticals on aging, cancer development, cancer stem cells and microRNAs. Aging 2017, 9, 1477–1536.
72. Malik, M.; Mendoza, M.; Payson, M.; Catherino, W.H. Curcumin, a nutritional supplement with antineoplastic activity, enhances leiomyoma cell apoptosis and decreases fibronectin expression. Fertil. Steril. 2009, 91, 2177–2184.
73. Tsuiji, K.; Takeda, T.; Li, B.; Wakabayashi, A.; Kondo, A.; Kimura, T.; Yaegashi, N. Inhibitory effect of curcumin on uterine leiomyoma cell proliferation. Gynecol. Endocrinol. 2011, 27, 512–517.
74. Feng, Y.; Zhao, Y.; Li, Y.; Peng, T.; Kuang, Y.; Shi, X.; Wang, G.; Peng, F.; Yu, C. Inhibition of Fibroblast Activation in Uterine Leiomyoma by Components of Rhizoma Curcumae and Rhizoma Sparganii. Front. Public Health 2021, 9, 650022.
75. Yu, C.H.; Zhao, J.S.; Zhao, H.; Peng, T.; Shen, D.C.; Xu, Q.X.; Li, Y.; Webb, R.C.; Wang, M.H.; Shi, X.M.; et al. Transcriptional profiling of uterine leiomyoma rats treated by a traditional herb pair, Curcumae rhizoma and Sparganii rhizoma. Braz. J. Med Biol. Res. 2019, 52, e8132.
76. Greco, S.; Islam, S.; Zannotti, A.; Carpini, G.D.; Giannubilo, S.R.; Ciavattini, A.; Petraglia, F.; Ciarmela, P. Quercetin and indole-3-carbinol inhibit extracellular matrix expression in human primary uterine leiomyoma cells. Reprod. Biomed. Online 2020, 40, 593–602.