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Use of dietary phytochemicals to target inflammation, fibrosis, proliferation, and angiogenesis in uterine tissues: Promising options for prevention and treatment of uterine fibroids?

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Abstract

Uterine leiomyomas (fibroids, myomas) are the most common benign tumors of female reproductive tract. They are highly prevalent, with 70–80% of women burdened by the end of their reproductive years. Fibroids are a leading cause of pelvic pain, abnormal vaginal bleeding, pressure on the bladder, miscarriage, and infertility. They are the leading indication for hysterectomy, and costs exceed 6 billion dollars annually in the United States. Unfortunately, no long-term medical treatments are available. Dysregulation of inflammatory processes are thought to be involved in the initiation of leiomyoma and extracellular matrix deposition, cell proliferation, and angiogenesis are the key cellular events implicated in leiomyoma growth. In modern pharmaceutical industries, dietary phytochemicals are used as source of new potential drugs for many kinds of tumors. Dietary phytochemicals may exert therapeutic effects by interfering with key cellular events of the tumorigenesis process. At present, a negligible number of phytochemicals have been tested as therapeutic agents against fibroids. In this context, our aim was to introduce some of the potential dietary phytochemicals that have shown anti-inflammatory, antiproliferative, antifibrotic, and antiangiogenic activities in different biological systems. This

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review could be useful to stimulate the evaluation of these phytochemicals as possible therapies for uterine fibroids.

Keywords

Antifibrotic; Antiproliferative; Dietary phytochemicals; Inflammation; Uterine fibroid

1 Introduction

Uterine leiomyomas (fibroids or myomas) are common benign smooth muscle tumors of the uterus [1–3]. They are highly prevalent, with 70–80% of women burdened by the end of their reproductive years [4]. Several studies have demonstrated that there are ethnic differences in fibroid burden [4–9]. African Americans have a higher (three times more) fibroid incidence [4, 5] and experience more severe symptoms with larger and more numerous leiomyomas compared with white women [6, 9]. The common symptoms associated with uterine leiomyomas are irregular and/or heavy menstrual bleeding, pain in the pelvic region and the back, bulk-related symptoms (pressure on bladder and bowel as well as increase in abdominal circumference), and subfertility [4, 10]. Uterine fibroids are the leading indication for hysterectomy in the United States [11], and fibroid associated costs $5.9– 34.4 billion annually [12]. This complicated disease process also exerts an enormous burden on health care resources in Australia [13] and European countries [14].

Despite the widespread prevalence of the disease, the pathogenesis of leiomyomas is not well understood. An increasingly popular view is that uterine leiomyoma arise as a consequence of a chronically active inflammatory immune system [15–17]. However, there is considerable evidence that estrogens and progestogens promote tumor growth [18, 19], as the fibroids rarely appear before menarche and tend to regress after menopause [20]. Besides growth factors, cytokines and chemokines may serve as mediators of sex steroids, and play an important role in the proliferation, fibrosis, and angiogenesis processes that are ultimately involved in the formation and growth of uterine fibroids [1, 2, 10, 17, 21].

Gonadotropin-releasing hormone agonist (GnRHa) is only medical therapy for leiomyoma treatment approved by US Food and Drug Administration. GnRHa was developed on the basis of the induction of a hypoestrogenic state. Although this treatment temporally (up to 6 months) is effective as preoperative therapy to reduce fibroid size and symptoms [22, 23], the benefits of GnRHa are tempered by significant side effects resulting from hypoestrogenism (e.g., hot flashes, vaginal dryness, bone demineralization) [24–26]. In addition to GnRHa, several potential therapies such as mifepristone (antiprogestin) [27], and selective progesterone receptor modulators such as asoprisnil [28], ulipristal acetate [29, 30], and proellex [31] have shown excellent therapeutic efficiency during the course of clinical trials. Additionally, aromatase inhibitors have shown therapeutic efficacy for uterine fibroids, but are not approved for that indication. Nonetheless, in comparison with the burden of disease to society, medical treatments for leiomyoma are still very limited and no preventative therapies have been developed.

Since ancient times, plants and plant-derived compounds have provided tremendous support in the traditional medicine systems, and have been used as source of new potential drugs in modern pharmaceutical industries. For example, from 1981 to 2010, natural products and their derivatives were the source of 41% of new drugs and 79.8% of all approved anticancer drugs [32]. In addition, the percentage of drugs from natural products without derivatives was greatly increased from 20.8% in 2009 to 50% in 2010 [32]. Recently, two systematic reviews assessed the efficacy of herbal preparations for uterine fibroids [33, 34]. Meta-analyses demonstrated that Guizhi Fuling Formula plus mifepristone were more effective than mifepristone alone in reducing the volume of fibroids [33]. In addition, the Guizhi Fuling Formula significantly improved symptoms of dysmenorrhea either when it was used alone or in combination with mifepristone [33].

At present, only few dietary phytochemicals such as epigallocatechin gallate (EGCG) [35, 36], curcumin [37], isoliquiritigenin [38], genistein [39], and resveratrol [40, 41] (Table 1) have been studied in myometrium and fibroids. A large number of phytochemicals remain to be tested for possible therapeutic effects against uterine leiomyoma. In this review, we introduce some of the more promising phytochemicals (Figs. 1 and 2) in the context of key features of leiomyoma development and growth: inflammation, fibrosis, cell proliferation, and angiogenesis.

2 Pathogenesis of uterine fibroids

2.1 Inflammatory mediators

Considerable evidence suggests that uterine leiomyoma development may be triggered, at least in part, by a chronically active inflammatory immune system [15–17]. The concept of inflammation actually fits into a theory of fibroid development based on an altered response to noxious stimuli; possibly tissue injury from extravasated menstrual blood into the myometrium, or hypoxia leading to altered tissue repair and fibrosis [15, 16]. Among major cytokines, the expression of IL-1, IL-6, IL-11, IL-13, IL-15, IL-33, tumor necrosis factor (TNF)-α, granulocyte-macrophage colony-stimulating factor have been implicated with their biological relevance to leiomyoma pathophysiology [42–47]. The expression profiles of many chemokines and chemokine receptors have also been characterized in leiomyomas and matched myometrium. These include monocyte chemoattractant protein (MCP)-1, IL-8, IL-8 receptor type A, macrophage inflammatory protein (MIP)-1α, MIP-1β, RANTES, eotaxin, eotaxin-2, IL-8, chemokine (cc-motif) receptor (CCR) 1, CCR3, CCR5, chemokine (cxc-motif) receptor (CXCR) 1, and CXCR2 mRNA [48–50]. Furthermore, inflammatory mediators such as cyclooxygenase-2 (COX-2) [51] and nitric oxide (NO) [52] have been implicated in myometrial pathophysiology. The involvement of nuclear factor kappa light chain enhancer of activated B cells (NF-κB) dependent inflammatory pathway has been documented in leiomyoma cells, as EGCG was reported to significantly decrease the expression of NF-κB-dependent pathway genes such as proliferating cell nuclear antigen (PCNA), cyclin-dependent kinase 4, and B-cell lymphoma 2 as well as increase the expression of the proapoptotic B-cell lymphoma 2 associated X in a dose-dependent manner [35]. The above information supports the tenet that the inflammatory response may play an

important role to initiate the development of uterine fibroids. Therefore, anti-inflammatory agents could represent pharmacological targets for fibroids.

2.2 Fibrosis

Fibrosis is a pathological feature of many chronic inflammatory diseases. It is defined by the accumulation of excess extracellular matrix (ECM) components. Uterine leiomyomas are typically considered as a fibrotic disorder as they contain 50% more ECM than the corresponding myometrium [53]. The ECM of leiomyomas consists primarily of collagen, fibronectin, and proteoglycans [21, 54–57]. The abnormal ECM structure and orientation found in leiomyomas [21, 54], and alterations in ECM modifies mechanical stresses on resident cells, which leads to activation of internal mechanical signaling and may contribute to leiomyoma growth [58, 59]. The inhibition of fibrosis is a big challenge to control this tumor; therefore, the development of novel antifibrotic agents could represent a tractable approach for medical therapy. Two growth factors from the transforming growth factor-β (TGF-β) superfamily are known to be involved in the accumulation of ECM in leiomyoma. TGF-β increases fibronectin mRNA expression in both myometrial [60] and leiomyoma cells [55, 60]. TGF-β also increases collagen 1A1 [60] and versican [57] mRNA expression in myometrial and leiomyoma cells. Recently, our group demonstrated that activin-A increased fibronectin, collagen 1A1, and versican expression in leiomyoma cells [61]. Furthermore, platelet-derived growth factor (PDGF) also reported to increase collagen α1 (I) in both leiomyoma and myometrial cells [62]. The overproduced ECM itself may play a dynamic role in the metabolic processes leading to tumor growth, by influencing cellular proliferation and differentiation and by serving as a repository for biologically active growth factors, cytokines, chemokines, angiogenic and inflammatory response mediators, and proteases produced by tumor cells.

2.3 Cell proliferation

At least one mechanism responsible for leiomyomas undergoing extensive enlargement is the increased rate of cell proliferation. Uterine cellular proliferation and differentiation are regulated by sex steroids, estrogen, and progesterone. Estrogen has traditionally been identified as the most important sex steroid for fibroid growth; however, progesterone seems to have the dominant steroidal influence on fibroids. This dominance is supported by the increased mitotic rates in fibroids during the secretory phase of the menstrual cycle [63]. There is growing evidence that signaling pathways are directly activated by estrogen and progesterone receptors, and these pathways can also interact with growth factors, cytokines, and chemokine signaling systems to promote proliferation of leiomyomas. Several growth factors such as epidermal growth factor (EGF), heparin-binding EGF, insulin-like growth factor (IGF), and PDGF have been identified, which are responsible for increasing myometrial and/or leiomyoma cell proliferation by activating various signaling pathways [1]. TGF-β exerts bimodal effects on cell proliferation and induces proliferation of cells at low concentrations by stimulating autocrine PDGF secretion, whereas it induces the opposite effect at higher concentrations via downregulation of the PDGF receptor (PDGFR) and by direct growth inhibition [64, 65]. Activin-A and myostatin have cytostatic effects in myometrial cells, but they do not have an antiproliferative effect in leiomyoma cells [61]. Oxidative stress has been shown to be an important player in uterine fibroids [66–68].

Fibroid cells are characterized by a unique nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX, a major source of superoxide and subsequent oxidative stress) profile. Expression of NOX4 increased in fibroid compared to myometrial tissues and cells [66]. In addition, fibroid cells are reported to have significantly lower antioxidant enzymes, superoxide dismutase, and catalase mRNA levels than normal myometrial cells [68]. Furthermore, NOX-derived reactive oxygen species (ROS) have been shown to be a critical component of the mitogen-activated protein kinase (MAPK) pathway of EGF and PDGF signaling in leiomyoma smooth muscle cell (SMC) proliferation [67]. A recent study reported that adipocytes can enhance the proliferation of human leiomyoma cells via TNF-α proinflammatory cytokine [69]. Therefore, an antiproliferative agent could also be useful for the treatment of this tumor.

2.4 Angiogenesis

Angiogenesis plays a critical role in physiological conditions such as embryonic development, reproduction, tissue repair, and bone remodeling. In contrast, angiogenesis is an important event for pathologic processes including primary tumor growth, invasion, and metastases [70, 71]. Angiogenesis is a multistep cellular process that involves endothelial cell (EC) proliferation, migration, tube formation, and ECM degradation [72]. It has been suggested that angiogenesis may play an important role in the regulation of leiomyoma growth [73, 74]. Multiple growth factors involved in angiogenesis are differentially expressed in leiomyoma compared with myometrium. These include vascular endothelial growth factor (VEGF), EGF, heparin-binding EGF, basic fibroblast growth factor, PDGF, activin-A, TGF-β, and adrenomedullin [74, 75]. Therefore, targeting angiogenic growth factors and growth factor receptors to block angiogenesis could represent an attractive therapeutic approach for fibroid treatment.

3 Dietary phytochemicals that have been studied in uterine fibroids

3.1 Epigallocatechin gallate

Dietary sources—EGCG is the ester of epigallocatechin and gallic acid, and is a type of catechin. Mostly, it is found in green tea [*Camellia sinensis* (L.) Kuntze] [76].

Therapeutic effects—EGCG inhibited the proliferation of human leiomyoma cells and induced apoptosis [35]. EGCG also effectively inhibited proliferation and induced apoptosis in rat ELT-3 (Eker rat-derived uterine leiomyoma cell lines) uterine leiomyoma cells in vitro and in vivo [77]. Interestingly, EGCG dramatically reduced the volume and weight of tumors of female mice (implanted with fibroid tumor cells) at 4 and 8 weeks after the treatment compared to control [77]. Furthermore, it has been reported that dietary supplementation with EGCG reduced the incidence and size of spontaneously occurring leiomyoma of the oviduct in Japanese quail [78]. Recently, a double-blinded, placebo-controlled randomized clinical trial reported that green tea extract (800 mg/day) treatment significantly reduced uterine fibroid volume, fibroid-specific symptom severity, and induced significant improvement in health-related quality of life in premenopausal women compared to the placebo group [36]. In addition, no adverse effects, endometrial hyperplasia, or other endometrial pathology were observed in both group [36].

3.2 Curcumin

Dietary sources—Curcumin is a polyphenol (bis-α, β-unsaturated β-diketone, commonly called diferuloyl-methane) derived from the rhizome of turmeric (*Curcuma longa* L.) [79].

Therapeutic effects—Curcumin has shown antiproliferative and antifibrotic effects on leiomyoma cells. Experimental data showed that curcumin inhibits uterine leiomyoma cell proliferation via regulation of apoptotic pathway [37]. Importantly, no statistically significant inhibition of growth was observed when patient-matched myometrial cells were exposed to equivalent concentrations of curcumin [37]. Furthermore, curcumin also inhibited expression of fibronectin in leiomyoma cells [37]. Tsuiji and colleagues demonstrated that curcumin significantly inhibited ELT-3 cell proliferation and the authors also found peroxisome proliferator-activated receptor gamma (PPARγ) was expressed in ELT-3 cells and that curcumin acted as a PPARγ ligand. The inhibitory effect of curcumin was attenuated by the treatment of cells with a PPARγ antagonist [80].

3.3 Isoliquiritigenin

Dietary sources—Isoliquiritigenin (4,2′,4′-trihydroxychalcone) is a calchone flavonoid found in licorice (*Glycyrrhiza uralensis*), shallot (*Allium ascalonicum*), and soybean (*Glycine max*) [81].

Therapeutic effects—Isoliquiritigenin has been reported to induce the growth inhibition and apoptosis in human uterine leiomyoma cells [38].

3.4 Genistein

Dietary sources—Genistein (5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one) is an isoflavone found in soybeans (*G. max*), lupine (*Lupinus* spp.), fava bean (*Vicia faba*), kudzu (*Pueraria lobata*), and psoralea (*Psoralea corylifolia*) [82].

Therapeutic effects—Stimulatory and inhibitory effects of genistein on human uterine leiomyoma cell proliferation have been reported [83, 84]. Lower concentrations (≤1 μg/mL) of genistein stimulated proliferation, increased PCNA labeling and the percentage of cells in the S-phase, but this did not occur in uterine SMCs [83]. The stimulatory effect of genistein was possibly mediated by interacting with estrogen receptor-α and IGF-IR [84]. On the other hand, higher concentrations (≥10 μg/mL) of genistein adversely affected the morphology, significantly inhibited proliferation, decreased PCNA labeling, and increased caspase activity and apoptosis in both myometrial and leiomyoma cells [83]. Later, Di and colleagues reported that genistein at more high concentration (50 μg/mL) also downregulated activin A, Smad3, and other TGF-β pathway genes in human uterine leiomyoma cells [84, 85]. Furthermore, it was reported that dietary supplementation (400 or 800 mg of genistein/kg) of genistein reduced the incidence and size of spontaneously occurring leiomyoma of the oviduct in the Japanese quail [86].

3.5 Resveratrol

Dietary sources—Resveratrol (RVS; trans-3,4′,5-trihydroxystilbene) is a polyphenolic phytoalexin produced in plants in response to environmental stress and infection by pathogenic microorganisms. It is found in more than 70 species of plants, including mulberries and peanuts. Grapevines (*Vitis vinifera*) are the main sources of resveratrol [87].

Therapeutic effects—Resveratrol has shown antiproliferative and antifibrotic effects on leiomyoma cells. Experimental data showed that resveratrol inhibits proliferation, induces apoptosis and cell cycle arrest in human uterine leiomyoma cells in vitro [40, 41]. In addition, resveratrol treatment reduced mRNA and protein expression of collagen types I and III in a dose-dependent manner in human uterine leiomyoma cells [40, 41].

4 Dietary phytochemicals of possible benefit for uterine fibroids

4.1 Allicin

Dietary sources—Allicin (diallylthiosulphinate) is an organosulfur compound obtained from garlic (*Allium sativum* L.), a species in the family Alliaceae [88].

Anti-inflammatory effect—Allicin has been shown to inhibit the TNF-α induced expression of NO and H_2O_2 in the human umbilical ECs [89]. Similarly, allicin inhibited spontaneous and TNF-α induced secretion of cytokines and chemokines IL-1β, IL-8 from intestinal epithelial cells [90]. Allicin alleviated inflammatory injury in the spine, possibly via a reduction in secretion of inflammatory factors (IL-6, IL-8, and TNF-α) in a murine model of ankylosing spondylitis [91].

Antifibrotic effect—Allicin protected against cardiac hypertrophy and fibrosis via attenuation of ROS-dependent signaling pathways [92], and through enhancement of Nrf2 antioxidant signaling pathways [93]. Allicin also protected against myocardial fibrosis in streptozotocin-induced diabetic rats by blocking the expression of connective tissue growth factor (CTGF) and TGF-β1 protein [94].

Antiproliferative effect—Allicin has been reported to induce caspase-mediated apoptosis in cervical cancer cells [95]. Allicin also induced apoptosis in gastric cancer cells [96], murine T-lymphocytes [97], colon cancer cells via nuclear factor erythroid 2 related factor 2 (Nrf2) [98], and in human glioblastoma cells through an extracellular signal-regulated kinase (ERK) dependent pathway [99]. Growth inhibition of breast cancer cells by allicin was accompanied by accumulation of cells in the G0/G1 and G2/M phases of the cell cycle [100].

Antiangiogenic effect—Allicin reduced angiogenesis in the aortic ring model as well as basic stages of vessel growth including ECs proliferation and tube formation. These effects were accompanied by downregulation of intracellular actin polymerization and protein kinase B (PKB/AKT) phosphorylation [101].

4.2 Ellagic acid

Dietary sources—Ellagic acid (EA; 2,3,7,8-tetrahydroxychromeno[5,4,3-cde]chromene-5,10-dione) is a polyphenol compound, found in many berries including strawberries, raspberries, cranberries, blackberries, pecans, pomegranates, walnuts, wolfberry, and grapes [102].

Anti-inflammatory effect—EA has been shown to downregulate inflammatory mediators such as IL-1β, IL-6, TNF-α, and MCP-1 mRNA expression in diabetic mice [103]. Additionally, EA decreased COX-2, inducible nitric oxide synthase (iNOS), TNF-α, IL-6, and NF-κB expression in 1,2-dimethylhydrazine-induced colon carcinogenesis [104]. EA also inhibited LPS-induced expression of enzymes COX-2, microsomal prostaglandin E (PGE) synthase-1, and cytosolic phospholipase $A_{2\alpha}$ involved in the synthesis of PGE2 in human monocytes [105]. In the chronic ulcerative colitis model, EA reduced intestinal inflammation, and downregulated COX-2 and iNOS and blocked signaling pathways such as p38 MAPK, NF-κB, and signal transducer and activator of transcription 3 [106].

Antifibrotic effect—EA protected against carbon tetrachloride-induced liver fibrosis [107] and ischemia/reperfusion-induced gastric injury [108]. EA has also been reported to block transformation of pancreatic stellate cells (PSCs) to an activated, myofibroblast-like phenotype. EA inhibited expression of α-smooth muscle actin (α-SMA) and collagen genes, and activation of AP-1 and MAPKs [(ERK, c-Jun N-terminal kinase, and p38 MAPK] in PSCs [109]. Suzuki et al. also reported that EA attenuated pancreatic fibrosis by decreasing collagen content, TGF-β1 expression, and the number of α-SMA-positive cells (activated PSCs) [110].

Antiproliferative effect—EA inhibited PDGF-BB-induced PSCs proliferation [109] and proliferation of primary cultures of rat aortic SMCs [111]. The antiproliferative effect of EA was also mediated by the induction of cell cycle arrest and/or apoptosis in many cancer cell types, including cervical carcinoma cells [112], pancreatic cancer cells [113], ovarian carcinoma cells [114], colon, breast, and prostatic cancer cells [115], and oral carcinoma cells [116]. EA inhibited bladder cancer cell proliferation via p38-MAPK and/or c-Jun medicated caspase-3 activation [117].

Antiangiogenic effect—EA inhibited VEGF-induced phosphorylation of VEGF receptor (VEGFR)-2 in ECs as well as PDGF-induced phosphorylation of PDGFR in SMCs. EA also inhibited VEGF-induced migration of ECs as well as their differentiation into capillary-like tubular structures and abolished PDGF-dependent SMCs migration [118]. EA exerted antiangiogenesis effects via a VEGFR-2 signaling pathway in breast cancer [119]. EA inhibited a series of VEGF-induced angiogenesis processes including proliferation, migration, and tube formation of ECs, and directly inhibited VEGFR-2 tyrosine kinase activity and its downstream signaling pathways, including MAPK and phosphoinositide 3-kinase (PI3K)/AKT in ECs [119].

4.3 Indole-3-carbinol

Dietary sources—Indole-3-carbinol (I3C; 1H-indol-3-ylmethanol) is found in cruciferous vegetables such as broccoli, cabbage, cauliflower, brussels sprouts, bok choy, collard greens, mustard greens, kale, Chinese cabbage, radishes, turnips, kohirabi, arugula, watercress, and daikon [120].

Anti-inflammatory effect—I3C has been shown to be an inhibitor of NF-κB and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (IκBα) kinase activation [121]. I3C also suppressed the production of proinflammatory mediators including TNF-α, IL-1β, IL-6, IL-12, and NO, but increased IL-10 levels in LPS-activated dendritic cells [122]. In addition, I3C suppressed the production of proinflammatory mediators (such as IL-6, IL-1β, TNF-α, IL-10, iNOS, and NO) in macrophages [123–125].

Antifibrotic effect—I3C inhibited hepatic stellate cells proliferation (with or without PDGF-BB stimulation) by blocking the NADPH oxidase/ROS/p38 MAPK pathway. The expression of α-SMA, levels of type I collagen, NOX activity, and ROS were decreased by I3C in this cell type [126].

Antiproliferative effect—I3C inhibited PDGF-BB-induced proliferation of vascular SMCs (VSMCs) by inducing an arrest of cells in both the G0/G1 and S phases [127]. I3C was also reported to suppress the proliferation of a wide variety of tumor cells, including breast [128], prostate [129], colon [130], lung [131], and leukemia [121] by inducing apoptosis and cell cycle arrest.

Antiangiogenic effect—I3C suppressed angiogenesis by inhibiting tube formation and VEGF secretion in ECs [132] and, at least in part, via inactivation of ERK1/2 in human umbilical vein ECs (HUVECs) [133]. Antiangiogenic activity of I3C in ECs stimulated with activated macrophages has also been reported [134].

4.4 Lycopene

Dietary sources—Lycopene is a carotenoid compound naturally found in tomato, watermelon, papaya, pink guava, pink grapefruit, and apricots [135].

Anti-inflammatory effect—Lycopene attenuated LPS-induced TNF-α secretion in macrophages [136] and inhibited NF-κB-mediated IL-8 expression in cigarette smoke-stimulated macrophages [137]. Lycopene also inhibited proinflammatory cytokines (MCP-1, IL-6), and activation Toll-like receptor 4 and its downstream ERK and the NF-κB signaling pathway in HUVECs [138].

Antifibrotic effect—Lycopene inhibited bleomycin-induced pulmonary fibrosis in rats [139], oral submucous [140], and liver fibrosis [141]. It improved cardiac function and myocardial fibrosis after acute myocardial infarction in rats via the modulation of p38 and matrix metalloproteinase (MMP)-9 [142].

Antiproliferative effect—Lycopene has been found to inhibit proliferation of several types of cancer cells by modulating growth factor mediated signaling pathways, inducing apoptosis, and arresting cell cycle. Lycopene suppressed IGF-I-stimulated growth of mammary cancer cells [143]. Similarly, lycopene inhibited PDGF-BB-induced proliferation of SMCs, and markedly inhibited PDGF-BB-induced PDGFR-β, phospholipase C-γ, and ERK1/2 phosphorylation in rat SMCs and primary cultured aortic SMCs [144]. The antiproliferative effect of lycopene in several cancer cells such as human hepatoma Hep3B cells [145], breast and endometrial cancer cells [146], prostate carcinoma cells [147], and colon adenocarcinoma cells [148] are mediated by inducing cell cycle arrest and apoptosis.

Antiangiogenic effect—An inhibitory effect of lycopene on proangiogenic agents, VEGF and TNF-α in HUVEC and rat aortic rings has been reported [149]. Lycopene may inhibit angiogenesis by inhibiting MMP-2 and the urokinase plasminogen activator system through the inhibition of VEGFR2-mediated PI3K-AKT and ERK/p38 signaling pathways [150]. High doses of lycopene reduced tumor growth in nude mice xenotransplanted with the prostate carcinoma cells, partly by decreasing the circulating levels of VEGF [151].

4.5 Quercetin

Dietary sources—Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a flavonol present in tea, lemon, tomato [152], onion leaves [153], and strawberries [154].

Anti-inflammatory effect—Quercetin attenuated TNF-induced inflammation in hepatic cells by inhibition of the NF-κB signaling pathway [155]. The inhibitory action of quercetin on the MIP-1α-induced inflammatory responses of macrophages was mediated by downregulation of CCR1/CCR5, and inhibition of activation of c-Jun N-terminal kinase, p38 MAPK, and IkB kinase, as well as IκBα degradation [156]. Quercetin also inhibited LPS-induced NO, PGE2, iNOS, COX-2, TNF-α, IL-1β, IL-6, and granulocyte-macrophage colony-stimulating factor mRNA and protein expression in macrophage cells [157]. Quercetin has been shown to inhibit IL-1β-induced production of MMPs, COX-2, and PGE2 by rheumatoid synovial fibroblast [158], and IL-6 and IL-8 mRNA expression in Graves' orbitopathy orbital fibroblasts [159]. Quercetin was also effective in attenuating TNF-α-mediated inflammation and insulin resistance in primary human adipocytes. It attenuated TNF-α-induced expression of inflammatory genes, such as IL-6, IL-1β, IL-8, and MCP-1 and the secretion of IL-6, IL-8, and MCP-1 [160].

Antifibrotic effect—Quercetin possessed antifibrotic properties in hepatic fibrosis [161], pulmonary fibrosis [162], kidney fibroblasts [163]. It suppressed TGF-β-induced collagen production in lung fibroblasts by quercetin-induced heme oxygenase-1 [164]. Additionally, quercetin improved hepatic fibrosis through induction of hematopoietic stem cells apoptosis and downregulation of profibrotic molecules such as TGF-β, collagen 1α, and CTGF [165]. In isoproterenol-treated myocardial tissues, quercetin reduced the overexpression of TGF-β1, CTGF, and excessive deposition of ECM [166]. Quercetin exhibited strong inhibitory effects on collagen and fibronectin production in vitro [167, 168], and TGF-β/Smad-signaling pathway in keloid fibroblasts. Quercetin was shown to improve liver histology and reduce collagen content in rats with carbon tetrachloride-induced cirrhosis in vivo [169].

Antiproliferative effect—Quercetin has been shown to inhibit TGF-α and EGF-induced human prostate cancer cell proliferation [170]. Similarly, quercetin suppressed IGF-1-induced phosphorylation of IGF-1R, insulin receptor substrate-1, AKT, and S6K, and inhibited IGF-1-stimulated proliferation of mouse skin cancer cells [171]. The antiproliferative effect of quercetin was also mediated by induction of apoptosis and/or cell cycle arrest via modulation of multiple signaling pathways [AMP-activated protein kinase, NF-κB, and signal transducer and activator of transcription] in wide variety of cancer cells. These include lung cancer cells [172], breast cancer cells [173], colon cancer cells [174], melanoma cells [175], and chronic lymphocytic leukemia cells [176].

Antiangiogenic effect—Quercetin regulated angiogenesis by downregulating hypoxia-inducible factor 1α and VEGF expression in Dalton's lymphoma ascites induced solid tumors [177]. In HUVECs, quercetin inhibited the expression of VEGFR-2 and tube formation, and suppressed the ERK signaling pathway [178]. Quercetin also inhibited angiogenesis mediated human prostate tumor growth by targeting VEGFR-2 regulated AKT/mTOR/P70S6K signaling pathways [179]. Furthermore, quercetin was shown to reduce VEGF levels in leukemia cells [180], human ovarian cancer cells [181], and swine granulosa cells [182].

4.6 Sulforaphane

Dietary sources—Sulforaphone (SFN; 1-isothiocyanato-4-methylsulfinylbutane) is an isothiocyanate derived from cruciferous vegetables and is found in especially high levels in broccoli and broccoli sprouts [183]. It is also found in brussels sprouts, cabbage, cauliflower, collard greens, kale, kohlrabi, mustard, rutabaga, turnips, bok choy, and Chinese cabbage [184].

Anti-inflammatory effect—SFN exhibited anti-inflammatory activity by downregulation of iNOS, COX-2, TNF-α, and NF-κB expression in LPS-activated macrophages [185]. SFN suppressed LPS-induced inflammation via Nrf2-dependent pathway in mouse peritoneal macrophages [186]. Also, SFN attenuated inflammation in oxyhemoglobin-induced rat VSMCs by enhancing the activity of the Nrf2-ARE pathway [187].

Antifibrotic effect—SFN attenuated hepatic fibrosis through Nrf2-mediated inhibition of TGF-β/Smad signaling following suppression of hepatic stellate cell activation and fibrogenic gene expression, such as type-I collagen, fibronectin, tissue inhibitor of metalloproteinase-1, and plasminogen activator inhibitor 1 [188]. SFN also prevented diabetes-induced cardiac fibrosis by reducing accumulation of collagen and expression of both CTGF and TGF-β [189]. SFN induced dedifferentiation of human pulmonary fibroblast in vitro from idiopathic pulmonary fibrosis patients via Nrf2 activation, and inhibited TGF-β profibrotic effects in idiopathic pulmonary fibrosis and control fibroblasts [190].

Antiproliferative effect—SFN has been shown to inhibit PDGF-induced proliferation of rat aortic VSMCs via upregulation of p53 leading to G1/S cell cycle arrest [191]. SFN was also reported to induce cell cycle arrest and/or apoptosis in various human cancers cells

including breast cancer [192], prostate cancer [193], hepatic cancer [194], colon cancer [195], and bladder cancer cells [196].

Antiangiogenic effect—SFN showed antiangiogenic properties by inhibition of hypoxia-induced mRNA expression of VEGF and two angiogenesis-associated transcription factors, HIP-1α and c-Myc, as well as the expression of the VEGFR-1/2 in HMEC-1 (an immortalized human microvascular EC line) [197]. SFN disrupted microtubule polymerization and prevented mitotic cell cycle progression in bovine aortic ECs and suppressed VEGF-stimulated angiogenesis within Matrigel implants in vivo [198]. Further, SNF inhibited angiogenesis through regulation of forkhead box O transcription factor induced by the inhibition MEK/ERK and PI3K/AKT pathways leading to suppression of cell migration and capillary tube formation in HUVECs [199].

4.7 Ursolic acid

Dietary sources—Ursolic acid (UA; 3-beta-3-hydroxy-urs-12-ene-28-oic-acid, 3-β-hydroxy-urs-12-en-28-oic acid) is a pentacyclic triterpene acid found in apples, basil, cranberries, peppermint, rosemary, oregano, and prunes [200].

Anti-inflammatory effect—UA has been shown to inhibit NF-κB activation [201]. In addition, UA attenuated d-galactose-induced inflammatory response in the mouse prefrontal cortex by downregulation of iNOS and COX-2 expression, and IL-1β, IL-6, and TNF-α level [202]. UA also attenuated LPS-induced cognitive deficits in the mouse by downregulation of proinflammatory markers including COX-2, iNOS, TNF-α, IL-1β, IL-2, and IL-6 production through suppression of p38/NF-κB-mediated inflammatory pathways [203]. Furthermore, UA suppressed ovalbumin-induced airway inflammation by downregulating IL-5, IL-13, and IL-17 in a murine model of allergic asthma [204].

Antifibrotic effect—UA reduced the development of fibrosis (collagen) in the myocardium of diabetic mice through partial inhibition of TGF-β1 expression [205]. UA ameliorated hepatic fibrosis, most likely through specific induction of apoptosis in activated hematopoietic stem cells [206].

Antiproliferative effect—UA has been shown to be an inhibitor of EGF receptor that eventually limits EGF-mediated breast cancer proliferation [207]. UA also suppressed proliferation and induced apoptosis and/or cell cycle arrest in wide variety of cancers such as colon cancer [208], ovarian cancer [209], prostate cancer [210], nonsmall cell lung cancer [211], gastric cancer, liver cancer [212], cervical cancer [213], pancreatic cancer [214], and bladder cancer [215], through modulating multiple signaling pathways (AKT/ERK, COX-2/PGE2, p300/NF-κB/CAMP response element-binding protein 2, and cytochrome c).

Antiangiogenic effect—UA inhibited key steps of angiogenesis in vitro, including EC proliferation, migration, and differentiation [216]. UA also inhibited tumor angiogenesis by the downregulation of VEGF in an Ehrlich ascites carcinoma tumor [217], VEGF-A and basic fibroblast growth factor in colorectal cancer [218], and VEGF in melanoma cells [219].

5 Concluding remarks

Uterine fibroids are extremely common benign tumors, and the condition exacts a significant morbidity on the health of women. Unfortunately, few medical treatments are available for this condition. In this context, dietary phytochemicals could play an important role in the new drug development for leiomyoma treatment. Currently, only EGCG [35], cur-cumin [37], isoliquiritigenin [38], genistein [39], and resveratrol [40, 41] (Table 1) have been tested for therapeutic efficacy for fibroids. Among these, EGCG has shown excellent efficiency to reduce leiomyoma cells proliferation in vitro [35], and to reduce the volume and weight of tumors of female mice (implanted with fibroid tumor cells in vivo [77]). A double-blinded, placebo-controlled randomized clinical trial has shown that green tea extract treatment significantly reduced uterine fibroid volume, fibroid-specific symptom severity, and induced significant improvement in health-related quality of life in premenopausal women compared to the placebo group [36]. In addition, in a case-control study of Italian women, it was shown that the risk of uterine leiomyoma was inversely associated with the intake of green vegetables and fruit [220]. Furthermore, in a prospective cohort study, investigators found that a high intake of fruit, particularly citrus fruit, was inversely associated with uterine fibroids risk among black women [221]. Therefore, considering the key characteristics of leiomyoma development and growth, inflammation, fibrosis, proliferation, and angiogenesis, our aim was to introduce some promising dietary phytochemicals (allicin, EA, I3C, lycopene, quercetin, sulforaphane, and UA) (Fig. 1) that have already shown multiple therapeutic effects in different biological conditions. Throughout this manuscript, we introduced and emphasized the enormous potential of dietary phytochemicals as possible effective therapeutic agents through (i) inhibition of inflammatory mediators; (ii) inhibition of fibrosis by decreasing ECM deposition, profibrotic growth factors expression, inactivation of activated cell types (responsible for myofibroblastic transformation); (iii) inhibition of cell proliferation via the activation of the apoptotic pathway and cell cycle arrest, as well as through inhibition of growth factors and/or their receptors; and (iv) inhibition of angiogenesis by reducing angiogenic growth factors/receptors and angiogenesis-related transcription factors. Based on the available evidence, these compounds modulate and regulate the key biological processes involved in leiomyoma development and growth (Fig. 2). Alone, these phytochemicals are promising, but it is also possible that in combination the therapeutic effects could be additive and the magnitude of the effect could translate to a significant clinical therapy. Lastly, further study of these promising compounds might lead to development of strategies to prevent the condition in women at risk for this extremely common, but debilitating disease.

In this review, dietary phytochemicals have been shown as tumor-fighting weapons. However, greater attention is needed to clarify the following important issues. (i) Poor potency and bioavailability of dietary phytochemicals creates challenges to scientists. However, introducing synthetic analogs of dietary phytochemicals could be a solution for these potency and bioavailability limitations. For example, the potency of synthetic curcumin analog EF24 was shown to be approximately tenfold greater than that of natural curcumin [222]. (ii) Instability of dietary phytochemicals is often associated with pH and/or enzyme-mediated degradation in the upper gut. These can be overcome by formulation

approaches such as enteric coating. A major stability factor that is often overlooked is the effect of microbiota in the gastrointestinal tract. The stability of a drug to the microbiota is clinically relevant as drug metabolism can render a drug pharmacologically active, inactive, or toxic. An important example of the significance of metabolism was seen in Japan in 1993 when sorivudine, a promising antiviral drug was introduced into the Japanese market. This was later discovered to be transformed by gut microbiota into (E)-5-(2-bromovinyl)uracil, which can inhibit the metabolism of the anticancer drug 5-fluorouracil leading to toxic levels of this drug [223]. (iii) Although most studies have suggested that dietary phytochemicals kill tumor cells selectively, phytochemicals may have similar effect on normal cells as well [224]. (iv) In many cases, the chemopreventive effects of dietary phytochemicals in cultured cells or tissues are only achievable at supraphysiological concentrations. Such concentrations might not be attained when the phytochemicals are administered as part of diet. (v) The efficacy of most dietary phytochemicals has been tested only in preclinical conditions, either in vitro or in vivo. However, the beneficial effects of dietary phytochemicals in humans are largely unknown. Based on the above facts, it is clear that there is huge need to better understand the efficacy of dietary phytochemicals in the prevention and treatment of uterine fibroids. Future studies should focus on careful and accurate characterization of dietary phytochemicals, better elucidation of the molecular mechanisms involved in their actions, determination of their efficacy by in vivo studies using proper animal models of uterine fibroids, and demonstration of their safety and effectiveness in clinical trials.

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Abbreviations

AKT/PKB	protein kinase **B**
α-SMA	α-smooth muscle actin
CCR	chemokine (cc-motif) receptor
COX-2	cyclooxygenase-2
CTGF	connective tissue growth factor
CXCR	chemokine (cxc-motif) receptor
EA	ellagic acid
ECM	extracellular matrix
ECs	endothelial cells
EGCG	epigallocatechin gallate
EGF	epidermal growth factor
ERK	extracellular signal-regulated kinase
GnRHa	gonadotropin-releasing hormone agonist
HUVECs	human umbilical vein ECs
I3C	indole-3-carbinol
IGF	insulin-like growth factor
IκBα	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha
iNOS	inducible nitric oxide synthase
MAPK	mitogen-activated protein kinase
MCP	monocyte chemoattractant protein

MIP	macrophage inflammatory protein
MMP	matrix metalloproteinase
NADPH	nicotinamide adenine dinucleotide phosphate
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
NO	nitric oxide
NOX	NADPH oxidase
Nrf2	nuclear factor erythroid 2 related factor 2
PDGF	platelet-derived growth factor
PDGFR	PDGF receptor
PGE	prostaglandin E
PI3K	phosphoinositide 3-kinase
PPARγ	peroxisome proliferator-activated receptor gamma
PSCs	pancreatic stellate cells
PCNA	proliferating cell nuclear antigen
ROS	reactive oxygen species
SFN	sulforaphone
SMCs	smooth muscle cells
TGF-β	transforming growth factor-β
TNF-α	tumor necrosis factor-alpha
UA	ursolic acid
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VSMCs	vascular SMCs

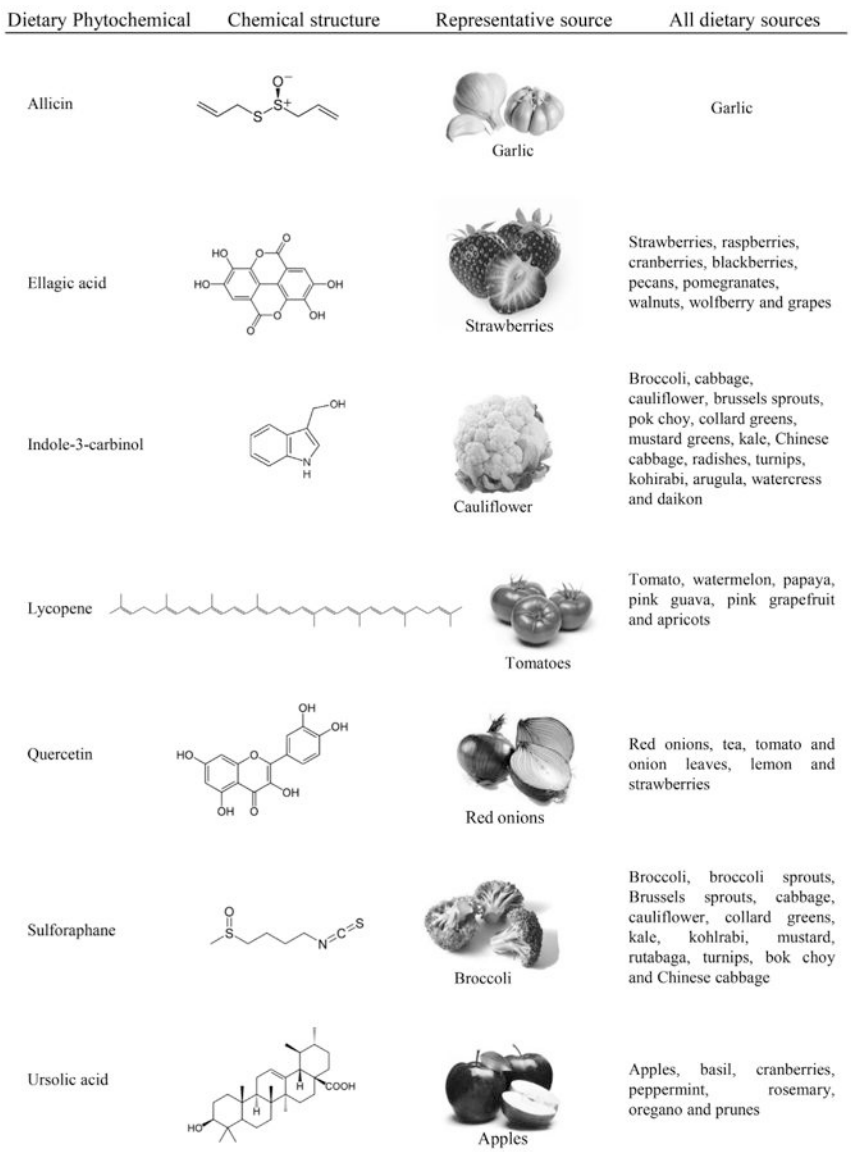

Figure 1.

Dietary phytochemicals not yet studied in uterine fibroids, their chemical structure, and food sources.

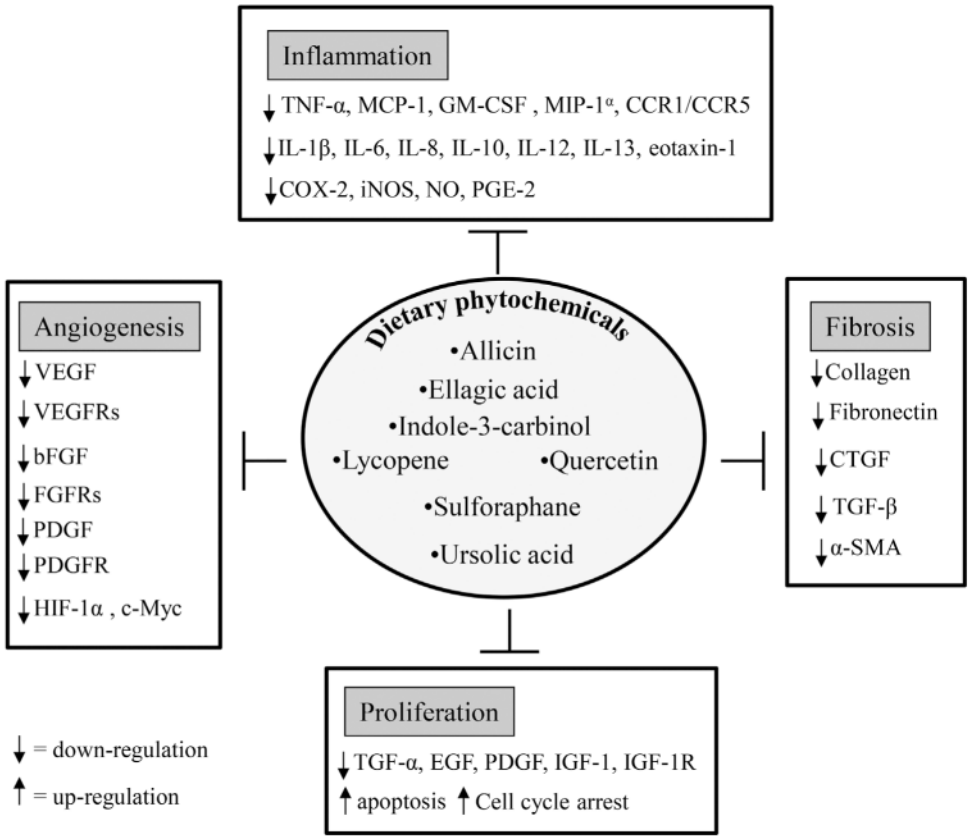

Figure 2.

Regulation of major cellular events, inflammation, fibrosis, cell proliferation, and angiogenesis, by dietary phytochemicals.

Table 1
Therapeutic effects of dietary phytochemicals on uterine fibroids

Dietary phytochemicals	Dietary sources	Therapeutic effects on uterine fibroids	
Epigallocatechin gallate	Green tea (*Camellia sinensis*)	**1**	Inhibits the proliferation of leiomyoma cells [35, 77].
		2	Induces apoptosis in leiomyoma cells [35, 77].
		3	Reduces the volume and weight of tumors of female mice [77].
		4	Reduces the incidence and size of spontaneously occurring leiomyoma of the oviduct in Japanese quail [78].
		5	Reduces uterine fibroid volume, fibroid-specific symptom severity, induces significant improvement in health-related quality of life in premenopausal women [36].
Curcumin	Turmeric (*Curcuma longa*)	**1**	Inhibits uterine leiomyoma cell proliferation [37].
		2	Induces apoptosis in leiomyoma cells [37].
		3	Inhibits fibronectin production in leiomyoma cells [37].
		4	Acts as PPARγ ligand [80].
Isoliquiritigenin	Licorice (*Glycyrrhiza uralensis*), shallot (*Allium ascalonicum*), soybean (*Glycine max*)	**1**	Induces the growth inhibition of leiomyoma cells [38].
		2	Induces apoptosis in uterine leiomyoma cells [38].
Genistein	Soybeans (*G. max*), lupine (*Lupinus* spp.), fava bean, (*Vicia faba*), kudzu (*Pueraria lobata*), psoralea (*Psoralea corylifolia*)	**1**	Stimulates leiomyoma cell proliferation at low concentration [83].
		2	Inhibits leiomyoma and myometrial cell proliferation at high concentration [83].
		3	Increases caspase activity [83].
		4	Induces apoptosis in myometrial and leiomyoma cells [83].
		5	Downregulates activin A, Smad3, and other TGF-β pathway genes in human uterine leiomyoma cells [84].
		6	Reduces the incidence and size of spontaneously occurring leiomyoma of the oviduct in the Japanese quail [86].
Resveratrol	More than 70 species of plants, including mulberries and peanuts. Grapevines (*Vitis vinifera*) are the main sources.	**1**	Inhibits proliferation of human uterine leiomyoma cells [40].
		2	Induces apoptosis in human uterine leiomyoma cells [40, 41].
		3	Induces cell cycle arrest in human uterine leiomyoma cells [40].
		4	Reduces collagen types I and III in human uterine leiomyoma cells [40, 41].