Chapter

Herbal Medicine in Uterine Fibroid

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Abstract

Uterine fibroids, also known as uterine leiomyoma is the most common benign tumor of the uterus found in women of reproductive age. Uterine fibroids are the cause of major quality-of-life issues for approximately 25% of all women who suffer from clinically significant symptoms of uterine fibroid. Despite the prevalence of fibroid, currently, there are no effective treatment options for fibroid. The lack of understanding of the etiology of fibroid contributes to the scarcity of medical therapies available. Sex steroid hormones, dysregulation of cell signaling pathways, miRNA expression, and cytogenetic abnormalities may all implicate in fibroid etiology. Several herbal medicines have been used as anti-inflammation and antitumor agents. All of them have a common capability to inhibit expression of pro-inflammatory cytokines, proliferative genes, and pro-angiogenetic genes. Exploring herbal medicines as remedies lighten the hope of treatment. In the current review article, we discuss signal transduction pathways activated herbal medicines. We also address the possibility of using herbal medicines for uterine fibroid treatment.

Keywords: uterine fibroids, herbal medicines, curcumin, resveratrol, THSG, pycnogenol, AFE, EGCG

1. Background

Uterine fibroids are common benign muscle tumors of the uterus. It affects the normal life of thousands of women of childbearing age, especially non-Caucasian women, which can be caused by genetic and environmental factors. It is not usually fatal but can produce serious clinical symptoms. The prevalence of uterine fibroids is predicted to be approximately 70% depending on the population [1]. Clinical symptoms caused by uterine fibroid include pelvic pain or compression, abnormal uterine bleeding, gastrointestinal and voiding problems. It also produces pregnancy complications as well as fertility impairment. Since there are no effective medical therapies, invasive surgeries have become a clear option for the treatment of this tumor.

Studies on the whole genome of uterine fibroid indicate that there are many new signal transduction pathways and how gene nets play a role in uterine fibroid development. Not only in its origin, the transcriptomic, and epigenetic profiles, as well as the impact of the inter-cell matrix are all involved in uterine fibroid growth [2]. Additionally, microRNA plays a role in regulating uterine fibroid pathogenesis [3].

Nowadays, numerous treatments for fibroids are available. Therapies include conservative medications to invasive surgeries. Up to now, the regular therapy of uterine fibroid is surgery, but its negative impact on future fertility is evidenced. Therefore, selecting appropriate individualized therapy and augmented modifications to fit patient's expectations are readily important. However, newly developing pharmaceutical prospects have significant adverse effects, such as liver function impairment, hot flashes, bone density loss, endometrial changes, and inability to attempt conception during treatment [4].

Numbers of natural compounds are demonstrated effectively to treat uterine fibroids and to relieve their symptoms. In this review, we will discuss potential available herbal medicine compounds that may be beneficial for uterine fibroid patients, particularly those who plan to conceive during therapy or desire to preserve their future fertility. Nonetheless, there is still no significant clinic evidence available so far. Therefore, it is highly recommended to obtain more clinical trials utilizing these compounds before endorsing widespread usage [5].

2. Mechanisms and signal transductions in uterine fibroid

As the pathogenesis of uterine fibroids has not been fully elucidated, many studies have been carried out in mechanisms involved in this area and are still ongoing. The involved mechanisms affect several categories of cellular and tissue functions. The presumptive identification of progenitor stem cells of uterine fibroids has produced fibroids and maternal junctions, providing new clues about the etiology of uterine fibroids [2]. There are two hypotheses raised for the development mechanisms of uterine fibroid. However, they may cross-talk with each other intimately. The genetic hypothesis is focused primarily on the mutant mediator complex subunit 12 (MED12) genes [6], suggesting it onsets in the side population of the female reproductive system embryonic myoblasts and contributed rise to multiple small and medium fibroids later on [2]. Most studies on uterine fibroids have focused specifically on somatic mutations in the MED12 gene [6, 7]. According to the available data, this mutation has been confirmed in more than 70% of patients with uterine fibroids depending on different populations [6, 8]. Alternatively, the single and usually large-size fibroids are induced by predominantly epigenetic disorders in uterine fibroid steam cells, provoked by enhanced expression of the DNA hypomethylation in HMGA2 gene and epigenetic deregulation enhanced by hypoxia, muscle tension, or chromosome instability/aberrations (**Table 1**).

The life cycle of uterine fibroid is divided into two stages: transformation and benign tumor development [7, 57]. Mutations are sources for normal myometrial stem cells to transform into abnormal cells. Additionally, some other factors may also cause immunological changes [58] to lead to altered DNA repair and cell mutation [59]. Finally, a mixture of early environmental exposure and hyperreactivity to estrogen may also play a role in fibroid development [60].

Reactive oxygen species (ROS) formed after exposure to oxidative stress and/or hypoxia are linked to the activation of a variety of signal molecules [61–66]. Various enzyme systems produce ROS, including the mitochondrial electron transport chain, cytochrome P450, lipoxygenase, cyclooxygenase, NADPH oxidase complex, and peroxisomes [61]. Hypoxia triggers many key adaptive changes that enable cell survival, including inhibition of apoptosis, changes in glucose metabolism, and angiogenic phenotypes [61]. Recent studies have shown that oxygen depletion promotes mitochondria to increase more ROS production, and then activate signaling transduction pathways, such as hypoxia-inducible factor (HIF)-1α to promote cell survival and increase fibrotic growth sequentially [61].

	Curcumin	**Resveratrol**	**THSG**	**Pycnogenol**	***Anoectochilus formosanus***	**EGCG**
ERK1/2	Inhibition [9, 10] Activation [11]	Activation [12–15]	Inhibition [16] Activation	Decrease expression levels [17] Suppression [18]	Suppression [19]	Inhibition [20] Activation
PI3K	Inhibition [21]	Inhibition [22]	Inhibition [23, 24]	Activation [25]	NA	Activation [26] Inhibition [27]
NF-κB	Inhibition	Inhibition	Inhibition [16]	Suppression [18]	Activation [28] Inhibition [19, 29]	Inhibition [20, 30]
STAT3	Inhibition	Inhibition	NA	NA	NA	Inhibition [31]
AMPK	Activation	Activation	Activation [32]	Expression [33]	Activation [34, 35]	Activation [36, 37]
Nrf2	Activation	Activation	Activation [16, 32, 38]	NA	NA	Activation [39]
PPAR	Activation [40]	NA	Suppression [41]	Suppression [42]	Activation [36]	Activation
Suppression of gene expression	*PD-L, IL-1, IL-6, TNF-a*	*PD-L1, MMPs* [43]	*PD-L1*	NA	*PD-L1, COX-2, TNF-α, CAK, MMP-9,* and *TRAP* [29]	Proliferative genes [44]
Activation of gene expression	*Caspase-3, caspase-9*	*Caspase-3, caspase-9*	Apoptotic-related protein expression [24]	NA	Anti-proliferative genes [45, 46]	*BAX, p21, MDM2,* and *TP53I3* [30].
Anti-oxidant	Yes [47]	Yes	Yes [48]	Yes [33, 49]	Yes [19]	Yes [50]
Anti-inflammation	Yes	Yes	Yes	Yes [51]	Yes [45]	Yes
Anti-Cancer growth	Yes	Yes	Yes	Yes [52, 53]	Yes	Yes
ECM production inhibition	Yes [54]	Yes	Yes	NA	NA	Yes [55, 56]

THSG: 2,3,5,4'-Tetrahydroxystilbene-2-O-β-glucoside; EGCG: Epigallocatechin gallate; PPAR: Peroxisome proliferator-activated receptor; ECM: Extracellular matrix.

Table 1.
Signaling pathways, gene expressions and activities induced by natural products curcumin, resveratrol, THSG, pycnogenol, AFE and EGCG.

Remarkably, ovarian sex hormones play an important role in uterine fibroid pathophysiology [7, 67, 68]. Primarily under the influences of sex hormone, myometrial stem cells transform into pathological cells and develop into uterine lesions [69]. Tumor growth occurs by a large number of cell growth and extracellular matrix (ECM) building up [70, 71]. Accumulation and remodeling of ECM are believed to be crucial for fibrotic diseases such as uterine fibroid. Indeed, ECM plays an important role in forming the bulk structure of fibroids. Rigid ECM-rich structure may cause abnormal bleeding and pelvic pain [70, 72]. Therefore, a better understanding of ECM accumulation and remodeling is critical for developing new therapeutics for uterine fibroid. The ECM is approximate twice the volume in uterine fibroid compared to those in healthy myometrium. ECM is mainly composed of different types of collagen, fibronectin, and proteoglycan [70, 71]. It has been found in ultrafiltration that different fibers forming the ECM have abnormal structures and are different from the corresponding fibers in the unchanged tissue [73].

Estrogen has been shown to stimulate proliferation in a dose- and time-dependent manner in uterine fibroid cell lines [68, 74]. Estrogen (17β-estradiol) binds to the nuclear estrogen receptor (ER)-α to modulate the expression of proto-oncogenes, cytokines, and growth factors [75–77]. Uterine fibroid cells are more accessible to actions of 17β-estradiol than normal myometrial cells [78]. Although estrogen is essential for uterine fibroid growth, progesterone now is considered the key hormone to initiate uterine fibroid pathological differentiation and growth [7]. Estradiol has a tolerant effect on the growth of uterine fibroids mediated by progesterone. Additionally, the combination of estrogen and progesterone significantly increased cellular expression of the proliferation marker Ki-67 [79] and the accumulation of ECM due to the accelerated synthesis of type 1 and type 3 collagen [80]. Studies of Ishikawa et al. have shown that combined estrogen and progesterone increased uterine fibroid size more than 3-fold higher than those treated with estradiol alone or untreated controls in a xenograft model [67]. These results highlight the significant role of progesterone in uterine fibroid growth.

Furthermore, disturbance of steroid hormone receptors may be a primary pre-requisite for development of uterine fibroid [81]. Adenovirus-mediated a dominant-negative *ER*-α gene delivery eliminates the expression of estrogen and progesterone-regulated genes in uterine leiomyoma cells *in vitro* and shrinks uterine fibroids *in vivo* [82, 83]. Steroid hormones can affect uterine fibroid cells by different mechanisms including paracrine [7]. Steroid hormones stimulate expression of cytokines and growth factors. Sequentially, the induced cytokines and growth factors affect signal pathways, growth, and survival of uterine fibroid cells. They also regulate angiogenesis and ECM formation [84]. Consequently, this influences uterine fibroid cells to grow and survive and ECM to accumulate. ECM may serve as a reservoir for growth factors and cytokines to increase their stability and extend their influence [70].

Different growth factors and signal pathways are involved in uterine fibroid formation processes [71, 84]. As one of the most important growth factors affect development of uterine fibroid, transforming growth factor-β (TGF-β) stimulates uterine fibroid progress [71]. TGF-β signaling connects with other different pathways such as Smad pathway, phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR), the mitogen-activated protein kinases (MAPK, ERK1/2) signaling cascade, and focal adhesion kinase (FAK) [71]. Expression of *TGF*-β is significantly increased in myometrial cells when they are directly in contact with the uterine fibroid tumor [85]. TGF-β1 stimulates expression of metalloproteinase-2 (*MMP-2*), *MMP-9*, and membrane-associated MMP inhibitor (*RECK*) [86]. TGF-β also modulates ECM production via cross-talk with growth factor and integrins [87, 88].

In addition to TGF-β, insulin-like growth factor–1 (IGF-1) is another growth factor that plays a vital role in the pathogenesis of uterine fibroid [89]. Studies of Boehm et al. indicated that more IGF-1 expression increases in uterine fibroid than in normal myometrium [90]. An animal model from Eker rat also showed upregulation of IGF-1 in uterine fibroid tissue [91]. We have shown how IGF-1R accumulated in uterine fibroid primary cell lines in response to IGF-1 to regulate cell proliferation [12]. Estrogen induces ERK1/2 activation and IGF-I, cell cycle regulating transcriptional factor A-Myb accumulation to stimulate uterine fibroid cell cycle progression in human uterine leiomyoma cell lines [92]. Additionally, growth hormone stimulates IGF-1 production to promote cell proliferation and to inhibit apoptosis in uterine fibroid [93, 94].

Wingless-type (Wnt)/β-catenin signaling also plays a role in somatic stem-cell function in both myometrium and uterine fibroid tissue [7]. Paracrine activation of the Wnt/β-catenin pathway in uterine fibroid stem cells can stimulate tumor growth [95]. Activin A, a product of macrophages, may also play a crucial role in uterine fibroid biology. Activin A is response for different immunological actions including cell transformation to lead to tumor development [58, 96]. Interactions between Wnt/β-catenin and TGF-β pathways, as well as with steroids and growth factors, give rise to the clonal formation of uterine fibroid tumors and are believed to be the basis of modern uterine fibroid biology hypothesis [7, 97].

The genetics of uterine fibroids and the etiology of epigenetic procedures have many peculiarities at first, then become quite similar and partially overlap due to the proximity of their genetic network and epigenetic environment. Research on the etiology of uterine fibroids to elucidate new strategies for the prevention and treatment of this common disease [2].

3. Treatment of uterine fibroid

Because the natural cause of uterine fibroid is not known, it makes the myomectomy or selected conditions hysterectomy to become the mainstay of management [98]. Genetic factors, epigenetic factors, and several pathogenic factors such as sex hormones, growth factors, cytokines, chemokines, and extracellular matrix components all of them have been implicated in development and growth of uterine fibroid [99, 100]. Although surgery has been suggested, it is not an attractive choice due to its serious consequences, especially with patients desiring to preserve their fertility potential [100].

Studies of El Andaloussi et al. [101] indicate that MED12 mutation presents a potential of dysregulating Wnt4/β-catenin to transform cells [101]. The dysregulating Wnt4/β-catenin affects mTOR signaling and caused autophagy abrogation, cell proliferation, and tumorigenesis [101]. Silenced MED12 gene reduces the proliferation of uterine fibroid cells [97]. In 2020, Ali et al. also found that β-catenin nuclear translocation contributes to uterine fibroid phenotype, and β-catenin signaling is modulated by estradiol and histone deacetylases activity [102]. Additionally, the Wnt/β-catenin pathway leads to increased levels of TGF-β3 [7, 71]. As we discussed above, different isoforms of TGF-β may play a crucial role in uterine fibroid development. Studies that used anti-uterine fibroid agents cause the attenuation of this pathway by reducing TGF-β3 signal and protein expression, resulting in a reduction in TGF-β canonical signaling [103]. Therefore, canonical Wnt pathway has been suggested to be a potential therapeutic target for the treatment of uterine fibroids [104].

It has been shown the proliferation of uterine fibroid is sensitive to the GnRH agonists [105, 106] or estrogen receptor antagonists. For those patients can be

applied with hormone treatment with GnRH agonists including Lupron, Synarel, and Zoladex and/or aromatase inhibitors such as anastrozole (Arimidex®), letrozole (Femara®), exemestane (Aromasin®), vorozole (Rivizor®), formestane (Lentaron®), fadrozole (Afema®), and testolactone (Teslac®). Treatment with medications such as tamoxifen may also reduce uterine fibroid size [106]. In addition, using an adenovirus-expressing dominant-negative ER-α reduces ER-α to arrest fibroid growth in a mouse model which may provide an optional treatment [107]. Besides, alternative medicine has been shown to improve the symptom of uterine fibroids [108–110].

Alternatively, several natural products have been suggested for the treatment of uterine fibroids based on their natural activities of anti-inflammation, anti-proliferation, and anti-angiogenesis. We will discuss mechanisms in the following sections.

3.1 Curcumin

Curcumin is a yellow active natural polyphenol of the perennial herb *Curcuma longa,* commonly known as turmeric. In addition, curcumin is commonly found as ingredients in food seasoning, cosmetics, or herbal supplements. It has traditionally been used for decades in Asian countries as a medical herb due to its antimicrobial, anti-inflammatory, anti-tumorigenic, and anti-mutagenic properties [111]. Curcumin has many medical effects such as suppression of thrombosis [112], reduction of blood cholesterol [113, 114], and reduction of myocardial infarction [115]. Evidence indicates that curcumin suppresses the growth of several tumor cell lines [116, 117]. All in all, curcumin is effective against a variety of inflammatory illnesses and modulates multiple cell signaling pathways. However, it is still not well understood which binding site or receptor for it. *In vitro* studies indicate that curcumin can interact with integral components of cell signaling pathways and therefore may be pharmacologically relevant. However, only limited studies have shown functional consequences of curcumin interaction [118]. The tumor suppression mechanisms of curcumin are accredited by modulation of numerous targets playing important roles in tumor growth [119–122]. Those targets include transcription factors, receptors, kinases, cytokines, enzymes, and growth factors. Therefore, curcumin has been demonstrated to suppress the growth of several tumor cell lines [123]. It also inhibits the growth of uterine fibroid cells, even though there has yet to be a report describing the precise mechanism of its inhibition.

Curcumin inhibits phorbol ester-induced activation of NF-κB and ERK1/2 [9, 10]. Alternatively, it induces apoptosis via activation of ERK1/2 or SAPK/JNK in cancer cells [11]. Role of ERK1/2 activation in curcumin-treated cancer cells is controversial [124]. Curcumin down-regulates endothelial cell fibrosis and inhibits uterine fibroid cell proliferation via regulation of the apoptotic pathway, and it also reduced production of the ECM component fibronectin (**Figure 1**). Curcumin has also been shown to attenuate TGF-β-induced endothelial-to-mesenchymal transition [125]. Extracts from *Curcuma zedoaria* inhibits uterine fibroid cell proliferation compared to normal myometrial cells [126]. On the other hand, it stimulates caspase-3 and caspase-9 expression in uterine fibroid cells. Curcumin provides a novel direction for uterine fibroid therapies [127].

Peroxisome proliferator-activated receptor (PPAR) is a ligand-dependent transcription factor of the nuclear hormone receptor superfamily. It is expressed in a tissue-specific manner and plays an important role in the differentiation of adipocytes [128, 129]. PPARγ exerts anti-inflammatory, anticancer, and insulin sensitivity effects and participates in the control, proliferation, and differentiation

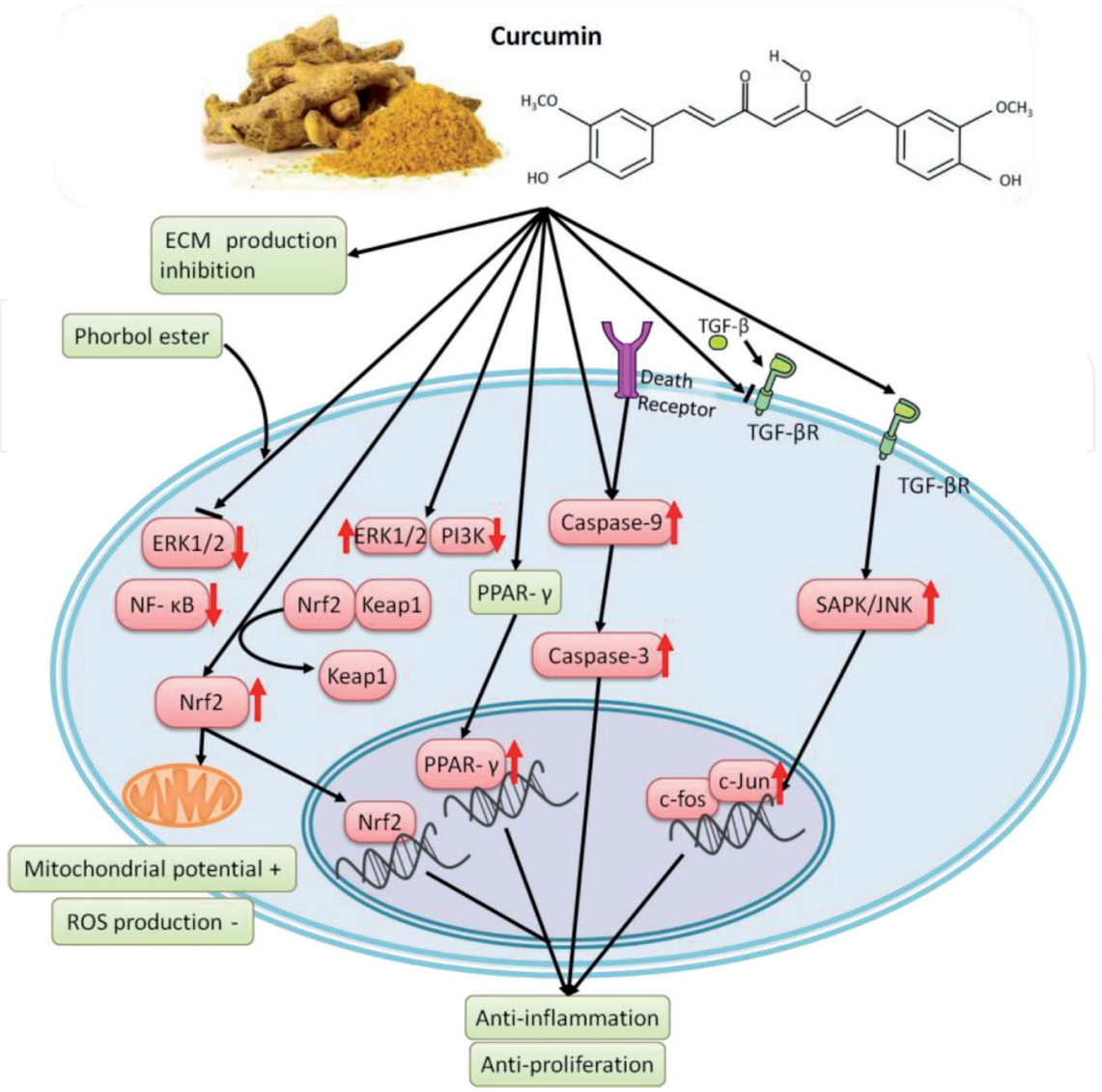

Figure 1.
Signaling pathways by which curcumin induces biological activities in cells. Curcumin binds to an unidentified cell surface binding site to activate the ERK1/2 cascade. On the other hand, in addition, to downregulate NF-κB activation, it inhibits phorbol ester-induced activation of NF-κB and ERK1/2. Curcumin also activates SAPK/JNK activation and Caspase-3 and -9-dependent apoptosis in cancer cells, may also including uterine fibroid cells. Curcumin inhibits TGF-β-induced ECM production. It also reduces inflammation and induces apoptosis.

of the cell cycle. Hepatic stellate cells are the type of hepatocyte responsible for fibrosis in liver damage and can lead to chronic liver damage and cirrhosis. Curcumin induces and activates PPARγ in rat hepatic stellate cells [40]. Curcumin considerably increases the proliferative inhibition of stellate cells by PPARγ. [40]. Besides, curcumin also enhances the activity of PPARγ in human colon cancer cell lines by reducing the expression of cyclin D1 and epidermal growth factor receptor (EGFR), thereby disrupting the cell cycle [130]. These two inhibitory effects depend on PPARγ activation. The study by Takashi Takeda et al. showed that uterine fibroids can share pathogenic characteristics with the development of metabolic syndrome [131]. PPARγ is also virtually involved in insulin signaling. A PPARγ agonist, thiazolidinedione, has been used to treat patients with type II diabetes [129]. Thiazolidinedione may be used to prevent the progression of atherosclerosis and metabolic syndrome [132]. On the other hand, curcumin directly inhibits fibroid proliferation, and curcumin-induced PPARγ activation can also prevent metabolic syndrome and indirectly inhibit fibroid growth [132]. However, since these findings were based on *in vitro* experiments, it raised concerns about

the observation limitations. Later, Kenji Tsuiji et al. have developed a new *in vivo* uterine fibroid model to study the inhibition of rat leiomyoma (ELT-3) cells by curcumin [132]. The IC50 of curcumin-induced anti-proliferation in uterine fibroid cell lines is 20 μM, however, when patient-matched myometrial cells were exposed to equivalent concentrations of curcumin, there was no statistically significant inhibition of growth [127].

Studies indicated that curcumin absorption rate in the intestine is very low [133–136]. Similar raising concerns were also in other herb medicines, such as resveratrol discussed in next section. Thus, some modifications of curcumin need to be taken to keep its high blood concentration. Some studies regarding increased absorption and bioavailability of curcumin have been reported. For instance, the co-administration of curcumin and piperine can increase the bioavailability of curcumin [135]. Another strategy is to develop new curcumin analogues with a higher cell growth inhibitory capacity. One such compound, GO-Y030, has been shown to exhibit an 8- to 40-fold greater growth inhibitory potential than curcumin in several cancer cell lines [137, 138]. It may be useful to use the compound to clinically treat uterine fibroids.

3.2 Resveratrol

Polyphenols have been attracting by their anti-oxidative effects during the past years for human chronic diseases involved in inflammation like diabetes mellitus, neurodegenerative diseases, cardiovascular diseases, and cancers [139]. Resveratrol is one of well-studied stilbenes found in peanuts, grapes, and some berries. It is a plant product in response to environmental stress, pathogen infection, and ultraviolet radiation [127]. Resveratrol has been known as chemo-preventive, serving to suppress DMBA-induced ductal breast carcinoma [140] and ultraviolet light (UV)-induced skin cancer [141] in mouse models. Resveratrol induces p53-dependent apoptosis in several human cancer cell lines, including thyroid, prostate, and breast cancer cells [13, 142–145]. It also induces p53-independent anti-proliferation against cancer cells [14, 146–148]. Resveratrol has been recommended to be a reversion molecule for multiple drug-resistant breast cancer [149]. Resveratrol is safe and well-tolerated by patients, with common adverse events including nausea, diarrhea, and weight loss [150].

Although surface receptors involved in the resveratrol signal transduction remain to be identified, resveratrol binds to cell surface integrin αvβ3 to activate ERK1/2 and ant-proliferation in cancer cells [13, 145, 151] (**Figure 2**). Integrin αvβ3 is also involved in AKT phosphorylation [15, 152]. Resveratrol inhibits PI3K-AKT signal pathway to induce anti-proliferation [22] or other biological activities as IL-33-mediated mast cell activation [153].

Overexpression of integrin αvβ3 is observed in several types of solid tumors [154, 155] and highly growing endothelial cells [154, 155]. Our studies indicate that integrin αvβ3 overexpresses in primary uterine fibroid cell lines [12]. The integrin αvβ3 overexpresses in primary human uterine fibroid Case 016 and Case 018 compared to normal Case 003 cells [12]. Therefore, it is a perfect target for resveratrol which has been shown to bind on integrin αvβ3 receptor [13]. Integrins are not classic signaling receptors in that they possess no enzymatic activity. Integrin signaling depends on the allosteric behavior of the receptors, their ability to concentrate into adhesion zones, and the recruitment to these zones of numerous other adhesome components to form complex integrin-based cell adhesions [156, 157]. Many adhesome components are enzymes that interact with classic signaling pathways. Resveratrol regulates signal transduction via integrin αvβ3 in human uterine fibroid cells. Resveratrol attenuates expression of integrin αv and integrin β3

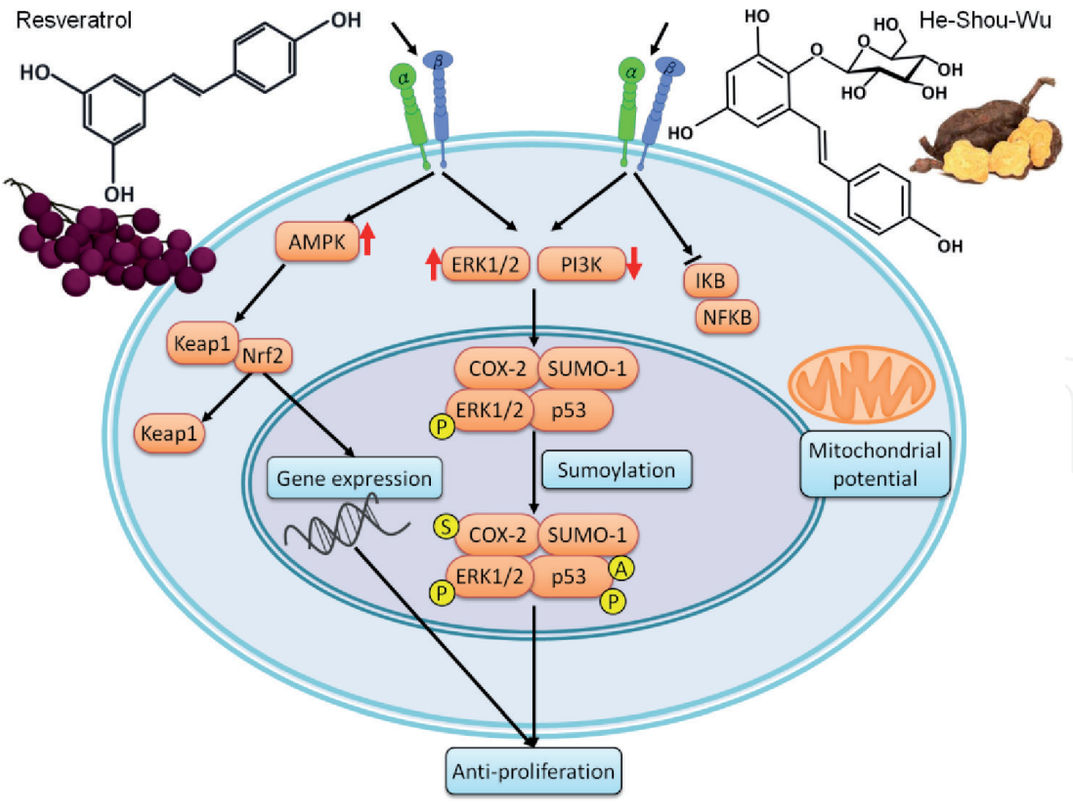

Figure 2.
Resveratrol/THSG activates signaling pathways in uterine fibroid cells. A stilbene receptor is present on integrin αvβ3 by which resveratrol activates ERK1/2 and induces nuclear accumulation of COX-2. On the other hand, 2,3,5,4′-tetrahydroxystilbene-2-O-β-glucoside (THSG) has a similar chemical structure and assumedly binds to integrin αvβ3 to activate the signal transduction pathway. In resveratrol-treated cancer cells, pERK1/2 also translocates to the cell nucleus and complexes with inducible COX-2. Phosphorylated ERK1/2 also translocates into the cell nucleus and forms a complex with inducible COX-2 in resveratrol-treated cancer cells. Resveratrol induces phosphorylation of the complexed p53 at Ser15 and p53-dependent antiproliferation. Blocking resveratrol-induced nuclear accumulation of COX-2 inhibits p53 phosphorylation and antiproliferation.

in primary uterine fibroid cell Case 016 and Case 018 but not in normal myometrial cells. Resveratrol induces ERK1/2 activation in uterine fibroid cells [12]. However, the constitutive phosphorylation of AKT in uterine fibroid cells was inhibited by resveratrol.

Integrin signaling and function are heavily dependent on cross-talk with other signaling pathways, especially growth factor signaling pathways [158–160]. Besides the aberrant integrin expression, IGF-1R highly expresses more in uterine fibroid compared to the normal tissues [161] indicating IGF-1 may also be involved in the abnormal proliferation [92, 162]. IGF-1 binds to IGF-1R to activate downstream AKT which is a target of resveratrol. Resveratrol did not inhibit IGF-1R phosphorylation in primary uterine fibroid cells [12]. These results suggest that the action of resveratrol on IGF-1R-dependent signal transduction is downstream IGF-1R at Akt level [12]. Resveratrol analogue, pterostilbene (3′,5′-dimethoxy-resveratrol) targets mTOR/PI3K/Akt signaling pathway to disrupt mitochondrial membrane potential, and induce apoptosis [163].

IGF-I mRNA is expressed significantly higher in leiomyoma cells than that in myometrial cells [12]. IGF-1 stimulates IGF-1R phosphorylation of but the action is blocked by resveratrol pre-treatment. Growth effect of IGF-1 can possibly reduce by resveratrol [164]. Resveratrol inhibits IGF-1-induced phosphorylated IGF-1R accumulation and proliferation consequently [12]. IGF-1 enhances leiomyoma cell proliferation and thereby accelerates uterine fibroid progression. In summary, resveratrol via a mechanism involved in crosstalk between integrin αvβ3

and IGF-1R-sensitive signal transduction pathways induces anti-proliferation in uterine fibroid.

Steroid hormones and thyroid hormone stimulate *TGF*-β expression [165]. Resveratrol blocks *TGF*-β expression and functions [166]. Cross talk among TGF-β signaling pathways, integrins, and ECM [88] is essential for uterine fibroid growth. Both Agarwal discussed the ability of resveratrol to infer with ECM formation and deposition in multiple diseases in their review article [53]. Resveratrol suppresses not only expression of fibronectin, fibromodulin, biglycan, and collagen types I and III, but also their protein levels in different cell lines [43]. Resveratrol also reduces MMP-9 protein accumulation but increases TIMP2 protein in ELT-3 cells and healthy uterine smooth muscle cells [43].

Resveratrol inhibits TGF-β signal downstream molecule AKT phosphorylation. Studies of confocal microscopy have shown resveratrol inhibits nuclear pAKT translocation in uterine fibroid cells. Alternatively, resveratrol does not interfere with pAKT nuclear translocation in normal uterine smooth muscle cells even though there are limited pAKT translocated [12]. Resveratrol reduces cellular levels of the phosphorylated/active form of anti-apoptotic kinase AKT in uterine cancer cells [167]. Sequentially, treatment of resveratrol reduces the endogenous cyclooxygenase-2 (COX-2) protein and produces PGE2 and PGF2α [167]. Evidence indicates that endogenous COX-2 is involved in inflammation, therefore, resveratrol inhibits AKT signaling pathway and COX-2 activity to induce anti-inflammation which plays vital roles in uterine fibroid cell growth.

β-catenin modulates and stimulates the stem cell renewal [168]. The regulation of the biologic functions for β-catenin is highly complex and not fully understood. Wnt proteins bind to a special cell-surface receptor, Frizzled, where it promotes activation of a cascade of proteins that leads to decreased β-catenin degradation in the cytosol and reduces nuclear β-catenin levels [7, 95]. The increased β-catenin expression is observed in uterine fibroids compared to the adjacent myometrium samples [169]. Ovarian steroids interact with the Wnt/β-catenin pathway to accelerate tumorigenesis [168]. Our studies also indicate that thyroid hormone increases nuclear β-catenin accumulation, thus β-catenin-dependent gene expression and proliferation [170, 171]. Resveratrol reduces expression and nuclear accumulation of β-catenin.

The expression of resveratrol-induced pro-apoptotic genes such as *COX-2* and *p21* induced in uterine fibroid cells. On the other hand, the expression of proliferative (anti-apoptotic) genes was either inhibited such as *BCL2*, and *CDKN2* or no changed as *Cyclin D1* and *PCNA*. The pro-apoptotic proteins such as caspase 3 and caspase 9, were also increased in resveratrol-treated cells [12]. Resveratrol-induced COX-2 facilitates p53-dependent anti-proliferation [172, 173]. Therefore, resveratrol induces anti-proliferation in uterine fibroid cells [12]. Kim et al. have also shown the extraction of herb medicine, *Scutellaria barbata D. Don* (*Lamiaceae*), down-regulates the IGF-I expression [174] and inhibits the proliferation of leiomyoma cells. *Scutellaria barbata D. Don* (*Lamiaceae*) induces the uterine smooth muscle cell differentiation markers in uterine smooth muscle cells and uterine leiomyoma smooth muscle cells, such as α smooth muscle actin (α-SMA), calreductin h1, and cyclin p27-dependent kinase inhibitor. In contrast, gene products linked to the G1 phase of the cell cycle, such as cyclin E and cdk2, are not affected by *Scutellaria barbata D. Don* (*Lamiaceae*) [175]. These observations agree with our studies. The expression of anti-apoptotic genes, such as *BCL2* and *CDKN2* are suppressed or unmodified *Cyclin D1* and *PCNA* [12].

Estrogen stimulates proliferation in breast cancer cells [176, 177], endometrial cancer [178, 179] and leiomyoma cells [180]. Estrogen also stimulates cell growth in uterine fibroid cells [12]. Resveratrol can inhibit estrogen-dependent cancer growth [176] and suppresses the proliferation of six sensitive uterine fibroid cases both in

the absence and presence of estradiol [12]. These results indicate the suppressing effect of resveratrol on uterine fibroid growth may not go through ER-α.

The immunomodulatory factor, checkpoint PD-1/PD-L1 has been shown to play an important role in uterine fibroid pathogenesis. They also attack attention to be therapeutic targets. Resveratrol suppresses PD-L1 expression. In the presence of thyroid hormone, resveratrol traps PD-L1 in the cytosol, meanwhile, resveratrol-induced COX-2, an inducible transcriptional co-activator [181], is trapped with thyroid hormone-induced PD-L1 in the cytosol [173].

Summarily, in the primary cell culture of patients with resveratrol-sensitive primary uterine fibroids, resveratrol can inhibit uterine fibroid proliferation, induce apoptosis, and transmit integrin-dependent signaling αvβ3. The transduction pathway promotes uterine fibroids cell cycle arrest. Additionally, resveratrol inhibits the activation of IGF-1R dependent signal transduction pathways, which play an important role in uterine fibroid proliferation. Resveratrol may or may not inhibit the expression of proliferation genes. Resveratrol also induces the expression of p21 and COX-2. Analysis of the DNA content of the PI stain indicates that resveratrol induces uterine fibroid cells cell cycle arrest at sub-G1 population [12]. Crosstalk between αvβ3 integrin and IGF-1R plays a crucial role in resveratrol-induced uterine fibroid anti-growth. In addition, resveratrol inhibits signal transduction pathways and gene expression dependent on TGF-β and β-catenin. Therefore, resveratrol can effectively prevent leiomyoma overgrowth and treat uterine fibroids.

3.3 Extract of He-Shou-Wu, 2,3,5,4′-Tetrahydroxystilbene-2-O-β-glucoside

The stilbene glucoside 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside (THSG) is one of the major bioactive components of *Polygonum multiflorum* Thunb (He Shou Wu). It is glycosylated resveratrol and it has been used as antiaging medicine [182]. THSG suppresses experimental colitis effectively by reducing the level of oxygen and nitrogen free radicals [48]. It also has been shown to exert a protective effect on cardiotoxicity induced by doxorubicin *in vitro* and *in vivo* [183]. THSG can also diminish peroxidation levels in the brain of a mouse model with Alzheimer's disease or cerebral ischemia–reperfusion. Administration of THSG not only prevents learning-memory deficits but also reverses the learning-memory deficit in disease-like mouse models with Alzheimer's [184].

Mechanism involved in *P. multiflorum*-induced anti-atherosclerosis may be caused by THSG-induced antagonistic effects on oxidation of lipoprotein, proliferation, and decrease of nitric oxide content of coronary arterial smooth muscle cells [185] which partially explains the antiatherosclerosis mechanism of *Polygonum multiflorum*. Recently, the pharmacological effects of *P. multiflorum* on atherosclerosis have been revealed with anti-inflammation and guy microbiota regulation of THSG in ApoE−/− mice [186]. The protective effects of THSG are mediated by modulation of JNK, SirT1, and NF-κB pathways [187] (**Figure 2**). As resveratrol, THSG can activate signal transduction pathways as AMPK. Treatment with THSG reduces the LPS-induced neuroinflammatory response, and that the mechanism by which THSG induces anti-neuroinflammatory effects may include the Nrf2/AMPK signaling pathways [38]. Consequently, THSG treatment leads to a decrease in the level of iNOS, TNF-α, and IL-6 production [184]. THSG-induced neuroprotective effects are via Akt signaling and TrkB activity [51]. THSG possessed an anti-inflammatory effect that may also be related to the inhibition of COX-2 enzyme activity and expression [188].

As a glycosylated analogue of resveratrol, THSG has similar effects as resveratrol. Studies indicate that resveratrol significantly stimulates cell proliferation of human gingival fibroblasts at low concentration (10 μM) but inhibited cell

proliferation at high concentrations (100 and 200 μM) significantly. On the other hand, THSG significantly enhances growth of human gingival fibroblasts when the concentration is over 25 μM and does not show any cytotoxic effect in human gingival fibroblasts [151]. It is evidenced that THSG may not cause cytotoxicity in normal human cells. Although there are no studies regarding effect of THSG on uterine fibroid, it should be more effective than resveratrol. THSG may not enter cells to induce superoxide which causes cytotoxicity to cells. However, studies also indicate that crude extract may cause damage in hepatocellular cells.

3.4 Pycnogenol, French maritime pine bark extract

Pycnogenol is a standardized extract of the bark of French maritime pine. Pycnogenol is composed of flavonoids, mainly proanthocyanidins, and phenolic compounds. It is a known potent antioxidant [49]. Owing to the basic chemical structure of its components, the most obvious feature of pycnogenol is its strong antioxidant activity. In fact, phenolic acids, polyphenols, and in particular flavonoids, are composed of one or more aromatic rings bearing one or more hydroxyl groups. The compositions are hence potentially able to quench free radicals by forming resonance-stabilized phenoxyl radicals [189]. Pycnogenol is a strong antioxidant that may interfere with different pathways, and it plays an important role in diseases associated with oxidative stress. Hyperglycemia is characteristic of diabetic nephropathy and induces renal tubular cell apoptosis. Pycnogenol has been demonstrated to significantly suppress the high glucose-induced morphological changes and the reduction in cell viability associated with cytotoxicity in high glucose-treated renal tubular cells [49]. Pycnogenol is able to protect high glucose-induced apoptosis increasing Bcl2/Bax protein ratio level. Combination treatment of pycnogenol and metformin improves blood glucose levels, vascular reactivity, and left ventricular hypertrophy in induced diabetic rats [33]. Furthermore, combined treatment increases expression of AMPK, glucose transporter 4 (GLUT4), and calcium/calmodulin-dependent protein kinase II (CaMKII) in left ventricle of the hearts. However, the combination of these interventions has failed to possess higher efficacy [33].

Pycnogenol has anti-oxidative and anti-inflammatory efficacy in suppressing lipid peroxidation, total reactive species, superoxide $\cdot O_2$, nitric oxide NO·, peroxynitrite ($ONOO^-$), pro-inflammatory inducible nitric oxide synthase (iNOS) and COX-2 [49]. It also inhibits NF-κB nuclear translocation [49]. The safety of use of pycnogenol is demonstrated by the lack of side effects or changes in blood biochemistry and hematologic parameters. Therefore, pycnogenol has been recommended both for prevention and treatment of chronic venous insufficiency and related veno-capillary disturbances [190].

3.5 Therapeutic orchid *Anoectochilus formosanus* extract

Traditional herb medicine, golden thread (*Anoectochilus formosanus Hayata*) has been used to treat various diseases in Asia. *A. formosanus* extracts (AFEs) have been reported to possess hepatoprotective, anti-inflammatory, and anti-tumor activates. AFEs reduced blood glucose in hyperglycemic mice while there was no change in control group [191]. AFE and metformin at the same administrated dose of 50 mg/kg showed a similar effect on intraperitoneal glucose tolerance test in hyperglycemic mice. Free-radical scavenger capacity of AFE was concentration-dependent and 200 μg/ml of AFE was able to reduce more than 41% of the free radical [191]. The immunomodulatory protein from *A. formosanus* (IPAF) stimulated the TNF-α and IL-1β production, upregulated the expression of CD86, MHC II, IL-12, and

Th1-associated cytokines/chemokines [28]. It also enhanced the phagocytic activity of macrophages [28]. AFE inhibited constitutive *PD-L1* expression and its protein accumulation in cancer cells. AFE also induced expression of pro-apoptotic genes but inhibited proliferative and metastatic genes. Furthermore, it induced anti-proliferation in cancer cells. The results suggested that AFE not only reduced blood glucose concentration as metformin but also showed its potential use in cancer immune chemoprevention/therapy via hypoglycemic effect, ROS scavenging, and PD-L1 suppression [191]. In addition, IPAF stimulated expressions of TLR signal-related genes and the activation of NF-κB. IPAF could induce classically activated macrophage differentiation via TLR4-dependent NF-κB activation and had potential of IPAF to modulate the Th1 response [28].

3.6 Epigallocatechin gallate

The green tea polyphenol epigallocatechin gallate (EGCG) has not shown cytotoxicity to normal cells but induces apoptosis and growth inhibition of cancer cells [192, 193]. EGCG inhibits uterine leiomyoma cell growth *in vitro* and *in vivo*. The use of a green tea extract with 45% EGCG content has demonstrated clinical activity without side effects in women with uterine fibroid symptoms [194]. However, there are several shortcomings of EGCG including low stability, poor bioavailability, and high metabolic transformations under physiological conditions. All present challenges for its development as a therapeutic agent [194].

The signal transduction pathway by which EGCG exerts cell cycle arrest and induction of apoptosis remains to be clarified. Several mechanisms of cell-cycle arrest by EGCG have been postulated [195]. Transcription factor, p53 regulates downstream genes important in cell cycle arrest, DNA repair, and apoptosis. Loss of p53 in many cancers leads to genomic instability, impaired cell cycle regulation, and inhibition of apoptosis [196]. EGCG-treated HuLM cells exhibited increased expression of several genes that represent p53 pathway such as *BAX*, *p21*, *transformed 3 T3 cell double minute 2* (*MDM2*) and tumor protein p53 inducible protein 3 (*TP53I3*) [30]. The NF-κB signal pathway was impaired by EGCG and the expression of bcl2A1, a key factor in NF-κB pathway, was reduced 11.8-fold in 100 μM EGCG-treated uterine fibroid HuLM cells [30] compared to untreated control.

The BCL family includes proapoptotic members and antiapoptotic members, such as BAX and BCL-2, respectively. The effects of apoptosis or anti-apoptosis supplementary depend on the balance between BCL2 and BAX rather than on the BCL2 quantity alone [197]. EGCG treatment causes BCL2 to dramatically decrease while BAX up-regulates [30]. Additionally, the D-type cyclins, through the interaction with CDKs-forming cyclin d1-CDK4/6 complexes, are mainly responsible for driving the cell cycle from G1 to S phase [198]. A significant decrease was observed in the expression of CDK4 and PCNA in EGCG treated uterine fibroid HuLM cells [30].

4. Conclusion remarks

The current clinical uterine fibroid therapies are restricted to their short-term efficacy and unpleasant side effects. Unless the patients are postmenopausal, hysterectomy is generally not recommended. In terms of expanding medical options, alternative therapies for uterine fibroids have been explored. In addition to herbal medicines we discussed, natural products such as vitamin D, berberine, and others are being used for alternative uterine fibroid treatments. Moreover, it may be more effective when natural compounds combined with hormonal agents for uterine fibroid therapy. We have shown that resveratrol combined with thyroid hormone

analogue, tetrac can compensate for resveratrol-induced RRM2 side effects in colorectal cancer animal xenograft model [199]. However, to search for a safe and effective medication for uterine fibroid requires further human clinical trials of these herbal compounds before promoting widespread usage.

Acknowledgements

The research described in this article from our team was supported in part by the Chair Professor Research Fund to Dr. K. Wang and Dr. J. Whang-Peng, by TMU Research Center of Cancer Translational Medicine from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan, by grants from the Ministry of Science and Technology, Taiwan (MOST107–2314-B-038-017 and MOST108–2314-B-038-050). We appreciate Miss Evelyn Yu-Chun Chen for her stunning proofreading expertise. The authors would like to extend their most sincere appreciation to Miss ABu and Miss Ya-Jung Shih for their prodigious research contributions from our group as mentioned in text.

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