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Review Article

A Review of the Anti-Fibroid Potential of Medicinal Plants: Mechanisms and Targeted Signaling Pathways

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ABSTRACT

Uterine fibroid or leiomyoma is the most common gynecological disorder affecting women. Treatment of symptomatic fibroids to date has been surgical, consisting of total abdominal hysterectomy or myomectomy. To decrease surgery's impact, patients are progressively looking for uterus-protecting, negligibly obtrusive therapies/prevention for asymptomatic/symptomatic uterine fibroids. Medicinal plants/herbs and their active phytoconstituents have been used for the therapy of fibroids and associated uterine complications. Therefore this review highlights mechanisms by which phytochemicals modulate fibroid growth pathways. To achieve this aim, we performed a systematic search within the two largest medical-related scientific databases, PubMed and SCOPUS. We considered all papers representing original research and reporting specific phytochemicals used in the studies. Of the 227 papers identified, only twenty-six of these met the required considerations: 80.77% *in vitro*, 15.39% *in vivo*, and 3.84% *in silico*. The most studied plants and phytoconstituents used in treatment/prevention to inhibit fibroid growth/proliferation pathways were: *Scutellaria barbata* D. Don, *Curcuma longa* L. (Turmeric), and resveratrol, curcumin, and anthocyanins, respectively. Also, the main pathways of target for fibroid inhibition were cell-cycle arrest, apoptosis through an increase in ROS above cell viability thresh-hold, and inhibition of ECM proteins via reduction of growth factors. This review highlights natural anti-fibroid phytoextracts and the pharmacological mechanism by which they modulate fibroid pathways, thus providing key insights to developing new and innovative therapeutic options for the management of symptoms in women with uterine fibroids.

Keywords: Phytochemicals/phytoconstituents, uterine fibroids, signaling pathways, cell cycle, medicinal plants.

Introduction

Uterine fibroids (leiomyomas) are typical benign smooth muscle pelvic tumors in women of reproductive years.[1-2] Its occurrence depends on age/race, occurs after menarche,[1, 3-4] and has been found to arise in about 4% of women 20–30 years of age, 11%-18% in those that were 30-40years, and 33% in women between 40–60 years.[5] In South-Western Nigeria, a prevalence of 6.83%,[6] and 35%–40%[7] was reported in Akure and Ile-Ife, respectively. Similarly, in the eastern part of Nigeria, a prevalence of 25% in Enugu State,[8] and 41.95% in Calabar were also recorded.[9] Fibroids present as symptomatic or asymptomatic forms, with a larger percentage of fibroid patients being asymptomatic and having multiple/solitary neoplastic growths. Symptomatic fibroids, on the other hand, accounts for about 25–50% of presented cases,[1-2, 10] characterized by reproductive complications, pelvic pressure (bladder and bowel), abnormal uterine bleeding/acute pelvic pain, hemorrhage or infection, abdominal protrusion, frequent urination and bloating as symptoms.[2, 11-12]

Leiomyomas stem from the excessive growth of connective and smooth muscle uterine tissues due to an alteration of normal myocytes, as well as high levels of genomic instability in differentiation, extracellular matrix (ECM) production, and cell proliferation genes.[13-14] These dysregulated genes could then be secondarily induced by other synergistic pathways, indirectly leading to fibroid growth.[15-16] Implicated pathways are a complex network of intracellular and extracellular signaling, involving growth factors, membrane-bound receptors of estradiol and progesterone-like receptor tyrosine kinases (RTKs), and PI3K/Akt/mTOR pathways.[17-19]

While early inception of menstrual cycles may multiply myometrium cell divisions during reproductive years, leading to an increased risk of the dysregulated gene(s) that mediate myometrial proliferation, age, epidermal/epigenetic growth factors, positive family history, hormonal/genetic factors associated with pre-menopause, obesity, exercise, racial/geographic differences, diet and use of oral contraceptives play facilitative or synergistic roles in fibroid growth.[20-21] Hyper-insulinemia is also regarded as a risk factor, as insulin affects fibroid growth by a direct trigger of myometrial smooth muscle cells or indirectly by an elevation in circulating ovarian hormone amounts.[22-24]

First-line therapies for uterine fibroid (UF) treatments are medical, and the choice of treatment is individualized based on symptoms, desire for subsequent fertility, fibroid size/location, and history of past therapies.[2, 25-26] Presently, there are three main classes of treatments: 1) Drugs, which help to reduce/manage pain and discomfort associated with heavy menstrual bleeding and also shrink the tumors.[27-28] 2) Surgery, the gold standard for UF management, ranging from partial to total uterus removal, abscission of the tumor, and anatomical re-modeling of the uterus.[29-31] 3) The use of non-invasive methods such as laser and radiofrequency for fibroid annihilation and reduction of blood supply to the uterus/fibroid cells.[32-34]

Although there is a wide range of treatment options for UFs, various issues such as infections, discomfort/pain, need for surgical intervention following non-surgical/surgical options, and fibroid

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regrowth has been recorded.[35-36] These complexities resulting from existing fibroid therapies and the cost of conventional treatments, necessitated the need for other novel options. Also, there is a rising commercial/scientific interest to develop novel antifibroid drugs from plants as naturally derived options having inherent properties.[37-38]
Plants produce a wide spectrum of bioactive compounds known as secondary metabolites. Flavonoids, terpenes, and phenol compounds are three main phytoconstituents with various biological roles in disease therapy that have been used together with existing medical treatments.[39] Despite prevailing prevention and fibroid management methods, identification of phytoconstituents with antifibroid abilities that have little/no adverse effects remains a major issue to the scientific and biomedical community, and in some cases, the mechanism of action of the recognized phytoconstituents is unclear.
Hence, this study discusses scientifically validated medicinal plants/phytoconstituents that possess potential therapeutic effects in fibroid management, growth/proliferation, and their mechanisms of action. This study would increase awareness and awaken the intervention of researchers for further scientific research in less invasive/absolute preventive fibroid treatment and prevention therapies, especially in Nigeria and Africa at large.

Materials and Methods

We carried out a comprehensive systematic literature search of the two largest medical-related databases: PubMed and Scopus till July 2020, using different combinations of the following keywords; plants OR phytochemicals OR "medicinal plants" OR "medicinal herbs" OR herbs AND fibroid OR leiomyoma OR "uterine leiomyoma" OR "uterine leiomyosarcoma" OR "uterine myomatosis" OR "uterine leiomyomata" OR fibromyoma OR fibroleiomyoma OR leiomyosarcoma. The articles were screened independently by KOD and AEN, first by title and abstracts followed by full-text screening. Discrepancies were resolved by discussion with OAR. The peer-reviewed/original articles reporting the use of medicinal plants/herbs and their respective phytoconstituents for the prevention and treatment of fibroids cells/cell lines were selected. Also, only those papers that showed the antifibroid effects of these plants/mechanisms by which they exerted their effects were included in this study.
We excluded review articles, case studies, letters to the editor, articles without full texts, and non-English articles. Studies that utilized other pharmacological administration methods from medicinal plants were also excluded.
The following data were obtained from included studies and used to collate a predesigned data collection table: author/year of publication, plants, phytochemicals, cell lines, treatment mechanisms/signaling pathways, and study type. Plants' names were also properly identified and authenticated by an experienced botanist.

Results and Discussion

Of the 26 articles selected from the databases following the search strategies described in Fig 1, 80.77% were *in vitro* studies on specific rat and human cell lines, 15.39% were *in vivo* studies, and 3.84% *in silico*. The plants and phytochemicals from the selected articles are listed in Table 1. Most of the identified articles had their studies conducted in China, Japan, and Korea. Many of the *in vitro* studies, involved leiomyoma and normal (myometrial) tissues cultured differently to study and compare the effects of the various phytochemicals on inhibition and protection from fibroid growth respectively. Also, the identified mechanisms targeted in fibroid reduction were: growth arrest via cell cycle inhibition (G2/M arrest, cyclin A1, cyclin B1, CDK1, CDK_4, BCL_2, BIM, BAX, p53, p21, TP53I3), AKT-mTOR, PARP, growth factors ($VEGFR_2$), glycolysis inhibition, induction of apoptotic pathways via caspase activation, and inhibition of ECM proteins (collagen1A1, fibronectin, and versican).
For the *in vivo* studies, experimental models used included female rodents: (BALB/cAJC female nude mice 5–6 weeks old, Sprague Dawley rats, Wistar rats), and 3 months old Japanese quails (*Coturnix japonica*). Japanese quail is a great experimental model for human uterine leiomyoma research because tumor occurs randomly in the bird's oviduct, an organ comparable to the human uterus.[40] The methods used for inducing fibroids in the *in vivo* studies included administration of diethylstilbestrol (DES),[25,26] and subcutaneous implantation of SK-UT-1 tumor cells in mice,[41] The duration of DES exposure varied from 14-20 weeks in rats to 365 days in the Japanese quail.[40] Also, 95% and 60% ethanol extraction, respectively, were used in two of the studies.[41-42] The methods of treatment administration also varied from intragastrical/gavage[42-43] to intraperitoneal.[41]In some of these studies, more than one plant was used jointly, whether as a measured concoction, or a mixture to test the synergistic effects of the combined plants. As shown in Figure 2, plants in the family of the Zingiberaceae and Paeoniaceaeoccurred the most in this review with a frequency of 13%, followed by plants from these families: Berberidaceae, Lauraceae, Rosaceae, Lamiaceae, Fabaceae, and the Vitaceae, with a frequency of 6% each. Similarly, *Curcuma longa*(Turmeric)[41,44] *Fragaria* × *ananassaDuch.* (Strawberry)[45-46] and *Scutellariabarbata* D. Don (SB)[47-50] were used in more than one study, with anthocyanins[45-46]curcumin[41, 44] fisetin,[78] and resveratrol[47,49,51-52]showing great antifibroid phytochemical abilities.
From the included studies as well, induced oxidative stress, induction of apoptotic pathways via caspase activation and mitochondrion pathways, PCNA/HSF-1 downregulation, growth factor modulation, glycolysis inhibition, and inhibition of ECM components (collagen1A1, fibronectin, and versican) were molecular mechanisms of the target for anti-fibroid treatment/prevention (plants/phytochemicals).[18, 53-54]
Medicinal plants are plants, which have inherent bio-active substances that can be utilized for treatment or which are precursors for producing drugs.[39, 55] Phytochemicals, on the other hand, are plant-based chemical constituents with disease-preventive properties.[55] Curcumin, EGCG (epigallocatechin gallate), resveratrol, anthocyanin, and quercetin[56-58] are only part of the wide range of phytochemicals that are still being studied in fibroid therapy/prevention, and although mostly known for their antiproliferative effects, the efficacy of these phytochemicals on signaling pathways is yet to be addressed sufficiently in leiomyoma cells.

Plants and phytochemicals targeting oxidative stress
Reactive oxygen species (ROS) are extremely reactive short-lived molecules whose production exists in equilibrium with several antioxidant defenses.[59] Oxidative stress is a key modulator of profibrotic gynecologic disorders such as fibroids and entails the accumulation of newly produced ECM components rising from a connective tissue manufacturing/degradation imbalance, including multiplication of distinct fibroblastic cells which contribute to ECM homeostasis/turnover and thus fibroid growth.[60-62] In physiological conditions, ROS production has double-edged sword features regarding its low-level cell signaling modulation, and its high-level cytotoxicity.[63] Therefore, ROS-inducing methods are based on the principle that raising ROS levels above cytotoxic thresholds breaks the redox homeostasis selectively to kill cancer cells. Thus, if exogenous ROS-producing factors are stimulated, the tumor cells that are redox-imbalanced are made more susceptible than normal cells, accordingly prompting cytotoxic effects by oxidative stress-dependent pathways to induce necroptosis, apoptosis, ferroptosis, anoikis, and autophagic cell death.[63-64] This mechanism poses an important apoptotic regulatory mechanism in fibroid prevention/therapy. In this review, Anthocyanins, in particular, induced fibroid cell death by the dual mechanisms via which ROS exerts therapeutic effects both at low and high concentrations, but especially by an overproduction of ROS in leiomyoma cells, resulting in apoptosis induction. Conversely, a different effect was observed in myometrial cells by the reduction in ROS concentrations that resulted in an improvement of cellular viability, thus indicating the preventive potential of strawberry extract in maintaining normal homeostatic cell conditions.[46, 51]

Plants and phytochemicals targeting apoptosis
Apoptosis (programmed cell death), is a highly regulated morphological and biochemical process essential for cell proliferation and cell cycle maintenance, as well as a defense mechanism during immune responses/cell damage by diseases.[65-67] Several critical cell

death checkpoints, occur during immune development and are under surveillance by the Bcl-2 protein members. These classes of proteins include both anti and pro-apoptotic members as well as the tumor necrosis factor death receptor family.[68]Alterations in the proper expression or functioning of these cell death modulators bring about pathological conditions, one of which is tumor growth.[68]

Therefore, the effect of cell proliferation in opposition to sustained cell survival in fibroid pathogenesis is of growing interest in the treatment of fibroids.[69-70]

Both BAX (Bcl-2-associated X) and Bcl-2 (B-cell lymphoma/leukemia-2) are apoptosis-regulating proteins. While Bcl-2 expression leads to extended cell survival by limiting caspase stimulation,[71-72] BAX overexpression leads to an increased speed in programmed cell death.[73-74] Based on earlier studies, the anti-apoptotic mechanism implicated in fibroid growth have shown an increased expression of the anti-apoptotic, Bcl-2, compared to homologous myometrium, which could be affected by the endocrine environment.[51, 75] The apoptotic process is also associated with a group of cysteine proteases (the caspases) that serve key apoptosis control functions. Phytochemicals reviewed below triggered apoptosis in fibroids by raising ROS levels, which in turn stimulates the release of p53 to regulate apoptosis.

From the papers included in this review, apoptotic cell death was induced through the intrinsic apoptotic pathway. Curcumin induced apoptosis as shown by DNA fragmentation: a late apoptotic event,[44] while *Euonymus alatus* (Thunb.) Siebold (EA) induced GSH-depletion, thus facilitating the release of cytochrome c, which suggests that EA-induced apoptosis was by intracellular redox. EA has also shown to act as a pro-oxidant, inducing activation of caspase-3 and thus apoptosis through the mitochondrial pathway.[76]

Fisetin-induced apoptosis on the other hand was not by a solitary pathway, but by several established apoptotic pathways including extrinsic, intrinsic, MARK, autophagy, and p53-mediated pathways,[77] while growth inhibition of Flavokawain B (FKB) was by the elevation of pro-apoptotic proteins: BIM, p53 upregulated modulator of apoptosis (PUMA) and death receptor-5 (DR5) and a reduction of Survivin, an inhibitor of apoptosis protein (IAP).[78]

Gyejibongnyeong-hwan (GBH) consisting of *Poriacocos* (Schw.) Wolf., *Cinnamomum cassia Blume*, *Paeonia suffruticosa Andrews*, *Paeonialactiflora Pallas*, and *Prunus semen* greatly altered Bax to Bcl-2 ratio, thus initiating intrinsic p53-dependent apoptosis by an increased level of mitochondrial superoxide anions.[79] GBH also amplified procaspase-9 expression and activated caspase-9/-3, thus stirring up apoptosis using caspase fragmentation in treated cells. *Orthosiphon stamineus* Benth. extracts inhibited proliferation and induced apoptosis against SK-UT-1 fibroid cells by the involvement of the Bcl-2/Bax signaling pathway, phase G0/G1 cell cycle arrest, and fibroid growth-related gene suppression.[80]

S. barbata triggered apoptosis by Caspase 3/Caspase 3-like protease activation.[48] Resveratrol treated cells proceeded to apoptosis, as the release of cytochrome c from the mitochondria activated pro-caspases, thus converting poly-ADP ribose polymerase (PARP) to cleaved PARP (inactive form).[51] Thus, DNA repair is affected, and apoptosis is induced. Berberine treatment also stimulated p53 expression, thus causing BAX-dependent apoptosis in fibroid cells, with little influence on the expression of similar genes and apoptosis in normal human uterine smooth muscle cells (UtSMCs). This suggests that (Berberine) BBR induces apoptosis via the p53-dependent pathway.[75] *Labisia pumila* (Blume) Fern.-Vill. was also found to moderately induce apoptotic cell death against SK-UT-1 in a concentration-dependent pattern.[81]

Plants and phytochemicals inducing cell cycle arrest

Induced cell cycle arrest is genetic manipulation or application of chemicals to halt cell cycle progression artificially.[82] Cell processes (genome duplication and cell division) could be halted either temporarily/permanently in the G1, S, or G2/Mitotic phases, where an induction by exogenous stimuli is required for the controlled artificial cell cycle checkpoint activation.[83-84]

Studies included in this review have shown antiproliferative effects of phytochemicals like EGCG, a green tea extract, flavokawain, and berberine. *In vitro*, EGCG dose-dependently increased apoptosis factors like BCL-2 and BCL-$2A_1$,[56] and decreased CDK_4 expression in EGCG- treated HuLM cells, thus leading to cell-cycle arrest caused by a reduction in cyclin D_1 mRNA and CDK_4 protein, thus impairing cyclin D_l-CDK_4 complex kinase function.[56] An elevation in cyclin-dependent kinase inhibitor 1A ($CDKN^1A$) mRNA levels is also noticed following treatment with EGCG. Studies with Eker rat tumor-derived uterine leiomyoma (ELT)-3 cells *in vivo* showed that EGCG also arrested fibroid enlargement and reduced uterine fibroid mass in Eker rats two weeks after treatment began.[54] Clinical trials are ongoing to evaluate EGCG efficacy in women with presented uterine fibroids.[57, 85-86]

BBR has been shown to significantly stimulate cell cycle arrest in the G_2/M phase by an alteration in G_2/M cell cycle arrest-related genes (cyclin B_1, A_1, CDK) and caused p53 and p21 overexpression, thus leading to G2/M cell-cycle arrest,[47, 75] while fibroid escalation inhibitory outcome of Flavokawain B (FKB) is coupled to G_2/M arrest. Similarly, SB treatment is characterized by a rise of cells in the G1 cell cycle phase, thus suggesting an inhibition of the G_1-S transition or a G_1 anti-proliferative arrest on human myometrium and leiomyoma SMCs.[78] Resveratrol also favored S and G_2/M phase cell cycle arrest in ELT3 cells and S phase arrest in UtSMCs and inhibited CDK_4, CDK_2/N cyclin D_1 protein expression in ELT_3 cells and UtSMCs.[51]

Plants and phytochemicals targeting PCNA/HSF-1

Heat Shock Transcription Factor 1 (HSF-1) is a stress-inducible DNA-binding transcription factor that mediates heat shock response (HSR) transcriptional activation, thus producing heat shock proteins (HSPs).[87-88] It is involved in cancer growth regulation, with a constitutive expression in HeLa cells leading to Fas-mediated killing.[89-90] Thus, an increased HSF-1expression in tumor cells through either gene therapy or pharmacologic approaches results in fibroid shrinking through the Fas receptor.[88,91] From the reviewed papers, only EGCG regulated heat-shock factor1 (HSF1).[56]

Proliferating cell nuclear antigen (PCNA) is a DNA clamp that serves processivity functions in eukaryotic cells, essential for DNA repair, chromatin remodeling, replication, and epigenetics.[92-93] PCNA is a homotrimer that encircles the DNA, thus acting as a protein recruit scaffold through two PCNA-interacting motifs: AlkB homolog 2 PCNA interacting motif (APIM) (mainly important in the context of genotoxic stress) and PCNA-interacting peptide (PIP) box (concerned in DNA replication).[94-95] PCNA labeling techniques, which is effective for evaluating cell proliferation rates in leiomyoma tissues was significantly elevated compared to typical myometrial tissues, and is associated with a cell's proliferative state, depth of invasion, vascular invasion, tumor stage, and organ metastasis, and is thus be used as a prognostic factor.[96] From the included *invitro* papers, EGCG, *S.barbata*, resveratrol, and berberine were reported to decrease PCNA levels.

Plants and Phytochemicals Targeting Extracellular Matrix (ECM) Reduction and Modulating Growth Factors

Increased ECM deposition of proteoglycans (fibromodulin/versican) and associated proteins (collagens/fibronectin) serve as key characteristics of uterine fibroids.[97-98] While collagen serves ECM's central structural role, maintaining cellular morphology and playing important roles in migration, proliferation, and fibrotic processes, Fibronectin, a glycoprotein, functions in cell growth, differentiation, and adhesion. Versican, a chondroitin sulfate proteoglycan, on the other hand, functions in cell adhesion, tissue stabilization, cell migration, tissue homeostasis, and inflammation.[99] Growth factor signaling can be controlled outside of cells by extracellular matrix proteins and proteolytic catalysts. Therefore, arising amount of growth factors, including TGF-beta's, FGFs, IGFs, and HGF, are associated with extracellular matrix proteins. These growth factors, then regulate cell differentiation, remodeling, synthesis, and proliferation of the extracellular matrix. From this review, Anthocyanins,[50] Quercetin, indole-3-carbinol,[100] and joint Curcumae rhizoma-Sparganii rhizoma (CRSR) herb extracts inhibited ECM components (fibronectin, versican, and collagen1A1).[42] Resveratrol also regulated fibronectin,

α-SMA, vimentin, COL1A1, and β-catenin proteins *in vitro* by interacting with these proteins, thus resulting in a downregulated expression.[51]

From this review, strawberry extracts down-regulated activin A-induced mRNA expression of ECM proteins in fibroid cells, thus suggesting potential antifibroid potentials of anthocyanins.[50] Stigmasterol reduced $VEGFR_2$ expression, thereby suppressing the activity of downstream signaling molecules through anti-inflammatory, anti-genotoxic, and anti-oxidant properties.[101] Berberine also reduced pituitary tumor-transforming gene-1 (PTTG-1) expression *in vitro*, containing bFGF, thus halting the interaction between PTTG-1 and bFGF and thus fibroid reduction.[75] SB also reduced the expression of IGF-I, thus suggesting that SB-induced fibroid reduction was by IGF-I reduction in the uterus.[49] CRSR combined extracts also regulated important fibroid signaling pathways: TGFbeta/Smad, MAPK, and PPAR signaling pathways.[42]

Plants and phytochemicals targeting glycolysis and cycloxygenase-2

Glycolysis and Oxidative phosphorylation (OXPHOS) work synergistically to maintain energetic and cellular balance. In normal conditions, OXPHOS supplies 70% of the energy consumed by the cell; however, in hypoxia conditions (inadequate oxygen supply), glycolysis is enhanced to repay the impaired OXPHOS function.[102-103] Fibroid cells are severely hypoxic than normal myometrium, thus indicating an elevated glycolytic action in these cells. The reliance of tumors on glycolytic pathways to generate ATP as a major energy supply serves as a biochemical basis for the formulation of treatments that selectively lead to tumor cell death by glycolytic inhibition. From this review, anthocyanins reduced glycolytic rates in fibroid cells.[45] Also, both leiomyoma and myometrial cells indicated no clear oxygen consumption rate (OCR) difference after anthocyanin treatment, which suggests that fibroid cell death, at least in part, by inhibiting glycolysis.[45]

Cycloxygenase-2 is an important enzyme that forms prostaglandin E_2 (PGE2) from arachidonic acid and is mostly up-regulated in solid tumors. Increased COX-2 expression significantly enhances cell proliferation/tumorigenesis and has been found significantly elevated in fibroid cells.[104-105] From this review, BBR down-regulated COX-2 expression in fibroid cells. Thus COX-2 reduction functions in BBR-induced apoptosis in fibroid cells.[75]

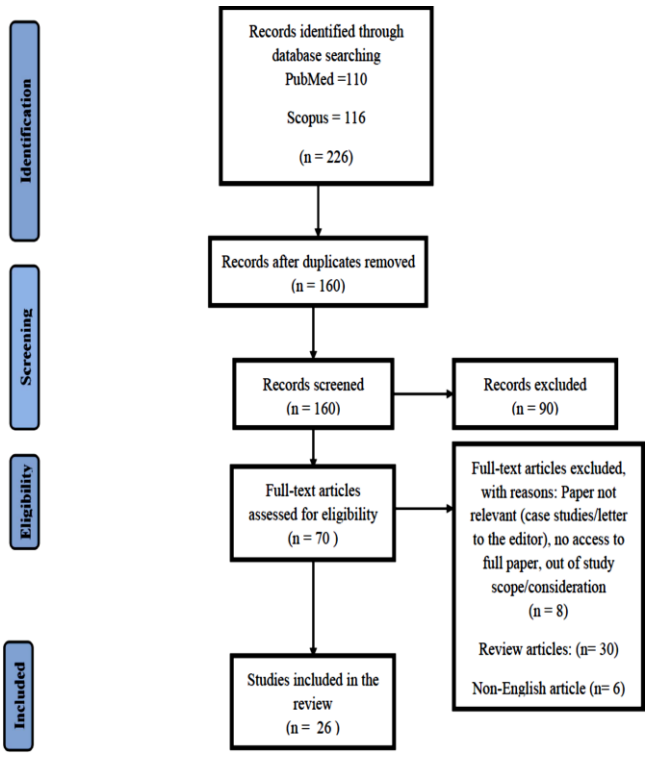

Figure 1: Flowchart of search and selection process

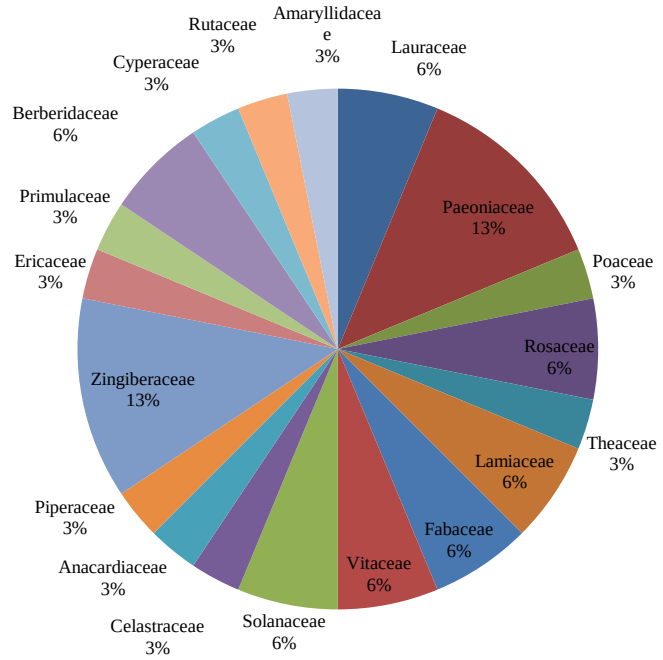

Figure 2: Frequency of Families of the Plants

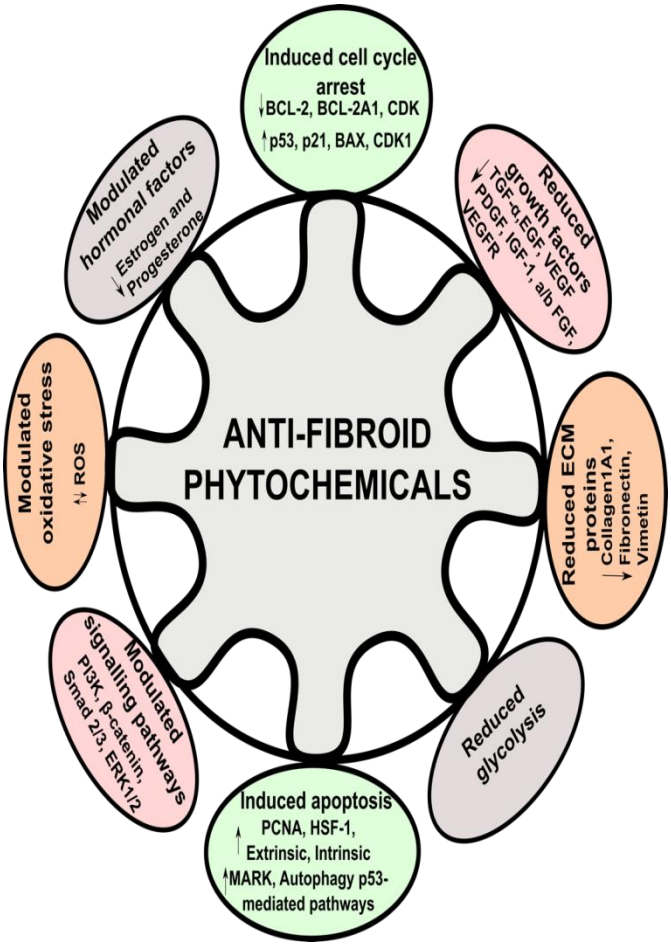

Figure 3: Summary of Phytochemical Target Mechanisms against Fibroids

Table 1: Plants and Phytochemicals with Anti-fibroid Properties

	References	Plants	Families	Bioactive Compounds	Cell Lines	Findings/MOA
1.	Lin *et al.*[101] (*in vitro*)	Adlay (Coxilachrtma-jobi L. var. ma-yuenStapf.), seeds of *Coixlacryma-jobi* L. var. ma-yuenStapf (Adlay seeds in this study were separated into four parts: testa, bran, hull, and polished adlay).	Poaceae	Stigmasterol, β-sitosterol, Campesterol	Eker rat-derived uterine leiomyoma (ELT3) cell line and primary human uterine smooth muscle (UtSMC) cells	Ethyl acetate fraction of the hull extract was used. Stigmasterol suppressed hUL cells and caused less toxicity in primary human normal uterine smooth muscle cells (UtSMC) compared to β-sitosterol Expression of $VEGFR_2$ was also decreased by stigmasterol, thus suppressing other signaling activity via its anti-inflammatory, anti-oxidant, and anti-genotoxic properties.
2.	Zeng *et al.*[106] (*in silico*)	Guizhi Fuling Wan (GFW) comprises of: Poria/ Indian bread (Fuling), a fungal herb from the dry sclerotium of *Poriacocos* (Schw.) Wolf. Cinnamomi Ramulus (Gui Zhi), the dried young stem of *Cinnamomum cassia* (L.) J.Presl. Cortex Moutan (Mu Dan Pi), the root bark of *Paeonia suffruticosa* Andr. Radix PaeoniaeRubra (Chi Shao), dried root of the plant *Paeonialactiflora* Pall. and *Paeoniaveitchii* Lynch	Lauraceae Paeoniaceae Paeoniaceae Paeoniaceae	Cinnamic aldehyde, oxypaeoniflorin, polyporenic acid C, 3-(2-methoxyphenyl)-2-propenal, mudanpioside H, pachymic acid, trametenolic acid, paeoniflorin, gallic acid, cinnamic acid, apiopaeonoside, suffruticoside B/D, paeonilide, galloylpaeoniflorin, benzoic acid, hexagalloyl-glucopyranose, mudanpioside C, benzoylalbiflorin, paeonol, albiflorin and amygdalin.		Network pharmacology showed several new signaling biological pathways mediating GFW efficacy on UFs, which supports studies on herbal formulae combinations, thus increasing the outcomes for TCM drug discovery.

3. Islam *et al.*[45] (*in vitro*)	Strawberry of Alba cultivar (*Fragaria* × *ananassa* Duch.) (Whole fruit)	Rosaceae	Quercetin, kaempferol, Ellagic acid, catechins and, flavonols, anthocyanins, flavanols, condensed tannins (gallotannins, and ellagitannins) hydroxycinnamic acid, and hydrolyzable tannins	Myometrial and leiomyoma cells	ROS production led to an elevation in the amount of dead and apoptotic cells, thus signifying an initiation of cell death via anthocyanins due to ROS overproduction. Anthocyanins also reduced ROS production in myometrial cells, as no major disparity was seen in the levels of the dead, live, and apoptotic myometrial cells, indicating their ability to regulate normal homeostatic cell conditions. Strawberry decreased glycolytic rate, and inhibited ECM proteins (fibronectin, versican, and collagen1A1), while inhibiting activin A-induced mRNA expression of these proteins in leiomyoma cells, these suggest strawberry as a glycolytic inhibiting and antifibrotic candidate for uterine leiomyoma treatment and/or prevention.
4. Zhang *et al.*[56] (*in vitro*)	Green tea. Green tea is derived from *Camellia sinensis*(L.) Kuntze	Theaceae	Epigallocatechin gallate (EGCG)	Human leiomyoma cells (HuLM)	The anti-proliferative effects of EGCG were shown to be both dose and time-dependent, leading to a significant PCNA and CDK_4 reduction in HuLM cells. The initiation of apoptosis was shown by a BCL_2 down-regulation at RNA and protein levels. BAX was also elevated, while a rise in BCL_2A_1 and BCL_2mRNA was observed. EGCG treated HuLM cells upregulated expression in genes that mediated the p53 pathway: cyclin-dependent kinase inhibitors (CDKN2B, CDKN1A) and tumor protein p53 inducible protein 3 (TP53I3).
5. Kim *et al.*[50] (*in vitro*)	*Scutellaria barbata* D. Don (Rhizomes)	Lamiaceae	Alkaloids and flavones, Apigenin and Luteolin	Human uterine LM cells and normal human myometrial SMCs	Leiomyomas treated with SB led to reduced Bcl-2 protein expression in cultured leiomyoma cells than in the control, as SB halted the transcription of Bcl-2 protein in leiomyoma cells.
6. Zakaria *et al.*[81] (*in vitro*)	*Labisia pumila* (Blume) Fern.-Vill. (whole plant)	Primulaceae	Caffeic acid and Gallic acid	Uterine leiomyosarcoma SK-UT-1 cells and normal A7r5 smooth muscle cell	*L. pumila* initiated apoptotic cell death against SK-UT-1 in a concentration-dependent pattern and was thus able to shrink tumor cells due to the synergistic effect of both Phytochemicals isolated from *L. pumila* extracts.

7. Kim *et al.*[76] (*in vitro*)	*Euonymus alatus* (Thunb.) Siebold (Whole plant)	Celastraceae	Cardenolides, 3,4-dihydroxycinnamic acid (caffeic acid)	Human ULSMC and human myometrial smooth muscle cells	Results showed that EA functioned as a pro-oxidant, inducing apoptosis and caspase-3 activation through the mitochondrial pathway.
8. Wu *et al.*[75] (*in vitro*)	*Berberis aristata* DC. and *Berberis aquifolium*Pursh	Berberidaceae Berberidaceae	Berberine (BBR)	Immortalized UtLM and (UtSMC) human myometrial cell lines	BBR inhibited human leiomyoma cells by apoptosis and cell growth inhibition. This was stimulated by G2/M phase cell arrest through the p53 dependent cell death pathway. BBR treatment inhibited UtLM cell proliferation and blocked the P4 and E2-induced proliferation of these cells. The study was not performed on the myometrium BBR also downregulated E_2F_1 and COX-2 expression in normal myometrial cells, thus indicating the preventive ability of BBR in transforming normal myometrial cells. Alternatively, in UtSMC cells, BBR did not affect PTTG1 expression but decreased E_2F_1 and COX-2 expression
9. Ju and Xiao,[43] (*in vivo*)	Xiang Fu (*Cyperus rotundus* L.) (Dried rhizomes)	Cyperaceae	Biflavone constituents: Amentoflavone, ginkgetin, isoginkgetin and sciadopitysin		Amentoflavone reduced serum progesterone and estrogen levels and inhibited uterine fibroids by upregulation of Bax, and a down-regulation of Bcl-2 levels in rats.
10. Wong *et al.*[44] (*in vitro*)	Turmeric (*Curcuma longa* L.)	Zingiberaceae	Curcumin	Human uterine LMS cell line- SKN	Curcumin induced both early and late apoptotic events in uterine LMS cells by PARP cleavage as an early apoptotic event, and DNA fragmentation respectively. Curcumin also inhibited growth by modulating the AKT-mTOR pathway.
11. Wong *et al.*[41] (*in vivo*)	Turmeric (*Curcuma longa* L.)	Zingiberaceae	Curcumin	Uterine LMS cell line, SK-UT-1	Curcumin suppressed tumor growth by modulating AKT–mTOR pathway *in vivo*.
12. Sahin *et al.*[40] (*in vivo*)	Tomato and tomato-based products (*Solanum lycopersicum* L.)	Solanaceae	Lycopene, phytoene, phytofluene, and the provitamin A carotenoid (ß-carotene)		Lycopene in tomato powder supplementation decreased the frequency and size of tumors in Japanese quail through an increase in antioxidant vitamins/maintenance of its serum levels.

13. Lee *et al.*[47] (*in vitro*)	*Scutellaria barbata* D. Don (Lamiaceae) (Rhizomes)	Lamiaceae	Steroidal saponins	Leiomyoma cells and normal SMC	SB significantly decreased the HCG-stimulatory effect on both myometrial and leiomyoma cells and decreased the production of cell cycle-related proteins in HCG-treated leiomyoma cells. In myometrial cells, there was no effect on proliferating cell nuclear antigen (PCNA), cyclin-E, CDC_2, or CDK_2 levels between HCG-treated cells and controls.
14. Lee *et al.*[48] (*in vitro*)	*Scutellariabarbata* D. Don	Lamiaceae		Uterine LMs and adjacent myometrial tissues	SB induced apoptosis through caspase 3 activation in leiomyomal LM-1 and LM-2 cell lines
15. Lee *et al.*[77] (*in vitro*)	Rhusverniciflua Stokes (RVS). Its accepted name is *Toxicodendronvernicif luum* (Stokes) F.A. Barkley	Anacardiace ae	Fisetin, Fustin, butein, gallic acid, butin, sulfuretin, quercetin, kaempferol-3-O-glucoside,coumaric acid and kaempferol	Uterine leiomyomas and normal myometrium cells	Fisetin induced cytotoxicity, apoptosis, and cell cycle arrest on leiomyoma cells but by all known apoptotic pathways: extrinsic, intrinsic, p53, autophagy, and MARK pathways.
16. Giampieri *et al.*[46] (*in vitro*)	Strawberries (*Fragariaxananassa*Duch.) (Whole fruit)	Rosaceae	Anthocyanin, Flavonol, vitamin C, and folic acids.	Myometrial and leiomyoma tissue	Outcome proved that strawberries reduced cellular viability in leiomyoma cells by increasing the rate of apoptotic and raising ROS concentration in leiomyoma cells. Strawberry also decreased the expression of fibronectin in leiomyoma cells.
17. Lee *et al.*[107] (*in vitro*)	Red clover [*Trifoliumpratense* L.]	Fabaceae	Irilone, prunetin, formononetin, and biochanin A	Ishikawa cells that stably expressing progesterone receptor B (PR-B)	Irilone exhibited synergistic interaction with progesterone to extenuate fibroids and endometriosis. Biochanin A, and formononetin, however, showed mixed antagonist action, while prunetin acted only as an antagonist against the progesterone-induced increase in Progesterone-response element (PRE/Luc) activity, which could increase endogenous PR expression.
18. Wu *et al.*[52] (*in vitro*)	Red wine, red grapes, and grape skin (*Vitis* spp. L.)	Vitaceae	Resveratrol	Eker uterine leiomyoma cell line (ELT-3)	Resveratrol induced apoptosis while reducing procaspase-3 and cytochrome c amounts in ELT3 cells and S phase in UtSMCs and decreased collagen I, fibronectin, fibromodulin, and biglycan levels in ELT-3 and UtSMCs.
19. Eskander *et al.*[78] (*in vitro*)	Kava Plant (*Piper methysticum* G. Forst.) and *Alpiniapricei* Hayata	Piperaceae Zingiberace ae	Flavokawain-B (FKB)	SK-LMS-1, ECC-1 (endometrial adenocarcinoma), and T-HESC (normal	FKB preferentially repressed the growth of uterine LMS by apoptosis and exhibited synergistic inhibitory effects on uterine LMS growth when combined with anti-

				endometrial fibroblasts) cells	tumor agents like docetaxel, and gemcitabine.
20. Kim *et al.*[49] (*in vitro*)	*Scutellaria barbata* D. Don (Stem)	Lamiaceae	Resveratrol, baicalin, berberine, apigenin, and luteolin	Uterine leiomyoma tissues and adjacent normal myometrial tissues	SB inhibited cell growth by blocking cells in G0/G1 phase of the cell cycle, thus inducing maximum apoptosis. SB also repressed leiomyomal cell expansion by IGF-I reduction in the human uterus.
21. Lee *et al.*[79] (*in vitro*)	Gyejibongnyeong-hwan (GBH): *Cinnamomum cassia* (L.) J.Presl., *Poriacocos* (Schw.) Wolf., *Paeonia suffruticosa*Andr., *Paeonia lactiflora* Pall., and *Prunusarmeniaca* L.	Lauraceae Paeoniaceae Paeoniaceae Rosaceae	Vanillic acid, cinnamic acid, caffeic acid, ferulic acid, quercetin and gallic acid.	Human uterine myoma cells (hUtMCs)	GBH elevated and reduced Bax and Bcl-2 proteins respectively, while caspase -3 and p53 were upregulated.
22. Lee *et al.*[47] (*in vitro*)	*Scutellaria barbata* D. Don (SB) (Rhizomes)	Lamiaceae	Emodin-8-O-glucopyranoside, baicalin, emodin, resveratrol and berberine	Myometrial and leiomyomal SMCs	SB showed anti-proliferative activity on leiomyoma cells through a G1 cell cycle arrest.
23. Chen *et al.*[51] (*in vitro/in vivo*)	Blueberries (*Vaccinium* L.), peanuts (*Arachishy pogaea* L.), and grapes (*Vitis* spp. L.)	Ericaceae Fabaceae Vitaceae	Resveratrol (RSV; trans-3,5,40 - trihydroxystilbene)	Eker rat-derived uterine leiomyoma (ELT-3) cell lines	RSV repressed primary human leiomyoma cell viability, mediated ECM genes (fibronectin) and proteins (vimentin, α-SMA, β-catenin, COL1A1) expression, and induced apoptosis *in vitro*. RSV also exhibited pleiotropic (pro-apoptosis, anti-proliferation, anti-oxidant, and anti-carcinogenic) effects both *in vitro* and *in vivo*
24. Pauzi *et al.*[80] (*in vitro*)	*Orthosiphonstamineus* Benth.	Lamiaceae / Labiatae	Terpenoid, phenolic, flavonoid, saponin, essential oil, and organic acids	Uterine leiomyosarcoma (SK-UT-1) cells	OS extracts inhibited proliferation and induced apoptosis against SK-UT-1 cells through the involvement of the Bcl-2/Bax signaling pathway.
25. Yu *et al.*[42] (*in vivo*)	Curcumaerhizoma-Sparganiirhizoma(CRSR) (Dried herbs)		Grailsine-Al-glycoside, Sparstolonin-B, Curcumenol	Myometrial and leiomyoma cells	Lowered serum levels of progesterone and estrogen and in CRSR-treated rats and markedly reduced uterine size by altering ECM-associated genes and/or their related pathways.
26. Greco *et al.*[100] (*in vitro*)	Curcumaerhizoma is the rhizomes derived from *Curcuma*	Zingiberaceae	Quercetin and indole-3-carbinol		I3C and Quercetin reduced fibronectin/collagen 1A1 mRNA expression in myometrial and leiomyoma

wenyujin	Zingiberaceae	cells, and reduced cell migration.
Rhizoma Sparganii is the dried rhizome of *Sparganium stoloniferum* (Buch.-Ham. ex Graebn.) Buch. Ham. ex Juz	Theaceae Rutaceae Solanaceae Amaryllidaceae	
Most edible vegetables and fruits, such as tea (*Camellia sinensis* (L.) Kuntze), lemon (*Citrus* x *limon* (L.) Burm. f. (pro. sp.), tomato (*Solanum lycopersicum* L.), onion leaves (*Allium* spp. L.) and strawberry (*Fragaria* x *ananassa* Duch.)	Rosaceae	

MOA=Mechanism of Action

Suggestions for future research

As established from this review, phytochemicals present as promising anti-fibroid agents. Nevertheless, increased attention is required to shed light on the following key issues:
(i) Despite Africans being at risk, we did not find plants indigenous to Africa in this review, and the cell lines were also not of African origin so future studies should include plants and cell lines of Africans. (ii)Need to overcome the limitations of poor bioavailability and potency of some phytochemicals. (iii) Most of the studies were *in vitro*. Therefore, there is a need for more *in vivo* and clinical studies on the therapeutic efficacy/mechanisms and dose intake of these phytochemicals. (iv) Targeted anti-fibroid therapy methods which selectively destroy fibroid cells while sparing the normal cells.

Limitation

This review was based on only two databases, and therefore may not be a total representation of all possible antifibroid plants and phytochemicals. Some target mechanisms might have also been left out.

Conclusion

Throughout this review, we discussed the inherent potentials of bioactive compounds as promising effective therapeutic agents via (i) halting cell proliferation via stimulation of cell cycle arrest, growth factors or their receptors, and the apoptotic pathway (ii) fibrosis inhibition through reducing expression of profibrotic growth factors, ECM deposition, arresting initiated cells that mediate myofibroblastic alteration; and (iii) downregulation of inflammatory mediators/glycolytic pathways. Based on the presented facts, these compounds modulated and regulated essential biological activities responsible for fibroid growth and development. Alone, these phytoconstituents are promising, but a combination of these could translate to additive therapeutic effects of substantial magnitude, which could result in a significant clinical therapy.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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References

1. Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. Int J Gynaecol Obstet. 2020; 149(1):3-9.
2. Donnez J and Dolmans MM. Uterine fibroid management: From the present to the future. Hum Reprod Update. 2016;22(6):665-686.
3. Khan AT, Shehmar M, Gupta JK. Uterine fibroids: Current perspectives. Int J Womens Health. 2014; 6:95-114.
4. Dvorska D, Brany D, Dankova Z, Halasova E, Visnovsky J. Molecular and clinical attributes of uterine leiomyomas. Tumour Biol. 2017; 39(6):1010428317710226.
5. Ukaonu CB. Prevalence and sonographic patterns of uterine fibroid among women of reproductive age in Jos, Plateau state, Nigeria. Radiol. 2017.
6. Ukwenya V, Maduemezia N, Afolayan O, Alese O, Thomas W. Prevalence of uterine fibroid in a south-western Nigerian population: A sonographic study. JECA. 2015; 14(1):24.

7. Fasubaa OB, Sowemimo OO, Ayegbusi OE, Abdur-Rahim ZF, Idowu BS, Ayobami O, Babalola OE, Akindojutimi AJ. Contributions of uterine fibroids to infertility at Ile‐ife, south‐western Nigeria. Trop J Obstet Gynaecol. 2018; 35(3):266-270.
8. Ozumba B, Nzegwu M, Anyikam A. Histological patterns of gynaecological lesions in Enugu, Nigeria. A five-year review from January 1, 2000 to December 31st 2004. Adv Biores. 2011; 2:132-136.
9. Eduwem D, Akintomide A, Bassey D, Ekott M. Hysterosalpingographic patterns and relevance in the management of infertility in a Nigerian tertiary health institution. Asian J Med Sci. 2016; 7(5):70-74.
10. Stewart EA, Laughlin-Tommaso SK, Catherino WH, Lalitkumar S, Gupta D, Vollenhoven B. Uterine fibroids. Nat Rev Dis Primers. 2016; 2(1):16043.
11. Ikhena DE and Bulun SE. Literature review on the role of uterine fibroids in endometrial function. Reprod Sci. 2018; 25(5):635-643.
12. Hoffman SR, Vines AI, Halladay JR, Pfaff E, Schiff L, Westreich D, Sundaresan A, Johnson L-S, Nicholson WK. Optimizing research in symptomatic uterine fibroids with development of a computable phenotype for use with electronic health records. Am J Obstet Gynecol. 2018;218(6):610.
13. Baranov VS, Osinovskaya NS, Yarmolinskaya MI. Pathogenomics of uterine fibroids development. Int J Mol Sci. 2019; 20(24):6151.
14. Botía C, Camarasa S, Baixauli F, Sanchez A. Uterine fibroids: Understanding their origins to better understand their future treatments. J Tumor Res. 2017; 3(130):2.
15. Medikare V, Kandukuri LR, Ananthapur V, Deenadayal M, Nallari P. The genetic bases of uterine fibroids; a review. J Reprod Infertil. 2011; 12(3):181-191.
16. Yarmolinskaya MI, Polenov NI, Kunitsa VV. Uterine fibroids: The role of signaling pathways in the pathogenesis. A literature review. J Obstet and Women's Dis. 2020; 69(5):113-124.
17. Islam MS, Segars JH, Castellucci M, Ciarmela P. Dietary phytochemicals for possible preventive and therapeutic option of uterine fibroids: Signaling pathways as target. Pharmacol Rep. 2017; 69(1):57-70.
18. Borahay MA, Al-Hendy A, Kilic GS, Boehning D. Signaling pathways in leiomyoma: Understanding pathobiology and implications for therapy. Mol Med. 2015; 21(1):242-256.
19. Borahay MA, Asoglu MR, Mas A, Adam S, Kilic GS, Al-Hendy A. Estrogen receptors and signaling in fibroids: Role in pathobiology and therapeutic implications. Reprod Sci. 2017; 24(9):1235-1244.
20. Pavone D, Clemenza S, Sorbi F, Fambrini M, Petraglia F. Epidemiology and risk factors of uterine fibroids. Best Pract Res Clin Obstet Gynaecol. 2018;46:3-11.
21. Sparic R, Mirkovic L, Malvasi A, Tinelli A. Epidemiology of uterine myomas: A review. Int J Fertil Steril. 2016; 9(4):424-435.
22. Soave I and Marci R. From obesity to uterine fibroids: An intricate network. Curr Med Res Opin. 2018; 34(11):1877-1879.
23. Tak YJ, Lee SY, Park SK, Kim YJ, Lee JG, Jeong DW, Kim SC, Kim IJ, Yi YH. Association between uterine leiomyoma and metabolic syndrome in parous premenopausal women: A case–control study. Med. 2016; 95(46).
24. Uimari O, Auvinen J, Jokelainen J, Puukka K, Ruokonen A, Jarvelin MR, Piltonen T, Keinanen-Kiukaanniemi S, Zondervan K, Jarvela I, Ryynanen M, Martikainen H. Uterine fibroids and cardiovascular risk. Hum Reprod. 2016; 31(12):2689-2703.
25. Sabry M and Al-Hendy A. Medical treatment of uterine leiomyoma. Reprod Sci. 2012; 19(4):339-353.
26. Bonine NG, Banks E, Harrington A, Vlahiotis A, Moore-Schiltz L, Gillard P. Contemporary treatment utilization among women diagnosed with symptomatic uterine fibroids in the united states. BMC women's health. 2020; 20(1):1-13.
27. Lewis TD, Malik M, Britten J, San Pablo AM, Catherino WH. A comprehensive review of the pharmacologic management of uterine leiomyoma. Biomed Res Int. 2018; 2018:2414609.
28. Ali M and Al-Hendy A. Selective progesterone receptor modulators for fertility preservation in women with symptomatic uterine fibroids. Biol Reprod. 2017; 97(3):337-352.
29. Metwally M, Raybould G, Cheong YC, Horne AW. Surgical treatment of fibroids for subfertility. Cochrane Database Syst Rev. 2020; 1(1):CD003857.
30. Mas A, Tarazona M, Dasi Carrasco J, Estaca G, Cristobal I, Monleon J. Updated approaches for management of uterine fibroids. Int J Womens Health. 2017;9:607-617.
31. Chittawar PB, Franik S, Pouwer AW, Farquhar C. Minimally invasive surgical techniques versus open myomectomy for uterine fibroids. Cochrane Database Syst Rev. 2014(10).
32. Gupta JK, Sinha A, Lumsden MA, Hickey M. Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database Syst Rev. 2014; 12:CD005073.
33. Wang Y, Zhang S, Li C, Li B, Ouyang L. Minimally invasive surgery for uterine fibroids. Ginekol Pol. 2020; 91(3):149-157.
34. Nezhat C, Vang N, Vu M, Grossman J, Skinner J, Robinson K, Saini K, Vaid A, Maule L, Adler JR. A novel approach for treatment of uterine fibroids: Stereotactic radiosurgery as a proposed treatment modality. Curr Obstet Gynecol Rep. 2020:1-6.
35. Taylor DK and Leppert PC. Treatment for uterine fibroids: Searching for effective drug therapies. Drug Discov Today Ther Strateg. 2012; 9(1):e41-e49.
36. Sohn GS, Cho S, Kim YM, Cho CH, Kim MR, Lee SR, Working Group of Society of Uterine L. Current medical treatment of uterine fibroids. Obstet Gynecol Sci. 2018; 61(2):192-201.
37. Ciebiera M, Ali M, Prince L, Jackson-Bey T, Atabiekov I, Zgliczynski S, Al-Hendy A. The evolving role of natural compounds in the medical treatment of uterine fibroids. J Clin Med. 2020; 9(5):1479.
38. Veeresham C. Natural products derived from plants as a source of drugs. J Adv Pharm Technol Res. 2012; 3(4):200.
39. Islam MS, Akhtar MM, Ciavattini A, Giannubilo SR, Protic O, Janjusevic M, Procopio AD, Segars JH, Castellucci M, Ciarmela P. Use of dietary phytochemicals to target inflammation, fibrosis, proliferation, and angiogenesis in uterine tissues: Promising options for prevention and treatment of uterine fibroids? Mol Nutr Food Res. 2014; 58(8):1667-1684.
40. Sahin K, Ozercan R, Onderci M, Sahin N, Khachik F, Seren S, Kucuk O. Dietary tomato powder supplementation in the prevention of leiomyoma of the oviduct in the Japanese quail. Nutr Cancer. 2007; 59(1):70-75.
41. Wong TF, Takeda T, Li B, Tsuiji K, Kondo A, Tadakawa M, Nagase S, Yaegashi N. Curcumin targets the akt-mtor pathway for uterine leiomyosarcoma tumor growth suppression. Int J Clin Oncol. 2014; 19(2):354-363.
42. Yu CH, Zhao JS, Zhao H, Peng T, Shen DC, Xu QX, Li Y, Webb RC, Wang MH, Shi XM, Peng C, Ding WJ. Transcriptional profiling of uterine leiomyoma rats treated by a traditional herb pair, curcumae rhizoma and sparganii rhizoma. Braz J Med Biol Res. 2019; 52(6):e8132.
43. Ju Y and Xiao B. Chemical constituents of cyperus rotundus l. And their inhibitory effects on uterine fibroids. Afr J Med Health Sci. 2016; 16(4):1000-1006.
44. Wong TF, Takeda T, Li B, Tsuiji K, Kitamura M, Kondo A, Yaegashi N. Curcumin disrupts uterine leiomyosarcoma cells through akt-mtor pathway inhibition. Gynecol Oncol. 2011; 122(1):141-148.
45. Islam MS, Giampieri F, Janjusevic M, Gasparrini M, Forbes-Hernandez TY, Mazzoni L, Greco S, Giannubilo SR, Ciavattini A, Mezzetti B. An anthocyanin rich strawberry extract induces apoptosis and ros while decreases glycolysis and fibrosis in human uterine leiomyoma cells. Oncotarget. 2017; 8(14):23575.
46. Giampieri F, Islam MS, Greco S, Gasparrini M, Forbes Hernandez TY, Delli Carpini G, Giannubilo SR, Ciavattini A, Mezzetti B, Mazzoni L, Capocasa F, Castellucci M, Battino M, Ciarmela P. Romina: A powerful strawberry with in vitro

efficacy against uterine leiomyoma cells. J Cell Physiol. 2019; 234(5):7622-7633.
47. Lee TK, Kim DI, Song YL, Lee YC, Kim HM, Kim CH. Differential inhibition of scutellaria barbata d. Don (lamiaceae) on hcg-promoted proliferation of cultured uterine leiomyomal and myometrial smooth muscle cells. Immunopharmacol Immunotoxicol. 2004; 26(3):329-342.
48. Lee TK, Lee YJ, Kim DI, Kim HM, Chang YC, Kim CH. Pharmacological activity in growth inhibition and apoptosis of cultured human leiomyomal cells of tropical plant scutellaria barbata d. Don (lamiaceae). Environ Toxicol Pharmacol. 2006; 21(1):70-79.
49. Kim D-I, Lee T-K, Lim I-S, Kim H, Lee Y-C, Kim C-H. Regulation of igf-i production and proliferation of human leiomyomal smooth muscle cells by scutellaria barbata d. Don in vitro: Isolation of flavonoids of apigenin and luteolin as acting compounds. Toxicol Appl Pharmacol. 2005; 205(3):213-224.
50. Kim KW, Jin UH, Kim DI, Lee TK, Kim MS, Oh MJ, Kim MS, Kwon DY, Lee YC, Kim CH. Antiproliferative effect of scutellaria barbata d. Don. On cultured human uterine leiomyoma cells by down-regulation of the expression of Bcl-2 protein. Phytother Res. 2008; 22(5):583-590.
51. Chen HY, Lin PH, Shih YH, Wang KL, Hong YH, Shieh TM, Huang TC, Hsia SM. Natural antioxidant resveratrol suppresses uterine fibroid cell growth and extracellular matrix formation *in vitro* and *in vivo*. Antioxidants (Basel). 2019; 8(4):99.
52. Wu C-H, Shieh T-M, Wei L-H, Cheng T-F, Chen H-Y, Huang T-C, Wang K-L, Hsia S-M. Resveratrol inhibits proliferation of myometrial and leiomyoma cells and decreases extracellular matrix-associated protein expression. J Funct Foods. 2016; 23:241-252.
53. Ciarmela P, Islam MS, Reis FM, Gray PC, Bloise E, Petraglia F, Vale W, Castellucci M. Growth factors and myometrium: Biological effects in uterine fibroid and possible clinical implications. Hum Reprod Update. 2011; 17(6):772-790.
54. Segars JH, Parrott EC, Nagel JD, Guo XC, Gao X, Birnbaum LS, Pinn VW, Dixon D. Proceedings from the third national institutes of health international congress on advances in uterine leiomyoma research: Comprehensive review, conference summary and future recommendations. Hum Reprod Update. 2014; 20(3):309-333.
55. Rates SMK. Plants as source of drugs. Toxicon. 2001;39(5):603-613.
56. 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(5):1887-1893.
57. Roshdy E, Rajaratnam V, Maitra S, Sabry M, Allah AS, Al-Hendy A. Treatment of symptomatic uterine fibroids with green tea extract: A pilot randomized controlled clinical study. Int J Womens Health. 2013; 5:477-486.
58. Malik M, Mendoza M, Payson M, Catherino WH. Curcumin, a nutritional supplement with antineoplastic activity, enhances leiomyoma cell apoptosis and decreases fibronectin expression. Fertil Steril. 2009; 91(5 Suppl):2177-2184.
59. Redza-Dutordoir M and Averill-Bates DA. Activation of apoptosis signalling pathways by reactive oxygen species. Biochim Biophys Acta. 2016; 1863(12):2977-2992.
60. Fletcher NM, Saed MG, Abu-Soud HM, Al-Hendy A, Diamond MP, Saed GM. Uterine fibroids are characterized by an impaired antioxidant cellular system: Potential role of hypoxia in the pathophysiology of uterine fibroids. J Assist Reprod Genet. 2013;30(7):969-974.
61. Fletcher NM, Abusamaan MS, Memaj I, Saed MG, Al-Hendy A, Diamond MP, Saed GM. Oxidative stress: A key regulator of leiomyoma cell survival. Fertil Steril. 2017; 107(6):1387-1394 e1381.
62. Asare GA, Akuffo G, Doku D, Asiedu B, Santa S. Dynamics of urinary oxidative stress biomarkers: 8-hydroxy-2'-deoxyguanosine and 8-isoprostane in uterine leiomyomas. J Midlife Health. 2016; 7(1):8-14.
63. Kim SJ, Kim HS, Seo YR. Understanding of ros-inducing strategy in anticancer therapy. Oxid Med Cell Longev. 2019; 2019:5381692.
64. Raza MH, Siraj S, Arshad A, Waheed U, Aldakheel F, Alduraywish S, Arshad M. Ros-modulated therapeutic approaches in cancer treatment. J Cancer Res Clin Oncol. 2017; 143(9):1789-1809.
65. Gibson SB. Investigating the role of reactive oxygen species in regulating autophagy. Methods in enzymology. 528: Elsevier; 2013; 217-235p.
66. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, Alnemri ES, Altucci L, Amelio I, Andrews DW, Annicchiarico-Petruzzelli M, Antonov AV, Arama E, Baehrecke EH, Barlev NA, Bazan NG, Bernassola F, Bertrand MJM, Bianchi K, Blagosklonny MV, Blomgren K, Borner C, Boya P, Brenner C, Campanella M, Candi E, Carmona-Gutierrez D, Cecconi F, Chan FK, Chandel NS, Cheng EH, Chipuk JE, Cidlowski JA, Ciechanover A, Cohen GM, Conrad M, Cubillos-Ruiz JR, Czabotar PE, D'Angiolella V, Dawson TM, Dawson VL, De Laurenzi V, De Maria R, Debatin KM, DeBerardinis RJ, Deshmukh M, Di Daniele N, Di Virgilio F, Dixit VM, Dixon SJ, Duckett CS, Dynlacht BD, El-Deiry WS, Elrod JW, Fimia GM, Fulda S, Garcia-Saez AJ, Garg AD, Garrido C, Gavathiotis E, Golstein P, Gottlieb E, Green DR, Greene LA, Gronemeyer H, Gross A, Hajnoczky G, Hardwick JM, Harris IS, Hengartner MO, Hetz C, Ichijo H, Jaattela M, Joseph B, Jost PJ, Juin PP, Kaiser WJ, Karin M, Kaufmann T, Kepp O, Kimchi A, Kitsis RN, Klionsky DJ, Knight RA, Kumar S, Lee SW, Lemasters JJ, Levine B, Linkermann A, Lipton SA, Lockshin RA, Lopez-Otin C, Lowe SW, Luedde T, Lugli E, MacFarlane M, Madeo F, Malewicz M, Malorni W, Manic G, Marine JC, Martin SJ, Martinou JC, Medema JP, Mehlen P, Meier P, Melino S, Miao EA, Molkentin JD, Moll UM, Munoz-Pinedo C, Nagata S, Nunez G, Oberst A, Oren M, Overholtzer M, Pagano M, Panaretakis T, Pasparakis M, Penninger JM, Pereira DM, Pervaiz S, Peter ME, Piacentini M, Pinton P, Prehn JHM, Puthalakath H, Rabinovich GA, Rehm M, Rizzuto R, Rodrigues CMP, Rubinsztein DC, Rudel T, Ryan KM, Sayan E, Scorrano L, Shao F, Shi Y, Silke J, Simon HU, Sistigu A, Stockwell BR, Strasser A, Szabadkai G, Tait SWG, Tang D, Tavernarakis N, Thorburn A, Tsujimoto Y, Turk B, Vanden Berghe T, Vandenabeele P, Vander Heiden MG, Villunger A, Virgin HW, Vousden KH, Vucic D, Wagner EF, Walczak H, Wallach D, Wang Y, Wells JA, Wood W, Yuan J, Zakeri Z, Zhivotovsky B, Zitvogel L, Melino G, Kroemer G. Molecular mechanisms of cell death: Recommendations of the nomenclature committee on cell death 2018. Cell Death Differ. 2018; 25(3):486-541.
67. Jan R and Chaudhry GE. Understanding apoptosis and apoptotic pathways targeted cancer therapeutics. Adv Pharm Bull. 2019; 9(2):205-218.
68. Cho YS. The role of necroptosis in the treatment of diseases. BMB Rep. 2018; 51(5):219-224.
69. Fulda S, Gorman AM, Hori O, Samali A. Cellular stress responses: Cell survival and cell death. Int J Cell Biol. 2010;2010:214074.
70. Flusberg DA and Sorger PK. Surviving apoptosis: Life-death signaling in single cells. Trends Cell Biol. 2015; 25(8):446-458.
71. Shalini S, Dorstyn L, Dawar S, Kumar S. Old, new and emerging functions of caspases. Cell Death Differ. 2015;22(4):526-539.
72. Yue J and Lopez JM. Understanding MAPK signaling pathways in apoptosis. Int J Mol Sci. 2020; 21(7):2346.
73. Csatlos E, Mate S, Laky M, Rigo J, Jr., Joo JG. Role of apoptosis in the development of uterine leiomyoma: Analysis of expression patterns of BCL-2 and BAX in human leiomyoma tissue with clinical correlations. Int J Gynecol Pathol. 2015; 34(4):334-339.

74. Naseri MH, Mahdavi M, Davoodi J, Tackallou SH, Goudarzvand M, Neishabouri SH. Up regulation of BAX and down regulation of bcl2 during 3-NC mediated apoptosis in human cancer cells. Cancer Cell Int. 2015; 15(1):55.
75. Wu HL, Chuang TY, Al-Hendy A, Diamond MP, Azziz R, Chen YH. Berberine inhibits the proliferation of human uterine leiomyoma cells. Fertil Steril. 2015; 103(4):1098-1106.
76. Kim C-H, Kim D-I, Kwon C-N, Kang S-K, Jin U-H, Suh S-J, Lee T-K, Lee I-S. Euonymus alatus (thunb.) sieb induces apoptosis via mitochondrial pathway as prooxidant in human uterine leiomyomal smooth muscle cells. Int J Gynecol Cancer. 2006; 16(2).
77. Lee J-W, Choi HJ, Kim E-J, Hwang WY, Jung M-H, Kim KS. Fisetin induces apoptosis in uterine leiomyomas through multiple pathways. Sci Rep. 2020; 10(1):1-12.
78. Eskander RN, Randall LM, Sakai T, Guo Y, Hoang B, Zi X. Flavokawain b, a novel, naturally occurring chalcone, exhibits robust apoptotic effects and induces g2/m arrest of a uterine leiomyosarcoma cell line. J Obstet Gynaecol Res. 2012; 38(8):1086-1094.
79. Lee SM, Choi ES, Ha E, Ji KY, Shin SJ, Jung J. Gyejibongnyeong-hwan (gui zhi fu ling wan) ameliorates human uterine myomas via apoptosis. Front Pharmacol. 2019;10:1105.
80. Pauzi N, Mohd KS, Abdul Halim NH, Ismail Z. Orthosiphon stamineus extracts inhibits proliferation and induces apoptosis in uterine fibroid cells. Asian Pac J Cancer Prev. 2018; 19(10):2737-2744.
81. Zakaria N, Mohd KS, Ahmed Saeed MA, Ahmed Hassan LE, Shafaei A, Al-Suede FSR, Memon AH, Ismail Z. Anti-uterine fibroid effect of standardized labisia pumila var. Alata extracts in vitro and in human uterine fibroid cancer xenograft model. Asian Pac J Cancer Prev. 2020; 21(4):943-951.
82. Banfalvi G. Overview of cell synchronization. Cell cycle synchronization: Springer; 2017; 3-27p.
83. Koç A, Wheeler LJ, Mathews CK, Merrill GF. Hydroxyurea arrests DNA replication by a mechanism that preserves basal dntp pools. J. Biol. Chem. 2004;279(1):223-230.
84. Purcell M, Kruger A, Tainsky MA. Gene expression profiling of replicative and induced senescence. Cell Cycle. 2014; 13(24):3927-3937.
85. Ahmed RS, Liu G, Renzetti A, Farshi P, Yang H, Soave C, Saed G, El-Ghoneimy AA, El-Banna HA, Foldes R, Chan TH, Dou QP. Biological and mechanistic characterization of novel prodrugs of green tea polyphenol epigallocatechin gallate analogs in human leiomyoma cell lines. J Cell Biochem. 2016; 117(10):2357-2369.
86. 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(6):3344-3351.
87. Prince TL, Lang BJ, Guerrero-Gimenez ME, Fernandez-Munoz JM, Ackerman A, Calderwood SK. Hsf1: Primary factor in molecular chaperone expression and a major contributor to cancer morbidity. Cells. 2020; 9(4):1046.
88. Dai C. The heat-shock, or hsf1-mediated proteotoxic stress, response in cancer: From proteomic stability to oncogenesis. Philos Trans R Soc Lond B Biol Sci. 2018; 373(1738):20160525.
89. Xia W, Voellmy R, Spector NL. Sensitization of tumor cells to fas killing through overexpression of heat-shock transcription factor 1. J Cell Physiol. 2000; 183(3):425-431.
90. Vilaboa N, Bore A, Martin-Saavedra F, Bayford M, Winfield N, Firth-Clark S, Kirton SB, Voellmy R. New inhibitor targeting human transcription factor hsf1: Effects on the heat shock response and tumor cell survival. Nucl Acids Res. 2017; 45(10):5797-5817.
91. Carpenter RL and Gökmen-Polar Y. Hsf1 as a cancer biomarker and therapeutic target. Curr Cancer Drug Targets. 2019; 19(7):515-524.
92. Khandagale P, Thakur S, Acharya N. Identification of PCNA-interacting protein motifs in human DNA polymerase delta. Biosci Rep. 2020; 40(4).
93. Boehm EM, Gildenberg MS, Washington MT. The many roles of PCNA in eukaryotic DNA replication. Enzym. 2016; 39:231-254.
94. Mailand N, Gibbs-Seymour I, Bekker-Jensen S. Regulation of PCNA-protein interactions for genome stability. Nat Rev Mol Cell Biol. 2013; 14(5):269-282.
95. Choe KN and Moldovan G-L. Forging ahead through darkness: PCNA, still the principal conductor at the replication fork. Mol cell. 2017; 65(3):380-392.
96. Strzalka W and Ziemienowicz A. Proliferating cell nuclear antigen (PCNA): A key factor in DNA replication and cell cycle regulation. Ann Bot. 2011; 107(7):1127-1140.
97. Jamaluddin MFB, Nahar P, Tanwar PS. Proteomic characterization of the extracellular matrix of human uterine fibroids. Endocrinology. 2018;159(7):2656-2669.
98. Islam MS, Ciavattini A, Petraglia F, Castellucci M, Ciarmela P. Extracellular matrix in uterine leiomyoma pathogenesis: A potential target for future therapeutics. Hum Reprod Update. 2018; 24(1):59-85.
99. Ko YA, Jamaluddin MFB, Adebayo M, Bajwa P, Scott RJ, Dharmarajan AM, Nahar P, Tanwar PS. Extracellular matrix (ecm) activates beta-catenin signaling in uterine fibroids. Reprod. 2018; 155(1):61-71.
100. Greco S, Islam MS, Zannotti A, Delli Carpini G, Giannubilo SR, 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(4):593-602.
101. Lin PH, Shih CK, Yen YT, Chiang W, Hsia SM. Adlay (coix lachryma-jobi l. Var. Ma-yuen stapf.) hull extract and active compounds inhibit proliferation of primary human leiomyoma cells and protect against sexual hormone-induced mice smooth muscle hyperproliferation. Molecules. 2019; 24(8):1556.
102. Liberti MV, Locasale JW. The warburg effect: How does it benefit cancer cells? Trends Biochem Sci. 2016; 41(3):211-218.
103. Belisario DC, Kopecka J, Pasino M, Akman M, De Smaele E, Donadelli M, Riganti C. Hypoxia dictates metabolic rewiring of tumors: Implications for chemoresistance. Cells. 2020; 9(12):2598.
104. Ke X, Dou F, Cheng Z, Dai H, Zhang W, Qu X, Ding P, Zuo X. High expression of cyclooxygenase-2 in uterine fibroids and its correlation with cell proliferation. Eur J Obstet Gynecol Reprod Biol. 2013; 168(2):199-203.
105. Szweda M, Rychlik A, Babińska I, Pomianowski A. Cyclooxygenase-2 as a biomarker with diagnostic, therapeutic, prognostic, and predictive relevance in small animal oncology. J Vet Res. 2020; 64(1):151.
106. Zeng L, Yang K, Liu H, Zhang G. A network pharmacology approach to investigate the pharmacological effects of guizhi fuling wan on uterine fibroids. Exp Ther Med. 2017; 14(5):4697-4710.
107. Lee JH, Dean M, Austin JR, Burdette JE, Murphy BT. Irilone from red clover (trifolium pratense) potentiates progesterone signaling. J Nat Prod. 2018; 81(9):1962-1967.