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Indian Medicinal Plants for the Management of Endometriosis: A Comprehensive Review on their phytopharmacology

Rustam Ekbbal [1], Aakash Kumar Jaiswal [2], Mansi Aggarwal [2], Mhaveer Singh [3], Shadab Ali [1], Sayad Ahad Ali [1], Gaurav Gautam [1,*]

[1]IIMT College of Medical Sciences, IIMT University, O Pocket, Ganga Nagar, Meerut, Uttar Pradesh 250001, India
[2]School of Pharmaceutical Sciences, IIMT University, O Pocket, Ganga Nagar, Meerut, Uttar Pradesh 250001, India
[3]Pharmacy Academy, IFTM University, Moradabad, 244102, Uttar Pradesh, India

ABSTRACT: Endometriosis is a chronic gynecological disorder characterized by the aberrant growth of endometrial tissue outside the uterus, resulting in severe pain and infertility. Conventional treatments often come with limitations and side effects, prompting a quest for alternative therapies. Medicinal plants, integral to traditional medicine systems, have emerged as potential solutions. This review delves into the phytopharmacology and chemistry of medicinal plants employed in endometriosis treatment. An exhaustive search revealed pertinent studies concerning medicinal plant use in endometriosis treatment. These studies were scrutinized for their phytopharmacological attributes and active chemical constituents. Numerous medicinal plants exhibited anti-inflammatory, analgesic, antioxidant, immunomodulatory, and hormone-regulating properties, pivotal in endometriosis management. Mechanisms encompassed the suppression of inflammatory mediators, modulation of estrogen signaling, mitigation of oxidative stress, and enhancement of immune function. Furthermore, key chemical constituents responsible for these effects were pinpointed and classified into classes such as flavonoids, terpenoids, alkaloids, and phenolic compounds. These bioactive agents elicited their actions via diverse molecular targets, including cyclooxygenase enzymes, estrogen receptors, nuclear factor-kappa B, and reactive oxygen species. The findings underscore the potential of medicinal plants as adjunct therapies for endometriosis. Nonetheless, additional preclinical and clinical investigations are imperative to substantiate their efficacy, safety, and optimal dosing. Grasping the phytopharmacology and chemistry of medicinal plants in endometriosis treatment lays the groundwork for novel therapeutic agent development, spotlighting the capacity of natural products to combat this intricate gynecological ailment.

1. INTRODUCTION

Endometriosis characterized by overgrowing endometrium tissue outside the uterus, on ovaries, fallopian tubes, and other pelvic organs. In rare cases, it may even spread beyond the pelvic region (Koninckx et al., 2021; Smolarz et al., 2021). Endometriosis is often a painful condition that primarily affects women of reproductive age. The exact cause of endometriosis is unknown, but retrograde menstruation (when menstrual blood flows back through the fallopian tubes), genetic factors, hormonal imbalances, and immune system disorders have been characterized for induction of the endometriosis. Painful periods, pain during bowel movements or urination, pain during sexual intercourse, heavy or irregular menstrual bleeding, fatigue, and infertility are the major symptoms of the endometriosis (Koninckx et al., 2021; Maulitz et al., 2022). However, it's important to note that the severity of symptoms can vary greatly among individuals. Endometriosis is diagnosed by detailed physical examination, medical history, ultrasound, and sometimes laparoscopic surgery and biopsy of the endometrial tissue. Laparoscopy is currently the most accurate method for diagnosing endometriosis. Hormonal therapies (such as birth control pills or gonadotropin-releasing hormone agonists), and surgery to remove or excise the endometrial implants are the most promising option for endometriosis (Agarwal et al., 2019; Smolarz et al., 2021).

* Corresponding author.
E-mail address: gautamgaurav878@gmail.com (Gaurav Gautam)

In cases where fertility is a concern, assisted reproductive technologies or surgery to address anatomical abnormalities may be considered. It's important for individuals experiencing symptoms suggestive of endometriosis to consult with a healthcare professional, preferably a gynecologist or a specialist in reproductive health (Agarwal et al., 2019).

Medicinal plants have been used for centuries in various traditional systems of medicine, and they continue to play a crucial role in modern healthcare. There are several approaches that makes medicinal plants enriched for treating various disease including natural source of therapeutic compounds, Medicinal plants contain a diversity of phytoconstituents such as alkaloids, flavonoids, terpenoids, and phenolics, which possess medicinal properties (Ahmad et al., 2021; Gaurav et al., 2023; Gautam et al., 2021). These natural compounds can be used as a source of drugs or serve as lead compounds for the development of synthetic drugs. Medicinal plants offer a vast reservoir of bioactive molecules that can be utilized for the treatment of various diseases (Gaurav et al., 2022; Zahiruddin et al., 2021). Traditional Medicine and Cultural Heritage: Medicinal plants are integral to traditional systems of medicine, such as Ayurveda, Traditional Chinese Medicine, and Indigenous healing practices. They form an important part of cultural heritage and traditional knowledge systems (Basist et al., 2022; M.U. Khan, Gaurav, et al., 2022). Many communities rely on medicinal plants for their healthcare needs, and their preservation and utilization contribute to the maintenance of cultural diversity and traditional healing practices. Medicinal plants can provide accessible and affordable healthcare options, particularly in regions where modern healthcare infrastructure is limited or expensive. Local communities often have direct access to medicinal plants and can use them for self-care and treatment of common ailments (Gaurav et al., 2022; A. Khan et al., 2021; M.U. Khan, Gautam, et al., 2022). Medicinal plants can serve as a cost-effective alternative or complement to conventional medicine, especially in resource-constrained settings. Medicinal plants have been a valuable source of drugs and have provided the foundation for numerous pharmaceutical compounds (Gautam, 2022; Ibrahim et al., 2021).

Many modern drugs have been derived from plant compounds or inspired by them. Active compounds isolated from medicinal plants have led to the development of drugs used to treat various conditions, including cancer, cardiovascular diseases, infections, and more. Medicinal plants play a significant role in biodiversity conservation. The preservation of diverse plant species and their ecosystems is crucial for maintaining a sustainable supply of medicinal resources (Gaurav et al., 2022; Z. Gaurav et al., 2020). Conserving medicinal plants not only protects their potential therapeutic benefits but also helps to preserve ecosystems, protect endangered species, and maintain ecological balance. Traditional Knowledge and Scientific Research: Traditional knowledge related to medicinal plants holds immense value and can guide scientific research (Gaurav et al., 2023; Zahiruddin et al., 2021). By studying the traditional uses and practices associated with medicinal plants, researchers can discover new bioactive compounds, validate traditional claims, and explore novel therapeutic avenues. Integrating traditional knowledge with scientific research promotes a holistic and comprehensive understanding of medicinal plants. It's important to note that while medicinal plants offer significant potential, proper research, quality control, and regulatory measures are necessary to ensure their safety, efficacy, and sustainable use (Gautam et al., 2023).

2. REVIEW FINDING

2.1. Phytochemicals reported for management of endometriosis

Various natural chemical constituents explored for their therapeutic effects in managing the symptoms and reducing inflammation associated with the condition. Among different phytoconstituents, multi-targeted therapeutic effect has been explored (Qi et al., 2021; Sheikholeslami et al., 2021).

Curcumin is a natural constituent sourced by turmeric or Curcuma longa; a spice used in Indian cuisine. It has antioxidant and anti-inflammatory properties that may help reduce pain and inflammation associated with endometriosis. It exhibits strong anti-inflammatory properties by inhibiting various inflammatory mediators, such as cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) and enzymes (such as cyclooxygenase-2 and 5-lipoxygenase). By reducing inflammation, curcumin may help to alleviate pain and reduce the inflammatory environment associated with endometriosis. It acts as a potent antioxidant and can scavenge free radicals and reduce oxidative stress. Oxidative stress is implicated in the pathogenesis of endometriosis, and curcumin's antioxidant activity may help to counteract cellular damage, reduce inflammation, and promote overall tissue health (Arablou & Kolahdouz-Mohammadi, 2018; Vallée & Lecarpentier, 2020).

Curcumin has been reported to modulate estrogen receptor signaling. It can act as a selective estrogen receptor modulator (SERM), exhibiting both estrogenic and anti-estrogenic effects depending on the context. By modulating estrogen receptors, curcumin may help regulate estrogenic activity in endometriotic lesions, potentially inhibiting their growth and reducing associated symptoms. Curcumin has been found to inhibit angiogenesis, the process of new blood vessel formation (Arablou & Kolahdouz-Mohammadi, 2018; Clower et al., 2022; Vallée & Lecarpentier, 2020). Angiogenesis plays a critical role in the growth and survival of endometriotic lesions. By inhibiting angiogenesis, curcumin may help to limit the blood supply to endometriotic lesions, impeding their growth and progression. It also influences various signaling pathways involved in cell proliferation, survival, and invasion. It can inhibit the activation of pathways such as mitogen-activated protein kinase (MAPK), nuclear factor-kappa B (NF-κB), and phosphatidylinositol 3-kinase (PI3K)/Akt, which are implicated in endometriosis pathogenesis. By interfering with these signaling pathways, curcumin may help regulate cellular processes and inhibit the growth and invasiveness of endometri-

otic lesions (Gautam et al., 2021; Kuttan et al., 1985). It has immunomodulatory effects and can regulate immune cell function and cytokine production. It regulates anti-inflammatory and pro-inflammatory cytokines, leading to a shift towards an anti-inflammatory environment. By modulating immune responses, curcumin may help reduce immune dysregulation and inflammation associated with endometriosis. (Chowdhury et al., 2019; S.Y. Kim et al., 2019).

Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) as well as docosahexaenoic acid (DHA), are found in different fatty fish like mackerel, salmon, and sardines. They possess anti-inflammatory properties and reduces symptoms such as pain as well as inflammation (Akyol et al., 2016; Khanaki et al., 2012; T.H. Kim et al., 2013). Resveratrol is a natural compound found in grapes, red wine, and berries. It has anti-inflammatory and antioxidant properties that may help manage inflammation associated with endometriosis. N-acetylcysteine (NAC) is a compound that acts as a precursor to glutathione, a powerful antioxidant in the body. It has been studied for its potential benefits in reducing oxidative stress and inflammation in endometriosis Bahat et al. (2022).

Quercetin is a flavonoid found in various fruits, vegetables, and herbs. It reduce inflammation and pain associated with endometriosis. Anti-inflammatory activity: Quercetin exerts potent anti-inflammatory effects by inhibiting the production and release of chemokines, pro-inflammatory cytokines, and inflammatory mediators. It regulates expression of transcription factors, such as nuclear factor-kappa B (NF-κB), that centrally trigger inflammatory response. By reducing inflammation, quercetin helps to alleviate pain and suppress the growth and progression of endometriotic lesions (Bahat et al., 2022). Quercetin possesses strong antioxidant activity, which helps to counteract oxidative stress in endometriosis. It scavenges ROS and inhibits lipid peroxidation, thereby reducing cellular damage and oxidative stress-induced inflammation. By protecting cells from oxidative damage, quercetin supports the maintenance of normal cellular function and helps to mitigate the pathological changes associated with endometriosis (Basist et al., 2022; Gautam et al., 2021).

Quercetin act as anti-angiogenesis, via interfering in the signaling pathways involved in angiogenesis and reduces the production of pro-angiogenic factors. This anti-angiogenic activity of quercetin can help to impair the blood supply to endometriotic lesions, inhibiting their growth and development. Quercetin exhibits estrogenic and anti-estrogenic effects, depending on the hormonal milieu. It can bind to estrogen receptors and modulate estrogen signaling pathways, which may help to counteract the proliferative effects of estrogen on endometrial and endometriotic tissues. By regulating hormonal balance, quercetin contributes to the control of endometriosis progression. Induction of apoptosis: Quercetin has also been found to induce apoptosis, or programmed cell death, in endometrial and endometriotic cells. This pro-apoptotic effect helps to promote the regression and reduction of endometriotic lesions (Cao et al., 2014; Lin et al., 2022).

Quercetin has immunomodulatory effects, influencing immune cell function and cytokine production. By modulating immune responses, quercetin helps to reduce immune dysregulation and inflammation associated with endometriosis. it is reported that quercetin exert epigenetic modifications, particularly DNA methylation and histone acetylation. These modifications can regulate gene expression patterns, including those involved in inflammatory pathways, cell proliferation, and angiogenesis. By influencing epigenetic mechanisms, quercetin may contribute to the modulation of key genes involved in endometriosis development and progression (Abramiuk et al., 2022; Jafarinia et al., 2020; Nathiya et al., 2014; Scheerer et al., 2016).

Endometriosis can be connected with the expansion of fibrotic tissue, which contributes to the formation of adhesions and scarring. Quercetin has been shown to have anti-fibrotic properties by inhibiting the production of collagen, and reducing the deposition of fibrotic tissue. This action helps to prevent the formation of adhesions and improve tissue remodeling in endometriosis (Matsuzaki & Darcha, 2015; Sheikholeslami et al., 2021). It can inhibit the activation of pathways such as PI3K/Akt, MAPK/ERK, and Wnt/β-catenin, which are implicated in endometriosis pathogenesis. By interfering with these signaling pathways, quercetin helps to regulate cellular processes and inhibit the growth and invasiveness of endometriotic lesions. It has also been reported to possess analgesic properties, helping to alleviate pain associated with endometriosis. It can modulate pain signaling pathways, including the inhibition of inflammatory mediators and the regulation of pain receptors. By reducing pain perception, quercetin contributes to the improvement of quality of life in individuals with endometriosis (Chanjitwiriya et al., 2020; Seo et al., 2015).

Bromelain is an enzyme found in pineapple stems exhibits anti-inflammatory properties and may help alleviate pain and inflammation in endometriosis. It exhibits significant anti-inflammatory properties by modulating the production and activity of various inflammatory mediators, such as cytokines and chemokines. It can inhibit the synthesis of prostaglandins and leukotrienes, which are involved in the inflammatory response. By reducing inflammation, bromelain may help to alleviate pain and reduce the inflammatory environment associated with endometriosis. it has been shown to possess fibrinolytic properties, meaning it can break down fibrin, a protein involved in blood clot formation. In endometriosis, the presence of excessive fibrin can contribute to the formation of adhesions and scar tissue (Agostinis et al., 2015; Lete et al., 2018). Bromelain's fibrinolytic activity may help to dissolve these adhesions and improve tissue remodeling, potentially reducing pain and improving fertility outcomes. It has also been reported to exhibit immunomodulatory effects that can influence immune cell function and regulate the immune response. It can modulate the production of cytokines and chemokines, thereby regulating immune cell recruitment and activation. By modulating the immune system, bromelain may

help to reduce immune dysregulation and the inflammatory response associated with endometriosis (Lete et al., 2018; Tucci et al., 2018).

Bromelain possesses antioxidant properties and can scavenge ROS and inhibit lipid peroxidation. Oxidative stress triggers the pathogenesis of endometriosis, and the antioxidant activity of bromelain may help to mitigate cellular damage and inflammation associated with oxidative stress. It also aids in digestion by breaking down proteins. Although the direct impact of bromelain's digestive properties on endometriosis is unclear, improved digestion and nutrient absorption may support overall health and well-being, potentially influencing the progression and symptoms of endometriosis (Lete et al., 2018; Saptarini et al., 2019; Tucci et al., 2018).

Moreover, magnesium containing products that plays a vital role in various bodily functions. It has been suggested that magnesium deficiency may contribute to increased pain sensitivity in endometriosis. Supplementing with magnesium may help reduce pain symptoms (Harris et al., 2013). Vitamin D is an essential nutrient that plays a role in immune function and inflammation regulation. Some studies have found an association between vitamin D deficiency and increased risk of endometriosis. Maintaining adequate vitamin D levels may be beneficial in managing the condition. Myo-inositol is a naturally occurring sugar alcohol that has been studied for its potential benefits in polycystic ovary syndrome (PCOS) and endometriosis. It may help improve hormone balance and reduce symptoms such as pain and irregular periods. Vitamin E is a fat-soluble vitamin with antioxidant properties. Some studies suggest that vitamin E supplementation may help reduce pain and inflammation associated with endometriosis. It is often recommended to be taken alongside other treatments (Bahat et al., 2022; Barnard et al., 2023; Miyashita et al., 2016).

Cannabidiol (CBD) found in cannabis plant, is a non-psychoactive compound exhibits anti-inflammatory and pain-relieving properties. Some individuals with endometriosis have reported finding relief from symptoms through the use of CBD products. However, more research is needed to establish its efficacy and safety for endometriosis specifically. Zinc is a mineral involved in various physiological processes, including immune function and hormone regulation. Some studies suggest that zinc deficiency may be associated with endometriosis. Supplementing with zinc may help support immune function and reduce inflammation. Endometriosis is associated with increased production of prostaglandins, which are hormone-like compounds that contribute to inflammation and pain. Evening primrose oil and borage oil contains gamma-linolenic acid (GLA) and omega-6 fatty acid inhibit the production of inflammatory prostaglandins and provide relief from symptoms (Mistry et al., 2022; NCT04527003, 2020; Rbr-6ryrpjs, 2021). Pelargonidin is a natural pigment found in various fruits and vegetables, such as strawberries and red peppers. It possesses antioxidant and anti-inflammatory properties, and some studies suggest that it may help reduce the growth of endometrial tissue and alleviate symptoms (Liu et al., 2020; Lodhi & Kori, 2021). Lycopene is a naturally occurring pigment found in tomatoes, watermelon, and other fruits (Campos et al., 2017; Van Steenwijk et al., 2020). It possesses antioxidant and anti-inflammatory properties and may help reduce the growth of endometrial tissue and alleviate symptoms.

Berberine is a naturally alkaloid found in various plants, such as *Tinospora cordifolia*, *Berberis aristate*, *Gymnema sylvestre*. It has anti-inflammatory and antimicrobial properties and may help manage inflammation associated with endometriosis. Berberine exhibits anti-inflammatory effects by modulating various inflammatory mediators, including cytokines and enzymes involved in the inflammatory response. It can inhibit the activation of NF-κB, a key transcription factor involved in inflammation. By reducing inflammation, berberine may help alleviate pain and reduce the inflammatory environment associated with endometriosis. It showed hormonal regulatory effects in endometriosis. It has been reported to influence hormone levels, particularly estrogen. Berberine can modulate estrogen receptors and affect estrogen signaling pathways. By regulating estrogenic activity, berberine may help to control the growth and development of endometriotic lesions. It exhibits anti-proliferative effects on various cells, including endometriotic cells. By suppressing the excessive proliferation of endometriotic cells, berberine may help to inhibit the growth and progression of endometriotic lesions (Zhang et al., 2019).

Berberine possess anti-angiogenic properties and help to limit the blood supply to endometriotic lesions, hindering their growth and development. It exhibits antioxidant properties and can scavenge ROS and reduce oxidative stress. Oxidative stress is implicated in the pathogenesis of endometriosis. The antioxidant effects of berberine may help to counteract cellular damage, reduce inflammation, and promote overall tissue health in endometriosis. It influences various signaling pathways involved in cell proliferation, survival, and invasion. It can modulate pathways such as AMPK and mammalian target of rapamycin (mTOR), which are involved in cell growth and metabolism. By interfering with these signaling pathways, berberine may help regulate cellular processes and inhibit the growth and invasiveness of endometriotic lesions (Z. Gaurav et al., 2020; Gautam, 2022; Gu & Zhou, 2021; Warowicka et al., 2021; Zhou & Zhou, 2011).

Berberine influence epigenetic modifications, such as histone acetylation and DNA methylation. Epigenetic alterations are implicated to develop endometriosis. Berberine's ability to modify epigenetic patterns may help regulate gene expression patterns, potentially influencing key genes involved in endometriosis pathogenesis. It has also been reported to have anti-fibrotic effects in various conditions. It can inhibit the activation of fibroblasts and the deposition of extracellular matrix components, helping to reduce fibrosis in endometriotic lesions. It has also been shown to regulate autophagy in different contexts. It can induce autophagy or inhibit excessive autophagy, depending on the cellular context. By modulating

autophagy, berberine may influence cellular homeostasis and survival in endometriotic lesions (Gu & Zhou, 2021; Saha & Khuda-Bukhsh, 2015).

Paclitaxel is a chemotherapy medication that has been used in the treatment of various types of cancer, including ovarian cancer. While it is not a standard therapy for endometriosis or polycystic ovarian syndrome (PCOS), there is some research exploring its potential use in these conditions. Paclitaxel belongs to a class of medications known as taxanes. It works by inhibiting microtubule depolymerization, thereby disrupting cell division and preventing cancer cells from growing and multiplying. Paclitaxel is administered intravenously. It is primarily metabolized by the liver, and its metabolites are eliminated through the bile and feces. It has a relatively long half-life, which can influence dosing schedules (Chen et al., 2022; Xu & Li, 2018).

Paclitaxel acts on microtubules via binding and stabilizing them and disrupts normal cellular processes, particularly in rapidly dividing cells such as endometriotic lesions. This disruption leads to cell cycle arrest and prevents cell division and proliferation. Paclitaxel interferes with the normal progression of mitosis, the process of cell division. It specifically targets the mitotic spindle apparatus, preventing its disassembly and resulting in mitotic arrest. This prevents the separation of chromosomes during cell division and leads to cell death. It also triggers apoptosis, a process of programmed cell death, in endometriotic cells. It activates signaling pathways that promote apoptotic cell death, leading to the elimination of abnormal cells. This apoptotic effect is thought to contribute to the reduction of endometriotic lesions (Li et al., 2022; Okimura et al., 2018; Smith et al., 2022).

Paclitaxel also exhibits anti-angiogenic properties and inhibits the proliferation of endothelial cells and disrupts the formation of blood vessels, thereby reducing the blood supply to endometriotic lesions and inhibiting their growth. It modulates the immune response and affect the function and activity of immune cells, such as T cells and dendritic cells. By modulating the immune response, paclitaxel may help to regulate the immune environment surrounding endometriotic lesions, potentially reducing inflammation and promoting immune-mediated clearance of abnormal cells (R et al., 2019; Xu & Li, 2018; Yee et al., 2013). It also inhibit the migration and invasion of endometriotic cells. It disrupts the dynamics of the cytoskeleton, preventing the rearrangement and extension of cellular structures necessary for cell movement thus it helps to limit the spread and dissemination of endometriotic lesions (Ota et al., 2020).

Paclitaxel modulate inflammatory responses by affecting the production and activity of pro-inflammatory cytokines and chemokines. In endometriosis, chronic inflammation is a key factor contributing to the development and progression of the disease. Paclitaxel's anti-inflammatory effects may help to reduce the inflammatory environment surrounding endometriotic lesions. It induces DNA damage in rapidly dividing cells, including endometriotic cells. It interferes with DNA replication and promotes the formation of DNA adducts, which disrupt the integrity of the DNA molecule. This leads to DNA damage and activates cellular mechanisms involved in DNA repair. Persistent DNA damage and impaired repair processes can result in cell death (Caillaud et al., 2021; Ferrandina et al., 2016). It can inhibit the activity of pathways such as the phosphoinositide 3-kinase (PI3K)/Akt pathway, which is associated with cell survival and proliferation. By modulating these signaling pathways, paclitaxel can disrupt the cellular processes necessary for the survival and growth of endometriotic lesions. It also has been reported to influence the expression and activity of hormone receptors, such as estrogen receptors, hence interfere with the hormonal environment necessary for the growth and progression of endometriotic lesions (Caillaud et al., 2021; Costa et al., 2018; Ferrandina et al., 2016).

2.2. Plants used for the treatment of endometriosis

Vitex agnus-castus, also known as chasteberry or vitex, contain different chemical sonstituents sch as agnuside, casticin, vitexin, casticin acetate, rotundifuran, flavonoids (orientin, isoorientin, isovitexin, apigenin), essential oils (cineole, sabinene, limonene) agnuside glucoside, vitexilactone, 3-hydroxy-4,5-dimethoxybenzoic acid, casticin glucoside, 6'-O-trans-p-coumaroylcasticin, 6'-O-trans-feruloylcasticin, vitexin-2″-O-rhamnoside, 7-O-trans-p-coumaroylvitexin. It has been traditionally used to regulate hormone levels in women. It may help balance estrogen and progesterone levels and alleviate some symptoms of endometriosis (Prilepskaya & Dovletkhanova, 2020).

Ginger is a root spice that contains several bioactive compounds such as gingerols, shogaols, gingerdiols, zingerone, gingerenone a, paradols, sesquiterpenes, gingerdiones, zingiberene, curcuminoids, etc. Essential oils, including gingerol. It has anti-inflammatory effects and may help alleviate pain and reduce inflammation in endometriosis (Filho et al., 2021). Green tea contains catechins, which are natural antioxidants that have anti-inflammatory properties. Some studies have suggested that green tea extracts may help reduce the growth of endometrial tissue and alleviate symptoms (Chen et al., 2022; Man et al., 2012). Traditional Chinese herbal medicine formulas have been used for centuries to manage gynecological conditions, including endometriosis. Herbal remedies such as Danazol and Tripterygium wilfordii Hook F (known as Lei Gong Teng) have been studied for their potential benefits in reducing pain and inflammation associated with endometriosis (Xiao et al., 2002). Frankincense oil, derived from the resin of Boswellia trees, has been used in traditional medicine for its anti-inflammatory properties. It may help reduce inflammation and pain associated with endometriosis when used topically or in aromatherapy (Almeida-Da-Silva et al., 2022).

Chasteberry *(Vitex agnus*-castus) is an herb that may help balance hormone levels by acting on the pituitary gland. It has been traditionally used to manage menstrual irregularities and hormone-related conditions such as endometriosis. Hormonal

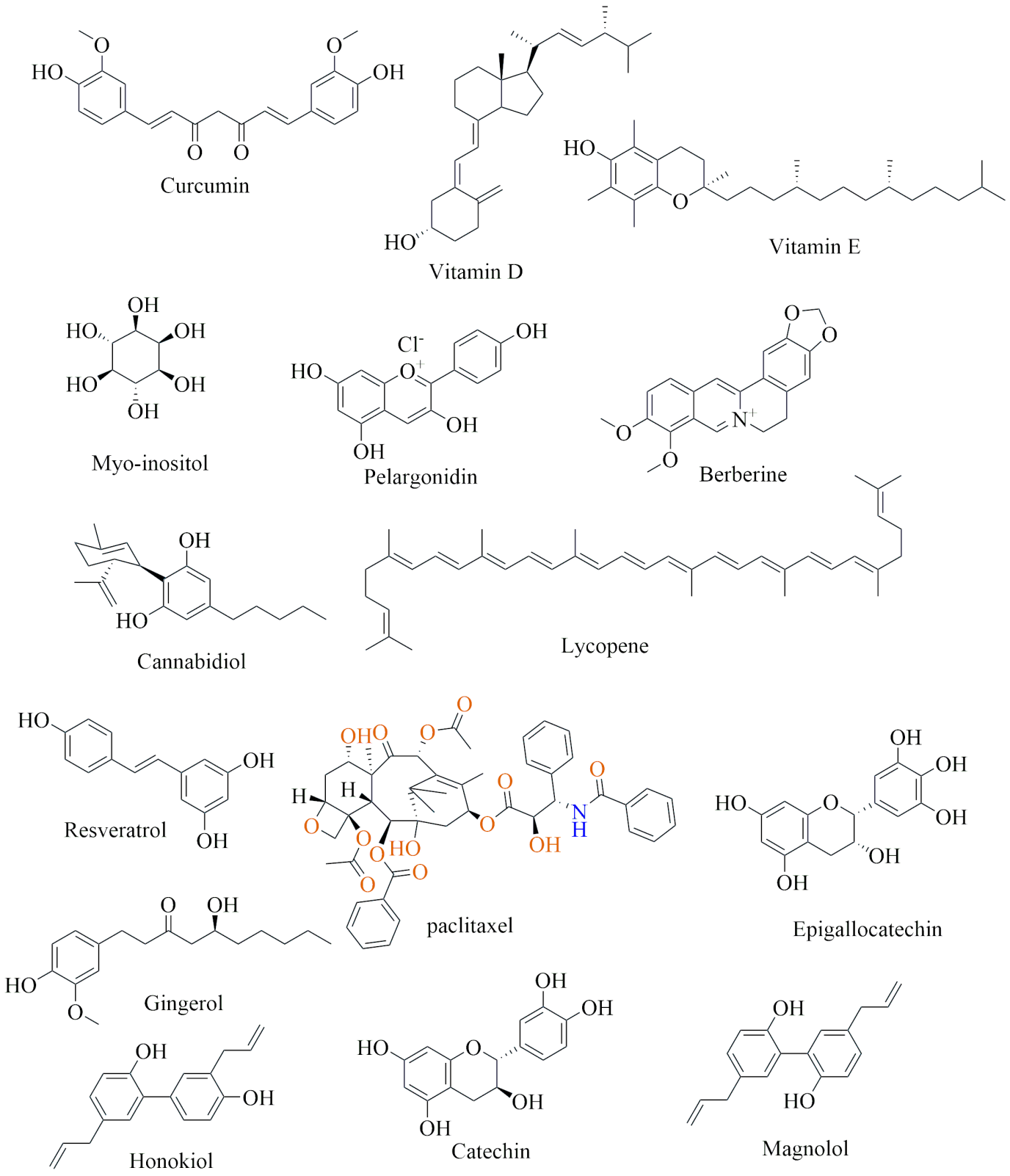

Figure 1. Reported chemical constituents used in endometriosis.

regulation: Chasteberry is thought to exert its effects on endometriosis by modulating hormone levels, particularly prolactin and progesterone. It acts on the hypothalamus and pituitary gland, leading to a decrease in prolactin secretion and an increase in progesterone production. By balancing hormone levels, chasteberry may help regulate the abnormal hormonal milieu associated with endometriosis, potentially reducing the growth and symptoms of endometriotic lesions. It has also been found to influence dopamine activity in the brain. It may enhance dopamine release or reduce dopamine degradation, resulting in an indirect effect on hormone regulation (Mollazadeh et al., 2020; Stute et al., 2019; Van Die et al., 2013). It can inhibit the production and activity of pro-inflammatory mediators, such as cytokines and prostaglandins. By reducing inflammation, it helps to alleviate pain and reduce the inflammatory environment associated with endometriosis. It may have immunomodulatory effects, influencing immune cell function and the immune response (Ogaly et al., 2021). It can regulate the balance of immune cells and modulate the production of cytokines, potentially helping to reduce immune dysregulation and inflammation in endometriosis. It also exhibits antioxidant properties, which can help counteract oxidative stress in endometriosis. It scavenges reactive oxygen species (ROS) and reduces oxidative damage, contributing to the overall reduction of cellular stress and inflammation (Ibrahim et al., 2021).

Chasteberry regulate the menstrual cycle by influencing the balance of hormones involved in menstrual cycle regulation, such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH). By promoting a more regular and balanced menstrual cycle, chasteberry may help to normalize the growth and shedding of endometrial tissue, potentially reducing the development and progression of endometriosis (Azarnia et al., 2007; Mayo, 1998). It is also reported to have anti-estrogenic effects, potentially inhibiting the effects of excessive estrogen in the body. It may compete with estrogen receptors or modulate estrogen signaling pathways, leading to a reduction in estrogenic activity. As estrogen plays a crucial role in the growth and proliferation of endometriotic lesions, the ability of chasteberry to reduce estrogenic activity may help to control the progression of endometriosis. It has also been shown to affect prolactin levels in the body (Mollazadeh et al., 2020). Chasteberry is reported to possess analgesic properties, potentially helping to reduce pain and discomfort associated with endometriosis (Seidlova-Wuttke & Wuttke, 2019; Van Die et al., 2013). Moreover, endometriosis has a significant impact on psychological well-being, including mood swings, anxiety, and depression. Chasteberry has been suggested to have positive effects on psychological symptoms by influencing neurotransmitter activity and promoting a sense of well-being, hence, by improving psychological well-being, chasteberry may contribute to overall symptom relief and better quality of life in individuals with endometriosis (Van Die et al., 2013).

Ashwagandha, also known as *Withania somnifera*, is an adaptogenic herb used in traditional Ayurvedic medicine. It has antioxidant and anti-inflammatory properties and may help regulate hormone levels and reduce stress, which could be beneficial in managing endometriosis symptoms. Serrapeptase is an enzyme derived from the silkworm. It has anti-inflammatory properties and is believed to help break down and dissolve scar tissue and adhesions associated with endometriosis. However, more research is needed to determine its efficacy and safety for this specific condition. Bee propolis is a resinous substance collected by bees from tree buds and used in their hives. It has anti-inflammatory, antioxidant, and antimicrobial properties. Some studies have suggested that bee propolis may help reduce inflammation and alleviate symptoms associated with endometriosis (Azgomi et al., 2018; Nishteswar, 2013; Sankar, 2018).

Magnolia bark extract obtained from *Magnolia officinalis* stem that exhibits anti-inflammatory and antioxidant properties due to chemicals namely honokiol, magnolol, magnaldehyde, honokiol glycoside, magnolol glycoside, dihydromagnolol, dihydrohonokiol, magnoflorine, norhonokiol, norisomagnolol, etc. Some research suggests that magnolia bark extract may help reduce pain and inflammation associated with endometriosis. (Szałabska-Rąpała et al., 2021). *Magnolia officinalis* L. bark extract reduced the secretion of IL-6 and IL-8 from HGF-1 cells to 72.5 $\pm$ 28.6% and significantly reduces the secretion of matrix metalloproteinase 9 (MMP-9) and matrix metalloproteinase 2 (MMP-2) from U-937 cells to 8.87 $\pm$ 7.97% compared to LPS-treated cells (100%). *Magnolia officinalis* L. extract with same as 5 μg/mL of Isodon japonicus L. extract exhibits potent anti-inflammatory effect.

Black cohosh (*Actaea racemosa*) is traditionally used to alleviate menopausal symptoms, but some studies suggest it may also have anti-inflammatory properties and could potentially help manage endometriosis symptoms. Furthermore, it has been suggested that the effectiveness and safety of black cohosh products in alleviating symptoms associated with menopause exhibiting a significant role in reproductive associated disorders. the majority of clinical trials represents that *Actaea racemosa* L. significantly makes better menopause and improve related symptoms as well as the associated complications such as liver disease, autoimmune diseases, or those taking medications that may affect liver function against using products containing black cohosh (Beer et al., 2013; Leach & Moore, 2012; Mahady et al., 2006; Salari et al., 2021).

Vitex trifolia, also known as Indian beech or chaste tree, is an herb traditionally used in Ayurvedic medicine. It has been studied for its potential benefits in hormonal imbalances, including endometriosis (Hakeem et al., 2016; Parkhe & Bharti, 2019; Wee et al., 2020). *Boswellia serrata*, also known as Indian frankincense, is an herbal extract that has been used in traditional medicine for its anti-inflammatory properties. It may help reduce inflammation and alleviate pain associated with endometriosis (Azemi et al., 2012). Myrrh is a resin obtained from trees of the genus Commiphora used in traditional medicine for its anti-inflammatory and analgesic properties. Myrrh essential oil or tincture may be used topically

Table 1
Medicinal plants and their reported pharmacological action against endometriosis.

S. No.	Plant/source	Chemical constituents	Mechanism of action
1.	*Vitex agnus-castus* (chasteberry or vitex)	Agnuside, casticin, vitexin, casticin acetate, rotundifuran, flavonoids (orientin, isoorientin, isovitexin, apigenin), essential oils (cineole, sabinene, limonene) agnuside glucoside, vitexilactone, 3-hydroxy-4,5-dimethoxybenzoic acid, casticin glucoside, 6'-O-trans-p-coumaroylcasticin, 6'-O-trans-feruloylcasticin, vitexin-2″-O-rhamnoside, 7-O-trans-p-coumaroylvitexin	Regulates estrogen and progesterone levels and alleviate some symptoms of endometriosis
2.	*Zingiber officinale* (Ginger)	Gingerols, shogaols, gingerdiols, zingerone, gingerenone a, paradols, sesquiterpenes, gingerdiones, zingiberene, curcuminoids, etc	Exhibits anti-inflammatory effects and may help alleviate pain and reduce inflammation in endometriosis
3.	*Camellia sinensis* (Green tea)	Catechins, phenol and flavonoids	Reduce the growth of endometrial tissue
4.	*Withania somnifera* (Ashwagandha)	Polyphenols, steroids such as Withanolide A, B	Exhibits antioxidant and anti-inflammatory properties and may help regulate hormone levels and reduce stress
5.	*Magnolia officinalis* (Magnolia)	Honokiol, magnolol, magnaldehyde, honokiol glycoside, magnolol glycoside, dihydromagnolol, dihydrohonokiol, magnoflorine, norhonokiol, norisomagnolol, etc	Help to reduce pain and inflammation associated with endometriosis
6.	*Actaea racemose* (Black cohosh)	Biphenyl compounds, caffeic acids, flavonoids, free radical scavengers, lignans, phenols, phenylacetates, picrates,	Alleviate menopausal symptoms, exhibits anti-inflammatory activity and potentially help to manage endometriosis symptoms.
7.	*Vitex trifolia* (Indian beech or chaste tree)	Matairesinol 4′-O-β-D- glucopyranoside, ecdysone, 20-hydroxyecdysone 2,3-monoacetonide, turkesterone, 20-hydroxyecdysone, and polypodine	Potential benefits in hormonal imbalances, including endometriosis
8.	*Boswellia serrata* (Indian frankincense)	Monoterpenes, diterpenes, triterpenes, tetracyclic triterpenic acids, pentacyclic triterpenic acids acetyl-β-boswellic acid, β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid.	Exhibits anti-inflammatory properties. It may help reduce inflammation and alleviate pain associated with endometriosis.

to help manage endometriosis symptoms (Rahmani et al., 2022; Suliman et al., 2022). Flaxseed is rich in omega-3 fatty acids and lignans, which possess anti-inflammatory properties. It may help regulate hormone levels and reduce inflammation associated with endometriosis. Ground flaxseed can be added to meals or smoothies (Collins et al., 2003). Dandelion root has been used in traditional medicine for its diuretic and anti-inflammatory properties. It may help support liver function, reduce inflammation, and manage symptoms of endometriosis (Bont et al., 2019; Mitkowski & Abawi, 2002). Licorice root has anti-inflammatory and antispasmodic properties. It may help reduce inflammation and alleviate pain associated with endometriosis. However, licorice root should be used with caution due to its potential effects on blood pressure and hormone levels (Minnetti et al., 2022). Red clover contains isoflavones, which are phytoestrogens that may help regulate estrogen levels. It has been studied for its potential benefits in managing hormonal imbalances and reducing inflammation associated with endometriosis (Hloucalová et al., 2016; Jing et al., 2021; Riggi et al., 2021). The potential medicinal plants that has been used for endometriosis are summarized in Table 1.

2.3. Therapeutic targets of recent pharmaceuticals in endometriosis

There are several pharmaceutical formulations used in the management of endometriosis. The specific treatment approach may vary depending on factors such as the severity of symptoms, the desire for fertility, and individual patient characteristics. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, and diclofenac are often prescribed to help relieve pain and reduce inflammation associated with endometriosis. They work by inhibiting prostaglandin production, which can alleviate pain symptoms. Various hormonal contraceptives such as estrogen and progestin, contraceptive patches, progestin-only pills, and contraceptive injections, are commonly used to manage endometriosis. These medications help regulate hormone levels and reduce the growth of endometrial tissue (Brown et al., 2017; Efstathiou et al., 2005; Stewart & Deb, 2016).

Gonadotropin-releasing hormone (GnRH) agonists and antagonists work by suppressing the production of estrogen, which can lead to the shrinkage of endometriotic implants

and a reduction in symptoms. Medications such as leuprolide, goserelin, and nafarelin fall into this category. GnRH agonists and antagonists have been extensively studied and utilized in the treatment of endometriosis. These medications target the GnRH receptor in the pituitary gland, leading to the suppression of gonadotropin release and subsequent reduction in ovarian estrogen production. This hormonal manipulation results in a hypoestrogenic state, which can alleviate symptoms associated with endometriosis and promote regression of endometrial lesions. GnRH agonists, such as leuprolide and goserelin, initially cause an initial surge in gonadotropin release before desensitizing the pituitary gland and ultimately downregulating GnRH receptors. This downregulation leads to the suppression of ovarian estrogen production, inducing a state of reversible pseudomenopause. While effective in alleviating pain and reducing endometriotic lesions, GnRH agonists are associated with side effects such as hot flashes, vaginal dryness, and bone loss (Hu et al., 2022; Kumar & Sharma, 2014; Leyland et al., 2021). To mitigate these adverse effects, add-back hormonal therapy, including low-dose estrogen and progestin supplementation, is often prescribed concurrently. GnRH antagonists, such as cetrorelix and ganirelix, work by directly blocking the GnRH receptor without an initial surge in gonadotropin release. This leads to rapid and reversible suppression of gonadotropin release and estrogen production. GnRH antagonists offer a more convenient dosing regimen and may have a lower risk of flare-up symptoms compared to GnRH agonists. However, their long-term efficacy and safety in endometriosis treatment require further investigation. While GnRH agonists and antagonists have demonstrated efficacy in managing endometriosis-related pain and lesions, their use is typically limited to short-term treatment due to the potential for adverse effects and the need for add-back therapy to mitigate hypoestrogenic symptoms. The decision to utilize GnRH agonists or antagonists should be based on individual patient characteristics, treatment goals, and consideration of potential side effects. Ongoing research is focused on optimizing the duration and combination therapies to maximize the benefits and minimize the drawbacks of these pharmacological interventions in endometriosis management (Hu et al., 2022; Kumar & Sharma, 2014).

Progestins are synthetic forms of progesterone, prescribed in various formulations, including oral pills, injections, or intrauterine devices (IUDs). Progestins help regulate hormone levels and can reduce the growth of endometrial tissue. Progestins exert their effect by inhibiting the secretion of FSH and LH from the pituitary gland. This leads to the suppression of ovulation, thereby reducing cyclic hormonal fluctuations and the subsequent growth and proliferation of endometrial tissue outside the uterus (Gezer & Oral, 2015).

Progestins promote the differentiation of endometrial cells into a decidualized state, similar to the changes that occur in the endometrium during pregnancy. Decidualization leads to reduced cell proliferation and angiogenesis, potentially causing regression and inhibition of endometriotic lesions. It also possess anti-inflammatory properties, which can help reduce the inflammatory response associated with endometriosis. They inhibit the production of pro-inflammatory cytokines and chemokines, thereby attenuating the recruitment and activation of immune cells in the endometriotic lesions. Progestins can modulate the activity of estrogen receptors in the endometrium. By competing with estrogen for binding to the receptors, progestins counteract the proliferative effects of estrogen on endometrial and endometriotic tissues. This antagonistic effect on estrogen signaling helps to control the growth and development of endometriotic lesions (Angioni et al., 2014; Vercellini et al., 2016).

Danazol is a synthetic androgen derivative that has been used in the treatment of endometriosis for several decades. Its mechanism of action involves a combination of hormonal and non-hormonal effects, which contribute to its therapeutic efficacy in managing endometriosis. Suppression of gonadotropin secretion: Danazol acts on the hypothalamic-pituitary-ovarian axis to suppress the release of FSH and LH. This leads to a state of reversible ovarian suppression, resulting in a hypoestrogenic environment. The reduced estrogen levels help to inhibit the growth and development of endometriotic lesions (Selak et al., 2007).

Danazol has anti-estrogenic properties, which means it competes with estrogen for binding to estrogen receptors. By occupying these receptors, danazol blocks the proliferative effects of estrogen on the endometrial and endometriotic tissues. This results in the suppression of cell proliferation and reduces the size and activity of endometriotic lesions. Aromatase inhibitors, such as letrozole and anastrozole, work by inhibiting the enzyme aromatase, which is responsible for the production of estrogen. By reducing estrogen levels, aromatase inhibitors can help suppress the growth of endometrial tissue. Danazol directly acts on the pituitary gland to suppress the release of FSH and LH. This effect reduces ovarian function and suppresses estrogen production, contributing to the inhibition of endometriosis growth. Inhibition of steroidogenesis: Danazol inhibits the enzymatic activity of various steroidogenic enzymes, including 17-alpha hydroxylase and 17,20-lyase. This leads to a decrease in the synthesis of ovarian androgens and estrogen precursors, further contributing to the hypoestrogenic state. Modulation of the immune system: Danazol has immunomodulatory effects, including suppression of immune cell function, alteration of cytokine production, and reduction of inflammatory response. These actions help to mitigate the inflammatory environment associated with endometriosis and alleviate symptoms (Igarashi, 1990; Selak et al., 2007; Wright et al., 1995).

Furthermore, selective progesterone receptor modulators (SPRMs), such as ulipristal acetate, act on progesterone receptors and can have both progestin and anti-progestin effects. They are used to manage moderate to severe endometriosis-associated pain and can help reduce the size of endometriotic lesions. SPRMs act as antagonists on progesterone receptors in endometrial and endometriotic tissues, inhibiting the

proliferative effects of estrogen. By blocking the activity of estrogen in these tissues, SPRMs help to reduce the growth and development of endometriotic lesions. SPRMs induce a state of progesterone resistance in the endometrium and endometriotic lesions. This resistance prevents the normal progesterone-mediated decidualization process, which is essential for the establishment and maintenance of endometriotic lesions. By disrupting this process, SPRMs contribute to the regression and inhibition of endometriosis. SPRMs have anti-inflammatory properties, which can help to mitigate the inflammatory response associated with endometriosis. They suppress the production of various cytokines and chemokines, thereby reducing immune cell recruitment and activation in endometriotic lesions (Chwalisz et al., 2005; Singh et al., 2020; Whitaker et al., 2014).

3. CONCLUSION

In conclusion, the phytopharmacology and chemistry of medicinal plants used traditionally for endometriosis and offer promising avenues for the development of alternative therapies. The identified medicinal plants possess diverse pharmacological properties and bioactive constituents that target multiple pathways involved in endometriosis pathogenesis. The anti-inflammatory, analgesic, antioxidant, immunomodulatory, and hormone-regulating effects of these plants provide potential benefits in managing endometriosis-related symptoms and improving reproductive outcomes. However, further research is needed to elucidate the precise mechanisms of action, optimize dosage regimens, and evaluate the safety and efficacy of these natural remedies. Integrating traditional knowledge with modern scientific approaches will contribute to the development of novel therapeutic agents for the effective management of endometriosis.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ORCID

Rustam Ekbbal	0000-0003-1862-9280
Aakash Kumar Jaiswal	0000-0001-8459-2610
Mansi Aggarwal	0000-0001-5396-5365
Mhaveer Singh	0000-0001-9951-5685
Shadab Ali	0009-0007-6832-0907
Sayad Ahad Ali	0000-0002-6837-1268
Gaurav Gautam	0000-0002-0530-0788

AUTHOR CONTRIBUTIONS

GG - Research concept and design, RE, AKJ, MA,MS, SAA - Collection and/or assembly of data, MA - Data analysis and interpretation, RA, SAA, GG - Writing the article, MS, GG - Critical revision of the article, GG - Final approval of the article.

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