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Review Paper

Role Of Natural Phytoconstituents in Endometrial Cancer

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ABSTRACT

Globally, endometrial cancer is among the most frequent cancers in females. The increase in the incidence of this cancer has been linked to obesity, metabolic syndrome, and the overall ageing of the population. While advances in surgical treatments and adjunctive therapies have taken place for the treatment of endometrial cancer and its recurrence, there are still limited options for patients with advanced and recurrent endometrial cancer; there is a clear need for new strategies for treating endometrial cancer. Natural phytoconstituents derived from plants are emerging as potential agents for both the prevention and treatment of cancer due to their multi-targeted actions, their safe profile, and their ability to regulate multiple major oncogenic pathways. The present comprehensive review of the literature will present information about the epidemiology, risk factors, histopathology, molecular classification, diagnosis, and current therapeutic approaches for endometrial cancer. Next, this review will consist of an extensive description of a number of different natural phytoconstituents (e.g., curcumin, resveratrol, quercetin, epigallocatechin gallate, kaempferol, berberine, ginsenosides, etc.) that may be used to treat endometrial cancer including the molecular mechanisms by which these phytoconstituents exert their anti-cancer effects (e.g., apoptosis, cell cycle arrest, inhibition of proliferation, inhibition of metastasis, and modulation of estrogen signaling).

INTRODUCTION

Endometrial cancer is the most commonly diagnosed gynaecological malignancy in developed countries and an important cause of morbidity and mortality for women internationally [1][63][64]. Endometrial cancer arises from the endometrial lining of the uterus. The tumour primarily occurs in post-menopausal women, and cases in pre-menopausal women are also being published [6]. Understanding and reviewing epidemiology, risk factors, histopathologic characteristics, molecular mechanisms, and diagnostic modalities that relate to endometrial

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carcinogenesis are necessary to formulate effective prevention and treatment strategies.

The pathogenesis of endometrial cancer involves complex interactions between hormonal, genomic, and environmental factors [65][66]. The clinicopathological classification of endometrial carcinomas into two different types has been used for years [7][19]. Type I tumours comprise approximately 80% of tumours and are primarily endometrioid adenocarcinomas that are generally estrogen-dependent, low grade, and have positive prognosis. Type II tumours are serous and clear cell carcinomas that do not use estrogen for growth, are high grade, and have poor prognosis [20].

The emergence of molecular profiling has changed how we understand the heterogeneity of endometrial cancer. The Cancer Genome Atlas (TCGA) Research Network published a groundbreaking report in 2013 identifying four groups with separate molecular characteristics. These are known as the POLE ultramutated, microsatellite instability hypermutated (MSIH), copy number low, and copy number high groups [11][12]. These classifications have important implications for prognosis and selection of treatment [13]. The use of molecular classification in clinical practice is a paradigm shift for the management of endometrial cancer [67].

As our conventional therapies for advanced disease have limits, and develop resistance, there is increased interest in the use of natural phytoconstituents, as adjuvant or alternative therapies . Natural products have been shown to have outstanding anti-cancer effects through the modulation of multiple signalling pathways leading to carcinogenesis [54]. The present review will provide a comprehensive overview of the role of natural phytoconstituents in endometrial cancer. We will elaborate the anti-cancer effects and summarize the existing evidence with respect to phytoconstituents in endometrial cancer. In addition to the coverage of advanced treatment options, epidemiology and histopathology elements, the diagnosis will be presented.

Histopathology and Pathological Classification

There are typically two types of endometrial cancer. The dominant form is Type I, which makes up more than 70% of cases. Endometrial adenocarcinoma is characterized by the presence of unopposed estrogen stimulation, which can lead to Type I tumours. The majority of these tumours are low grade. High grade and papillary serous or clear cell histological type are more common in Type II tumours. Their prognosis is poor and their risk of relapse and metastasizing is high. Only 10% of endometrial cancers are caused by Type II. Lynch syndrome, which is associated with hereditary nonpolyposis colorectal cancer, typically involves familial tumours. A genetic disease accounts for 10% of endometrial cancer cases. Endometrial hyperplasia is a precursor condition that leads to endometrial cancer [10]. The risk of developing cancer with hyperplasia is between 1%- 3%.

The risk of cancer is higher in patients with atypical hyperplasia than those with simple or complex hyperplasia, and concomitant occurrence of neoplasma is also present in 30% to 40% of the patients.

Feature	Type I (Endometrioid)	Type II (Non-Endometrioid/Aggressive)
Prevalence	Most Common	Less Common
Histology	Endometrioid Adenocarcinoma	Serous, Clear Cell, Carcinosarcoma, Undifferentiated
Grade	Low-grade	High-grade
Underlying Cause	Estrogen-driven (Obesity, Hyperplasia)	Sporadic (Atrophic endometrium)

Molecular Subtype	MMRd, NSMP, POLEmut	p53-abnormal
Prognosis	Good (Often presents early)	Poor (High risk of metastasis)

Epidemiology and Risk Factors

Global Burden and Trends: Approximately 5% of all female cancers are endometrial cancers. It is the sixth most prevalent cancer globally [2]. The highest incidence rates of endometrial cancer occur in North America and Northern Europe, with reported rates of over 20 per 100,000 female cases. On the other hand, there are lower rates in Africa and South Asia. In contrast to this, both developing and developed regions of the world are seeing a consistent rise in mortality since early detection or treatment could not fully account for the increase in annual frequency [2].

In the US alone, the American Cancer Society estimates there will be 69,120 new cases and 13,350 deaths from endometrial cancer in 2025, which reflects a 1.5% increase annually between 2013 and 2022 [3]. In addition to this, an increase in the risk of developing endometrial cancer correlates strongly with an increase in obesity, which is one of the primary modifiable risks for endometrial cancer and is expected to continue to rise due to a lack of effective population-level interventions [3].

Established Risk Factors

➢ Hormonal and Metabolic Risk Factors

The hypothesis that unopposed estrogen is a major factor in developing endometrial cancer (EC) remains a significant part of developing EC. The stimulation of the endometrium by estrogen, with no opposing effects of progesterone, is thought to lead to hyperplasia and, ultimately, neoplastic transformation when there is prolonged exposure to estrogen. There are numerous factors that can lead to increased estrogenic stimulation, which increase the risk of developing cancer. These include obesity, polycystic ovary syndrome (PCOS), the use of estrogen-only hormone replacement therapy, reaching menarche at an early age (younger than 12 years old), no previous pregnancies, and reaching menopause at an older age (older than 55).

Obesity accounts for almost 40% of the incidence of EC worldwide. Adipose tissue functions as an endocrine organ; therefore, it will convert androgens to estrogens through the aromatase enzyme and increase the amount of circulating estrogen. Hyperinsulinemia and chronic inflammation associated with obesity will also stimulate hyperproliferation of endometrial cells through the insulin-like growth factor (IGF) signaling pathway and inflammatory cytokines such as IL-6 and TNF-α[10].

Diabetes mellitus and metabolic syndrome are significant independent risk factors associated with EC, even after accounting for BMI. Hyperinsulinemia causes mitogenesis through both the phosphoinositide 3-kinase/AKT (PI3K/AKT) and mitogen-activated protein kinase (MAPK) signaling pathways. Also, oxidative stress from dysregulated glucose metabolism may cause damage to DNA and contribute to carcinogenesis.[6]

➢ Genetic and Hereditary Factors

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer, is responsible for 5-10% of Endometrial Carcinomas (EC). With Lynch syndrome, germline mutations occur in mismatch repair genes (MLH1, MSH2, MSH6, and PMS2), creating microsatellite instability (MSI) which results in a lifetime risk of developing EC of up to 60% [22][23].Therefore testing for MMR deficiency or MSI has become standard at the universal level as a screening tool to identify those who may be at increased risk of

developing EC due to Lynch syndrome.Furthermore, associations exist between the increased risk of developing EC to Cowden syndrome (PTEN mutations) and Peutz-Jeghers syndrome (STK11 mutations) as a result of the loss of tumor suppressor function [10].

➢ **Reproductive and Lifestyle Factors**

High parity, use of combined oral contraceptives (COCs), and smoking are paradoxically protective against EC. COCs reduce risk by 50–70% due to the anti-proliferative effect of progestins on endometrial tissue. Physical activity, a balanced diet, and maintenance of healthy body weight reduce risk, whereas a Western diet rich in saturated fats and red meat is associated with increased incidence[11].Conversely, tamoxifen, a selective estrogen receptor modulator (SERM) used in breast cancer therapy, increases EC risk due to its partial agonist activity on endometrial tissue. Prolonged tamoxifen use (>5 years) correlates with a 2- to 3-fold higher risk, necessitating careful surveillance. [8]

Molecular Classification and Advance Diagnosis

Evolution from Histopathologic to Molecular Classification

The historical separation of endometrial carcinoma into the Bokhman dualistic model (Type I and Type II) resulted in the loss of applicable predictive information related to prognosis, as well as therapeutic outcome. The documents arising from the TCGA project (2013) provided genomic information that would form the basis for future study and lead to a four-part dividing (via molecular classification) of EC on a genomic basis, with all four groups exhibiting different outcomes [5].

The Cancer Genome Atlas (TCGA) Molecular Subgroups

The TCGA analysis of 373 endometrial carcinomas identified four reproducible subgroups based on integrated genomic, transcriptomic, and proteomic data [7]

1. **POLE ultramutated (7–12%):** characterized by mutations in the DNA polymerase epsilon (POLE) exonuclease domain, leading to an extremely high mutation rate (>100 mutations/Mb). These tumours have a favorable prognosis despite high-grade histology. They exhibit intense lymphocytic infiltration and increased neoantigen load, making them potential candidates for immunotherapy [4].
2. **Microsatellite instability-high (MSI-H) hypermutated (25–30%)** – associated with defects in the DNA mismatch repair (MMR) pathway, either by MLH1 promoter hypermethylation or germline MMR mutations (as in Lynch syndrome). These tumours show intermediate prognosis and respond favourably to immune checkpoint [5].
3. **Copy-number low (endometrioid) (40%)** – mostly low-grade endometrioid carcinomas with few somatic copy-number alterations. They display frequent PTEN, PIK3CA, and ARID1A mutations and generally have favourable outcomes [7].
4. **Copy-number high (serous-like) (10–15%)** – characterized by extensive somatic copy-number alterations, frequent **TP53** mutations, and a poor prognosis. This group includes most serous and high-grade endometrioid carcinomas [8].

This molecular stratification provides a biologically meaningful prognostic model**,** superior to traditional histology alone, and offers a foundation for personalized therapy**.**

The ProMisE Classifier

The Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) converts TCGA

molecular classification into a practical, clinically usable test [6]. The ProMisE Test uses a sequential diagnostic process that incorporates testing for immunohistochemical MMR proteins and p53; determining POLE mutations; and classifying tumors into four similar categories, as follows:

 POLE-mutated
 MMR-deficient
 p53 wild-type
 p53 abnormal

Based on the reproducibility shown across many clinical scenarios within ProMiSE, ProMiSE correlates well to prognosis, and is useful in making treatment decisions for patients receiving adjuvant therapy. Molecular classification recently added to the 2023 ESGO/ESTRO/ESP Guidelines, provides framework for modern risk stratification in the evaluation of EC.[7]

Key Molecular Pathways in Endometrial Carcinogenesis

Molecular studies reveal several key pathways implicated in EC pathogenesis:

- **PI3K/AKT/mTOR pathway**: Activated in ~80% of ECs through mutations in PTEN**,** PIK3CA**,** and AKT1**,** promoting proliferation and resistance to apoptosis [16].
- **Wnt/β-catenin pathway**: Dysregulation via CTNNB1 mutations contributes to tumorigenesis, particularly in low-grade endometrioid carcinomas.
- **p53 pathway**: Aberrant TP53 mutations occur in >90% of serous carcinomas, leading to genomic instability and aggressive phenotype.
- **DNA mismatch repair (MMR) deficiency**: Leads to MSI-H phenotype and increased tumor mutational burden (TMB), enhancing susceptibility to immune checkpoint inhibitors [14].
- **Hormonal receptor signaling**: Estrogen receptor (ER) and progesterone receptor (PR) expression influence tumor biology and therapeutic responsiveness; ER-positive tumors typically have a better prognosis [5].

Clinical Implications of Molecular Subtypes

Each molecular subgroup correlates with distinct clinical behavior and therapeutic response**:**

- **POLE-mutated**: Excellent prognosis; adjuvant therapy may be omitted.
- **MMR-deficient (MSI-H)**: Intermediate prognosis; candidates for PD-1 blockade [14].
- **p53-abnormal (copy-number high)**: Poor prognosis; benefit from aggressive multimodal therapy and targeted drugs.
- **p53-wild-type (copy-number low)**: Generally good prognosis; managed conservatively in early-stage disease.

Molecular classification thus enables risk-adapted adjuvant therapy, reducing overtreatment in low-risk cases and intensifying treatment in aggressive subtypes [7].

Diagnostic Advances and Staging

Clinical Presentation and Initial Evaluation: Abnormal bleeding in the uterus, including postmenopausal bleeding, usually is reported by most women who have been diagnosed with endometrial cancer (approximately 90% of cases). The identification of early symptoms enables approximately 70-80% of patients to be diagnosed at a stage when their cancer can still be treated successfully.

The initial evaluation of patients with abnormal bleeding includes the use of transvaginal ultrasound, an inexpensive, non-invasive technique that allows for the measurement of endometrial thickness. Postmenopausal women will require a histological evaluation of their endometrial stripe if it exceeds 4 mm [5].

Endometrial Sampling Techniques: The gold standard for diagnosis continues to be an endometrial biopsy. Both an office-based technique (Pipelle) and another office-based technique (Tao brush) have very good sensitivity (>90%) for diagnosing carcinoma. If there is an inadequate sample when performed using either of these techniques, a dilation and curettage (D&C) or hysteroscopy assisted biopsy may be used.

A hysteroscope permits direct visualization of the endometrial cavity, which allows targeted biopsy as well as the evaluation of focal lesions, such as polyps or hyperplasia.

Imaging for Staging and Preoperative Evaluation: Preoperative imaging is crucial for assessing myometrial invasion, cervical involvement, and lymph node metastasis**.**

- **Magnetic Resonance Imaging (MRI)** is the preferred modality for local staging, with accuracy of ~85% for assessing depth of myometrial invasion.
- **Computed Tomography (CT)** aids in detecting distant metastases and assessing pelvic or para-aortic lymphadenopathy.
- **Positron Emission Tomography (PET-CT)** has high sensitivity for detecting nodal and distant disease, especially in high-grade or recurrent tumors [6].

Histopathologic and Immunohistochemical Evaluation: Histologic classification is performed according to the World Health Organization (WHO, 2020) system [10], which recognizes several subtypes:

- Endometrioid carcinoma (low and high grade)
- Serous carcinoma
- Clear cell carcinoma
- Carcinosarcoma
- Undifferentiated/dedifferentiated carcinoma

Immunohisto chemistry (IHC) is essential for confirming histologic subtype and assessing prognostic markers, including p53**,** MMR proteins (MLH1, MSH2, MSH6, PMS2)**,** ER/PR**,** and HER2. Aberrant p53 expression is strongly associated with serous histology and poor outcome.

Revised FIGO Staging

The FIGO 2023 staging system incorporates molecular and histologic parameters for a more precise classification. Major updates include:

- Integration of TCGA molecular subgroups for prognostic assessment.
- Recognition of lymphovascular space invasion (LVSI) as a key prognostic factor.
- Improved definitions for cervical stromal and adnexal involvement [11].

Biomarkers for Early Detection and Prognostication: While no serum biomarker is currently validated for EC screening, several molecules show promise:

- CA-125 and HE4 (human epididymis protein 4) have diagnostic utility in advanced disease.
- Circulating tumor DNA (ctDNA) and microRNAs (miR-200 family, miR-205) are being investigated as non-invasive biomarkers for early detection and recurrence monitoring.
- Epigenetic markers such as MLH1 promoter methylation and global DNA hypomethylation may aid in risk stratification [6].

Integration of molecular diagnostics, advanced imaging, and minimally invasive sampling will shape the future of precision diagnosis in EC.

Treatment Strategies and Emerging Therapies

Overview of Management: Endometrial cancer treatment depends on multiple factors which include cancer stage, histopathology, cancer subtype and patient factors such as their age and other medical issues. Surgical excision is the

primary treatment option; however, patients may also receive postoperative radiotherapy, chemotherapy or hormonal therapy based on their level of risk for recurrence. Recent advancements in technology have produced a change in the way EC will be treated due to the development of personalized, molecularly-based therapies. This may include targeted therapy and immunotherapy. [11]

Surgical Management

- **Standard Surgical Procedures:** Surgery is still the gold standard for treating EC. The traditional surgical procedure comprises total abdominal hysterectomy and bilateral oophorectomy/bilateral salpingo-oophorectomy plus or minus evaluation of lymph nodes.

Innovations in surgery, such as laparoscopic and robotic-assisted surgical methods, are replacing open surgery for early-stage EC due to less postoperative pain, shorter recovery times, and comparable oncological outcomes [9].

- **Sentinel Lymph Node (SLN) Mapping:** The sentinel lymph node (SLN) biopsy has largely replaced full lymphadenectomy in apparent early-stage EC. Using indocyanine green (ICG) with near-infrared imaging, SLN mapping achieves high sensitivity for detecting nodal metastases while minimizing lymphedema risk.

Studies such as FIRES demonstrated a sensitivity of 97.2% and a negative predictive value of 99.6%, supporting SLN biopsy as a standard of care [25].

- **Fertility-Sparing Surgery:** Progestin hormone therapy alone can be an option for preserving the ability to have children in younger women who have early stage, low grade endometrioid cancer. Progesterone medications such as megestrol acetate, medroxyprogesterone acetate or levonorgestrel containing IUD can help control growth and may lead to size reduction in approximately 70-80% of selected patients [11]. It is essential to perform regular imaging and endometrial biopsies on these individuals to detect recurrence.

Adjuvant Radiotherapy

- **Vaginal Brachytherapy (VBT):** For early-stage disease, vaginal brachytherapy alone is preferred over external beam radiotherapy (EBRT) due to reduced toxicity and comparable efficacy in preventing vaginal recurrence.
- **External Beam Radiotherapy (EBRT):** EBRT is indicated for high-intermediate or high-risk disease with deep myometrial invasion, LVSI, or serous/clear cell histology. The PORTEC-3 trial demonstrated improved progression-free survival when combined with concurrent chemotherapy in advanced cases [15].

Chemotherapy

- **First-Line Chemotherapy:** For advanced or recurrent EC, the combination of carboplatin and paclitaxel remains the standard first-line regimen [21]. This combination provides similar efficacy to cisplatin-based regimens with improved tolerability and reduced nephrotoxicity [11].
- **Second-Line and Recurrent Disease:** Response rates to second-line chemotherapy are modest (10–15%), and median survival rarely exceeds one year. Agents such as doxorubicin**,** liposomal doxorubicin, and gemcitabine have been used, though their roles are limited by resistance and toxicity [11].

Hormonal Therapy

Endometrial cancer is hormone-responsive, especially in ER/PR-positive tumours. Progestin-based therapy is effective in both

fertility-sparing and advanced settings, inducing tumour regression by antagonizing estrogen-driven proliferation. Aromatase inhibitor (letrozole, anastrozole) and selective estrogen receptor modulators (SERMs) have shown efficacy in recurrent, low-grade EC. Combination therapy with everolimus (mTOR inhibitor) and letrozole demonstrated response rates up to 32% in advanced endometrioid EC [9].

Immunotherapy

- **Combination Immunotherapy:** Combining ICIs with antiangiogenic agents enhances response in MMR-proficient EC, which typically shows limited immunogenicity. The KEYNOTE-775 trial demonstrated that pembrolizumab + lenvatinib significantly improved overall survival compared with chemotherapy in previously treated advanced EC [12]. This regimen is now a standard option for MMR-proficient and p53-abnormal tumors [13].

Targeted Therapies

- **mTOR Inhibitors:** Deregulation of the PI3K/AKT/mTOR pathway makes it a major therapeutic target.Everolimus and temsirolimus inhibit mTOR signaling, reducing tumor proliferation. Their use in combination with hormonal therapy (letrozole) improves outcomes in recurrent disease [16].
- **HER2-Targeted Therapy:** Adding trastuzumab to carboplatin paclitaxel significantly improved progression-free survival in HER2-positive serous carcinoma. This combination is now incorporated into standard care for this subtype [25].
- **Anti-Angiogenic Agents:**Bevacizumab, an anti-VEGF antibody, has shown modest activity in advanced EC, especially when combined with chemotherapy or immunotherapy. Trials combining bevacizumab with temsirolimus or PD-1 inhibitors are ongoing [20].

Natural Phytoconstituents in Endometrial Cancer

Introduction:

Natural product research for cancer prevention and treatment has increased tremendously in recent years; one such study detailed the use of natural products in preventing and treating endometrial cancer that involved multiple mechanisms of action. Natural products induce apoptosis (programmed cell death), making it viable for therapeutic use in cancers. Natural compounds known as phytochemicals, which are abundant in women's cancers, including endometrial cancer, have also been assessed thoroughly with respect to their various mechanisms of action and benefits.

Researchers have reported that the anti-cancer effects of phytochemicals are due to their ability to induce apoptosis, inhibit cell proliferation or metastasis, and modulate the expression of estrogen receptors (preventing angiogenesis). Phytochemicals including curcumin, EGCG, sulforaphane, resveratrol, and genistein are the "Big Five" phytochemicals with potential value against cancer stem cells, while quercetin, EGCG, kaempferol, apigenin, and curcumin have all been shown to inhibit human carcinoma cell line proliferation.

Key Phytoconstituents Studied in Endometrial Cancer:

- **Curcumin:** Curcumin from Curcuma longa is known for its incredible cancer-fighting ability against multiple cancer types including endometrial cancer. The most extensive review of the benefits of curcumin so far describes curcumin as an "old spice, new agent" in the treatment of endometrial carcinoma. Due to its pleiotropic effects, curcumin has great potential for preventing and treating cancer.

Mechanistic studies have shown that curcumin has the ability to trigger apoptosis (programmed death) in human endometrial carcinoma cells by decreasing levels of the androgen receptor via the Wntsignaling pathways. [79] This finding is significant because Wnt/β-catenin signaling plays an important role in the development of endometrial carcinoma. Another compound with similar properties is curcusone C, which also causes the death of endometrial cancer cells through a mitochondrial dependent pathway as well as ERK signalling. [80]

The multi-target nature of curcumin gives it the ability to affect many cancer pathways such as: transcription factors, growth factors, inflammatory cytokines, and apoptotic proteins, making it a strong candidate for use in combination therapies.

- **Resveratrol and Pterostilbene**: Resveratrol is a naturally occurring compound found in many foods including grapes, red wine, and various berries. It has been studied for its ability to fight cancer, particularly endometrial cancer [82]. One of the reviews published on the use of resveratrol to treat gynecological cancers looked at the possible ways that resveratrol can work as an effective therapy against endometrial cancers [83]. The findings from early research showed that resveratrol was able to block activity of the AKT pathway and initiate apoptosis in human cells that had been derived from tumors of the uterine endometrium [84]. Resveratrol also has been found to inhibit estrogen effects while also working as a cytostatic (stop cell growth) in a cell line of endometrial adenocarcinoma (Ishikawa). They showed that apoptosis in Ishikawa cells was increased when autophagy inhibitors were used in combination with resveratrol.

Furthermore, it was shown that resveratrol inhibited EGF expression (down regulated) leading to decreased proliferation of Ishikawa cells [87]. In uterine sarcoma cells, resveratrol blocked growth via apoptosis through the Wnt signaling pathway [88]. Both resveratrol and EGCG have been demonstrated to inhibit VEGF expression in endometrial tumor cells suggesting they have anti-angiogenic properties.

- **Quercetin:** One of the most widely found flavonoids found throughout nature is quercetin, which occurs mainly in fruits, vegetables and herbal remedies. It has demonstrated great potential in the treatment of endometrial carcinoma. In particular, we focused our review on its potential therapeutic application and benefit of treating endometriosis and endometrial carcinoma. In the most recent research with respect to quercetin and endometrial carcinoma, it was noted that quercetin inhibited the proliferation of endometrial HEC-1-A cells through modulation of the new form of iron-dependent cellular death known as ferroptosis in addition to the more well-established apoptotic mechanisms [91].A systematic review of the therapeutic effects and underlying molecular mechanisms associated with quercetin in the management of gynecologic disorders was conducted [92].

In a separate analysis of the pharmacological properties and targets associated with quercetin, network pharmacology was utilized to characterize the multi-target nature of quercetin as it relates to therapeutic strategies for the diagnosis and treatment of endometrial carcinoma [93]. It has also been demonstrated through previous studies that quercetin can significantly inhibit both primary ovarian and endometrial carcinoma and has functional synergy with cisplatin [94]. Additionally, multiple population-based case-control research studies evaluated the relationships between the consumption of phytoestrogen food sources including quercetin and the risk of developing endometrial carcinomas [95].

- **Epigallocatechin Gallate (EGCG):** Epigallocatechin gallate (EGCG), the primary

catechin in green tea, has demonstrated anticancer effects against endometrial cancer through multiple mechanisms. A recent review article focused on the epigenetic effects of EGCG on benign/malignant gynaecological diseases. It provided insight into the protective effects of EGCG against endometrial, breast, and ovarian cancers, based on a literature review. [96]

To explore the mechanism of action of EGCG, studies demonstrated that reactive oxygen species (ROS) generation and p38 mitogen-activated protein (MAP) kinase activation occurred in the EGCG-induced apoptotic death of human endometrial adenocarcinoma cells. The antiproliferative and pro-apoptotic effects of EGCG were exhibited in Ishikawa cells through downregulation of sex steroid receptors, suggesting an additional indirect antiestrogenic mechanism of action. [99]

Pro-EGCG, a novel prodrug formulation of EGCG, has been developed and acts as an angiogenesis inhibitor in endometrial cancer. The prodrug formulation addresses the bioavailability limitations associated with natural EGCG. The effect of EGCG on specific female malignant neoplasms is still being studied, as further evidence becomes available.[101]

➢ **Ginsenosides and Terpenoids:** Ginsenosides are the main bioactive constituents of Panax ginseng. Terpenoids may also inhibit the growth of endometrial cancer through apoptosis. Zingiber officinale terpenoids has been shown to induce p53-mediated apoptosis in endometrial cancer [102]. Ginsenoside-Rh2 induces apoptosis and reduces epithelial-mesenchymal transition in HEC1A and Ishikawa endometrial cancer cells. Ginsenoside 20(S)-protopanaxadiol also causes cell death through inducing apoptosis in human endometrial cancer cells. Ginsenoside Rb2 has previously been shown to inhibit the invasive potential of endometrial cancer cells to the basement membrane. The ginsenoside-PPD mediated anti-endometriosis effects can also be attributed to the inhibition of estrogen receptor mediated inhibition of the autophagy and natural killer cell cytotoxicity against endometrial stromal cells. Mechanisms of action of ginsenosides related to tumor growth and metastases have already been reviewed [104].

➢ **Genistein and Apigenin:** Major isoflavone of soybeans, genistein; apigenin, a flavonoid in many plants, exhibit modulating effects on endometrial cancer [108]. Genistein activates long-term expression of progesterone receptor regardless of estrogen receptor level; therefore, offers potential benefits for patients with endometrial cancer. This finding provides different therapeutic options for hormone therapies.

Apigenin possesses the ability to inhibit cancer cell proliferation by means of binding with estrogen receptor beta (ERβ). The endocrine disrupting potential of flavonoid nutraceuticals (e.g., luteolin, quercetin) has been documented [111]. These compounds have been shown to demonstrate both pro- and anti-estrogen activity depending on the cellular context.

Compound	Natural Source	Molecular Target/Mechanism	Effect
Curcumin	*Curcuma longa*	Inhibits PI3K/AKT, NF-κB	Anti-proliferative, pro-apoptotic
Resveratrol	Grapes, berries	Suppresses STAT3, VEGF	Anti-angiogenic, apoptosis
Genistein	Soy	Modulates ER/ERK	Anti-estrogenic, growth inhibition
EGCG	Green tea	Blocks VEGF, PI3K/AKT	Anti-metastatic
Quercetin	Onion, apple	Inhibits MAPK, Wnt	Pro-apoptotic, anti-invasive
Luteolin	Celery, parsley	Inhibits IL-6/STAT3	Anti-inflammatory, cytotoxic

➢ **Traditional Herbal Medicines and Other Natural Compounds:**

Traditional herbal medicines have been investigated for anti-tumor effects against endometrial carcinoma through mechanisms involving estrogen receptor-alpha [115]. These studies scientifically support traditional medicinal practices and identify potential lead compounds for drug development.

Anti-cancer effects against endometrial cancer have been demonstrated by several other natural compounds. Psammaplin A is a natural histone deacetylase inhibitor that induces cell cycle arrest and apoptosis in human endometrial cancer cells [118]. Hyperin extracted from manchurian Rhododendron leaf induces apoptosis in human endometrial cancer cells through a mitochondrial pathway. [119]

α-Terthienylmethanol isolated from Ecliptaprostrata induces apoptosis by generating reactive oxygen species via NADPH oxidase in human endometrial cancer cells. [120]

Future Perspectives and Challenges:

The use of natural compounds found in plants to prevent or treat endometrial cancer seems very promising, but it also presents many problems. Some of these issues include low bioavailability, variable pharmacokinetics and no standardised extraction procedures across the country. Developing new delivery systems, creating prodrugs [100], or using other methods (combining treatments) may overcome these obstacles.

The classification of endometrial cancer into molecular subtypes [84][85] opens up exciting possibilities for phytochemical therapies that are more tailored to the patient's specific needs. Endometrial cancers that have certain molecular characteristics (e.g., PI3K/AKT/mTOR pathway activation and/or dysregulation of the Wnt/β-catenin pathway) have a higher likelihood of responding favorably to targeted phytochemical therapies.

All clinical studies involving phytoconstituents must be conducted through controlled scientific trials designed to assess the safety and effectiveness of a treatment, the proper dose and which patients will benefit most from the treatment. Additional research is still needed to evaluate phytoconstituents in combination with traditional treatments such as chemotherapy, hormonal therapy and immunotherapy.

CONCLUSION

EC is emerging as an exciting area of research in gynecologic oncology as advances in research have allowed for increased understanding of the molecular and biological diversity associated with EC, leading to the advancement of targeted therapeutic strategies. The use of traditional histopathological classifications are now complemented, and in some instances have been replaced, by genomic profiling methodologies, most notably with regard to the TCGA molecular subtypes that provide clinicians with much more accurate prognostic information and allow them to create individualized treatment plans for their patients based on the molecular characteristics of the tumour. The results of these molecular systems including the clinically applicable ProMisE classifier have led to an area of precision oncology that has changed how practitioners manage patients in uniform ways. As such, these patients are being treated with therapies that are consistent with the biological behavior of their tumours.

Although there has been significant advancement in the understanding of EC, the global burden of EC continues to increase primarily as a result of the increasing prevalence of obesity, diabetes, and increasing life span of the general population. This epidemiological trend supports the necessity of developing both novel and improved therapeutics aimed at EC and at developing preventive and

early detection strategies aimed at addressing the hormonal, metabolic, and hereditary risk factors associated with EC. Surgical intervention remains the primary treatment of patients with early-stage cancers; however, early-stage surgery remains ineffective for patients with advanced, recurrent, or metastatic cancers due to the complexities associated with successfully managing these patients.

In recent years, significant advancements have been made in the field of immunotherapy and targeted therapies for advanced endometrial carcinoma (EC), as they are now considered vital components of treatment protocols. Pembrolizumab and dostarlimab, two PD-1 inhibitors, have shown exceptional efficacy against tumours with mismatch repair deficiencies and microsatellite instability and have produced durable responses that were not achievable with traditional cytotoxic chemotherapy alone. In addition, the combination of pembrolizumab and lenvatinib has become the first-line therapy for patients with MMR-proficient EC by delivering significant improvements in overall survival for a population that has historically not responded well to immunotherapy. Furthermore, there has been considerable expansion of the therapeutic landscape with the addition of PI3K/AKT/mTOR inhibitors, HER2-targeted therapies and hormonal therapies, which creates new treatment options that hold promise for improving outcomes in patients with aggressive histologies of EC, such as serous carcinoma.

Parallel to these biomedical innovations, there is growing scientific interest in the therapeutic potential of phytoconstituents. Bioactive plant-derived compounds—including curcumin, resveratrol, genistein, EGCG, quercetin, luteolin, and others—have demonstrated significant anticancer effects in preclinical models. These compounds act on multiple hallmarks of cancer, including cell-cycle regulation, apoptosis, angiogenesis, inflammatory signaling, oxidative stress, and estrogen-receptor modulation. Many phytochemicals show synergy with chemotherapy, enhancing cytotoxicity or reversing drug resistance. While promising, these findings remain largely experimental; clinical applicability is currently limited by poor bioavailability, rapid metabolism, and the lack of standardization in dosing and formulation. Ongoing research into nano-delivery systems and molecular optimization is likely to advance the clinical utility of phytochemicals in EC prevention and therapy.

Altogether, the literature indicates that future progress in EC management will depend on integrating genomic profiling**,** immune-based therapies**,** rational targeted agents**,** and potentially phytochemical-based adjuvant strategies. The convergence of these fields has the potential to address current challenges, including treatment resistance, disease recurrence, and the need for more personalized, less toxic therapeutic options. As EC incidence continues to climb, especially in younger and obese women, the importance of translational research, preventive approaches, and innovative therapeutics becomes even more urgent.

In summary, endometrial cancer is no longer viewed as a single disease but rather a spectrum of biologically distinct entities requiring tailored interventions. Advances in molecular diagnostics and targeted treatments have improved outcomes, yet significant gaps remain—particularly in advanced-stage disease. Phytoconstituents, with their multi-targeted mechanisms and favorable safety profiles, represent an emerging frontier that may complement conventional therapies. Continued interdisciplinary research, clinical trials, and technological innovation will be essential to fully realize the potential of both precision medicine and natural-product-based interventions in the fight against endometrial cancer.

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