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REVIEW ARTICLE

Integrative Strategies for Ovarian Cancer Treatment: A Comprehensive Review from *Ayush* Perspectives

Alluri Pavani Gayatri[1], Bhaskara Raju Vatchavai[2], Nirmala Korukola[3], Naga Raju Bandaru[4], Srikanth Kumar Karumanchi[5], Afrin Sulthana[6] and Mohan Gandhi Bonthu[4*]

[1]Sandip Institute of Pharmaceutical Sciences, Nashik - 422213, Maharashtra, India
[2]Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem - 534101, Andhra Pradesh, India
[3]K.G.R.L. College of Pharmacy, Bhimavaram - 534201, Andhra Pradesh, India
[4]School of Pharmaceutical Sciences, Sandip University, Nashik - 422213, Maharashtra, India; bmgandhipharma@gmail.com
[5]Institute of Pharmaceutical Science and Research for Girls, Bhigwan - 413130, Maharashtra, India
[6]V.V. Institute of Pharmaceutical Sciences, Gudlavalleru - 521356, Andhra Pradesh, India

Abstract

Background: Ovarian Cancer remains a crucial reason for mortality among gynaecological diseases despite advancements in surgical techniques and chemotherapy. Delayed diagnosis often contributes to the unfavourable prognosis of the disorder. Though the initial platinum-based doublet chemotherapy and successful surgical intervention are done, a considerable proportion of individuals ranging from 70 to 80 per cent experience disease recurrence. **Aim:** In this current review, the authors aim to explore the potentiality of *Ayush* (*Ayurveda*, *Unani*, *Siddha*, *Yoga* and Naturopathy and Homeopathy) approaching modern medication for treating ovarian cancer. *Ayush* encompasses various therapeutic modalities, including herbal remedies, diet and nutrition, *yoga* and meditation, and *Panchakarma*, which have been traditionally used or studied for their potential benefits in cancer management. **Methods:** We will discuss the fundamental aetiology, pathology, risk factors, and basic signs and symptoms of ovarian cancer, along with the available *Ayush* treatment options. Specifically, we will focus on *Ayurvedic* approaches, such as Rasayanas (Rejuvenated therapies) and *Ayurveda* Maintenance Therapy (AMT), which have shown promise in managing recurrent ovarian cancer. **Results:** Studies investigating the efficacy of *Ayush* interventions, including herbal and herbal-mineral formulations, in treating ovarian cancer reported sustainable outcomes. We will examine the documented Platinum-Free Interval (PFI) and Progression-Free Survival (PFS) following *Ayush* treatments to assess their potential impact on patient outcomes. **Conclusion:** This review provides a comprehensive overview of *Ayush* treatment options for ovarian cancer, aiming to improve the chances of survival for patients, particularly those diagnosed with advanced disease. Integrating *Ayush* approaches with modern medical interventions may provide a comprehensive strategy for the management of ovarian cancer, confronting both psychological and physical aspects of this disorder.

Keywords: *Ayush*, *Ayurveda* Maintenance Therapy (AMT), Ovarian Cancer, Treatment

Abbreviations: ADME: Absorption, Distribution, Metabolism, and Excretion; AH: Amra Haridra; AMT: Ayurveda Maintenance Therapy; BRAF: V Raf murine sarcoma viral oncogene homolog B; CA-125: Cancer antigen 125; CCOC: Clear-Cell Ovarian Cancer; CTA: Cancer Testis Antigen; ENOC: Endometrioid Ovarian Cancer; HGSOC: High Grade Serous Ovarian Cancer; IK: Indukant kwatham; JB: Jasad bhasma; KRAS: Kirsten RAt Sarcoma virus; LGSOC: Low-Grade Serous Ovarian Cancer; LMP: Low Magnetic Potential; MOC: Mucinous Ovarian Cancer; NF-Kb: Nuclear factor kappa B; OC: Ovarian cancer; PFI: Platinum Free Interval; PFS: Progression-Free Survival; POTEE: POTE Ankyrin Domain Family Member E; PTEN: Phosphate and TENsin homologs are deleted on the 10th chromosome; ROC: Recurrent Ovarian Cancer.

*Author for correspondence

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1. Introduction

Cancer is generally a pathological state marked by vast proliferation of cells abnormally within the human body. Cancer is commonly referred to by the location in the body where it initially originates, even if it subsequently metastasises to other regions[1,2]. The term "cancer" encompasses a wide range of over 100 diseases that impact various organs and cell types. Nevertheless, the occurrence of abnormal cell growth resulting from genomic instability and mutations, whether inherited or caused by environmental factors, is a defining characteristic of all forms of cancer[3]. Cancer is characterized by a multitude of factors, including cellular modification, dysregulation of apoptosis and other forms of cell death, increased proliferation, angiogenesis, evasion of the immune system, inflammatory responses, and, ultimately, the spread of cancer cells to distant sites (metastasis)[4].

Gynecological cancers, such as cervical, vulvar, endometrial, ovarian and vaginal malignancy conditions, impose a substantial worldwide impact on women's health with their rapid prevalence and rate of mortality[5,6]. According to existing knowledge, Ovarian Cancer (OC) is estimated to cause the demise of approximately 152,000 women each year, accounting for approximately 4.3% of all cancer-related deaths. Consequently, it ranks as the second most prevalent gynecologic ailment affecting women[6]. The primary factor contributing to this outcome could be attributed to the lack of screening instruments for early detection[7]. According to sources[8–10], a significant proportion of ovarian cancers in the early stages have a high potential for successful treatment, estimated to be around 90%. Regrettably, during the period of diagnosis, a majority of OC patients, specifically over 75%, had progressed to IIIC or IV stage[11]. The issue significantly diminishes the potency of surgical procedures, chemotherapies, and radio-therapeutic interventions. Gynaecological malignancies encompass the entirety of dysregulated and aberrant cellular proliferation within the female reproductive system. Despite the continuous progress in therapeutic interventions, the fatality rate remains high, substantial side effects persist, and drug resistance poses significant challenges, thereby rendering the treatment process arduous and intricate. OC is a classification of diseases that originate within the ovaries or near fallopian tubes and the peritoneum. In the female pelvis, each ovary is positioned bilaterally adjacent to the uterus. The ovaries play a key role in female hormone production and eggs are required for reproductive purposes. The female reproductive system comprises a bilateral set of elongated and slender tubes referred to as the fallopian tubes. These tubes are situated on two sides of the uterus. The fallopian tubes mainly take part in the transportation of ova (eggs) from the ovaries to the uterus. The anatomical structure responsible for safeguarding the abdominal organs is referred to as the peritoneum. Ovarian cancer has a greater rate of fatality than breast cancer, with a threefold increase, despite its comparatively lower occurrence rate. The dearth of reliable screening methodologies for timely identification has resulted in a projected significant surge in mortality rates associated with ovarian cancer by the year 2040[12–15].

2. Pathological Categorization

Benign and malignant ovarian tumours arise specifically from stromal, epithelial and germ cells. In the developed nations, the prevalence of comas, granulosal cell tumours and other sex cord-stromal malignancies are estimated to be 5-6 % of all tumours and 2-3 % of germ cell tumours of all tumours. Over 90% of malignant ovarian tumours can be attributed to epithelial origins, such as teratomas and dysgerminomas[16]. Chen *et al.,* presented a comprehensive elucidation of the pathology and classification of ovarian malignancies[17–19].

The histologic subtypes, also known as histotypes, of epithelial OC demonstrate a diverse disease characterized by different cellular origins, causes, molecular alterations, gene expression patterns, and prognostic outcomes[20–24]. The five main histotypes of malignant ovarian cancer also referred to as carcinomas: High Grade Serous (HGSOC) – 70%, Endometeroid (ENOC) – 10%, Clear cell (CCOC) – 10%, Mucinous – 3%, Low grade (LGSOC) – less than 5%. Borderline or low malignant potential (LMP) tumours exhibit ambiguous malignant behaviour belonging to any of these groups, although serous and mucinous tumours tend to manifest more frequently[25]. These tumours have microscopic indicators of malignancy, although they do not exhibit overt infiltration into the surrounding stroma.

Several theories on the high-grade tumour genesis lacking a prominent progression model have been formulated based on morphological and genetic research[26–29]. Compelling data reveals that high and low-grade neoplasms originated from the epithelium of the fallopian tube. Additionally, endometriotic cysts associated with endometriosis are believed to be the source of CCOC and ENOC. Furthermore, the tubal-mesothelial junction is postulated to be the origin of MOC, as supported by the available evidence[30,31]. High-grade and low-grade ovarian cancers evolved from tubal epithelium, albeit for different reasons. Serious tubal intraepithelial carcinomas, characterized by atypical lesions in the fimbriated end of the fallopian tube, exhibit comparable morphology and TP53 signatures to HGSOC. Tubal lesions are the source of neoplastic process development that later extends to the ovary and turns into an aggressive progression[32–34]. Progression of benign serous cystadenoma to the borderline serous tumour and finally to lower-grade carcinoma is noticed in the manifestation of LGSOC tumours. The cystadenoma originates from the ovary and arises from epithelial inclusion glands that display tubal characteristics. This suggests that these glands formed from transplanted tubal epithelium[35]. Type I tumours include mucinous, clear cell and endometrioid carcinomas that evolved from borderline tumours and finally become low-grade serous tumours[36]. HGSOC is categorized as Type II due to its absence of an identifiable precursor lesion and its aggressive nature. Tumours differentiated into Type-I and Type-II have diverse mutational patterns, often characterized by a lack of overlap between the two types. Type I malignancies, including serious and mucinous tumours, as well as endometroid tumours, have been associated with specific genetic abnormalities in the oncogenes BRAF, KRAS, and PTEN. The presence of these mutations is atypical in HGSOC tumours, which are primarily characterized by the prevalence of p53 mutations, accounting for 50% to 80% of cases.

3. Detailed Epidemiology

The occurrence of OC exhibits significant regional variations, as depicted in Figure 1[37,38]. The regions that have undergone significant development, including Eastern Europe and Central and North America, exhibit the most notable age-adjusted incidence rates, often surpassing 8 per one lakh individuals. The numerical value provided by the user is 100. The observed rates of incidence exhibit the most minimal values within the geographical regions of Asia and Africa, as evidenced by a documented numerical value of 3 per 100,000 individuals. The numerical value provided by the user is 100. In contrast, the rates observed in South America exhibit an intermediate level, quantified at 5.8 for 1 lakh individuals[39]. Migration from lower migration rate countries to higher migration countries is associated with an increased level of risk[40,41]. Emphasizing the non-genetic risk factors importance, the incidence and

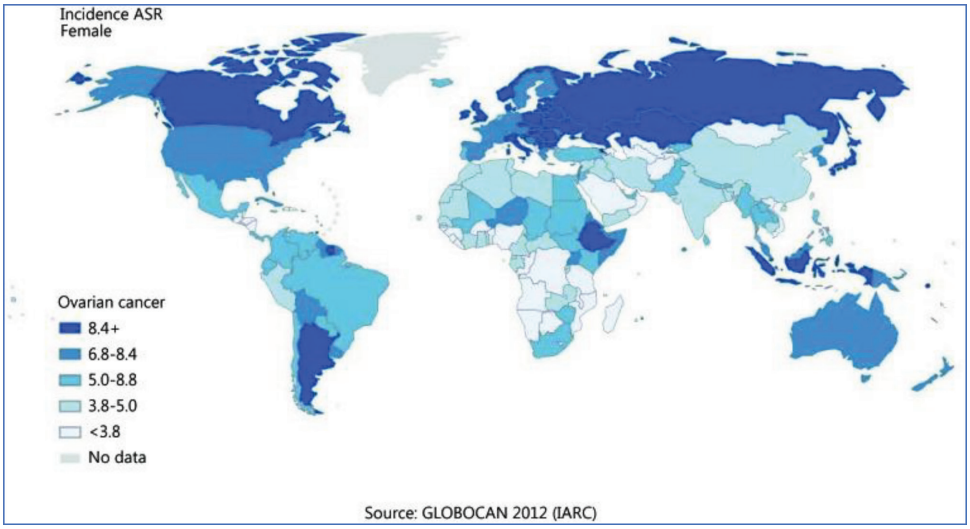


Figure 1. The ovarian cancer spreadsheet varies greatly by region.

death rates among different racial groups in the United States reflect the established international variance. The rates of occurrence are observed to be highest among individuals of White ethnicity, intermediate among individuals of Hispanic ethnicity, and lowest among individuals of Black and Asian ethnicities[42,43]. Variation in incidence and death rates is observed both domestically and internationally, particularly in developed urban centres of large countries such as China (Figure 1)[44-47].

The incidence rates and mortality connected with ovarian cancer have shown a progressive decline in rich nations, particularly in Europe and North America since the 1990s[48-51]. On the contrary, there has been an increase in the occurrence and death rates in traditionally less developed countries that have experienced recent economic advancements and shifts in lifestyle. The surge in question is primarily affecting rural women in China, whereas those residing in metropolitan regions with higher socioeconomic status are not experiencing the same increase[52-56].

4. Risk Factors

There exists a correlation between ovulation duration and ovarian cancer susceptibility. Consequently, the absence of offspring heightens the susceptibility to ovarian cancer, perhaps due to the diminished frequency of ovulation resulting from pregnancy. Ovulatory cycles are characterized by the ongoing stimulation of cell division during the process of ovulation. Consequently, nulliparous women face a double-fold elevated risk of being prone to ovarian cancer as compared to parous women. An additional risk factor is an extended ovulation cycle resulting from the early onset of menstruation and a postponed onset of menopause. Both hormone replacement therapy and obesity contribute to an increased risk (Figure 2)[57].

The available scientific literature indicates that there exists a correlation between certain factors and less likelihood of ovarian cancer progression in women. Factors mainly include a decrease in the frequency of menstrual cycles, absence of monthly periods, engagement in breastfeeding, use of oral contraceptives, experience of multiple pregnancies, and conception at an early age. Females undergoing hysterectomy (uterus removal) and sometimes the cervix, tubal ligation (often referred to as "tubes tied"), or bilateral oophorectomy (the removal of both ovaries) exhibit a reduced susceptibility to the development of ovarian cancer. Another risk factor that has been identified in previous studies is age[58].

5. Signs and Symptoms

Ovarian cancer might potentially manifest with either asymptomatic or moderate symptoms. In a significant proportion of cases, symptoms sometimes remain unperceived and misdiagnosed for an extended period of many months. Misdiagnosis of symptoms such as irritable bowel syndrome is a plausible occurrence. In the initial stages, ovarian cancer frequently manifests without the presence of pain. Symptoms may vary depending on the specific subtype. Low Malignant Potential (LMP) ovarian tumours, alternatively referred to as borderline ovarian tumours are featured by the absence of elevated CA125 values and the inability to detect them using ultrasonography. Abdominal distension and pelvic discomfort are the two often observed symptoms of LMP tumour. Tumours of considerable size often exhibit characteristics that indicate a borderline or benign nature. The primary

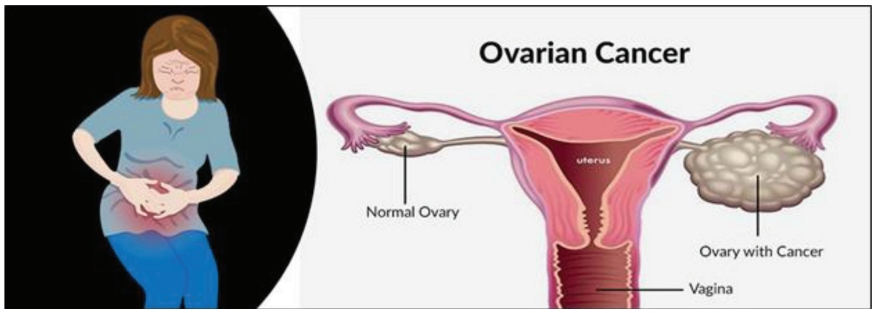


Figure 2. Displaying differences among the two ovaries[59].

symptoms associated with ovarian cancer include bloating, postmenopausal vaginal bleeding, abdominal or back pain, irregular menstruation, pelvic pain, as well as pain or bleeding[60-62].

6. Treatment

Surgical intervention, chemotherapy administration, and radiation therapy are the standard treatments for ovarian cancer. The optimal approach for managing ovarian cancer is contingent upon various factors that comprise the overall health status of the patient, disease stage, histological subtype, and individual preferences. The selection procedure for complex therapy strategies is influenced by a multitude of elements. Medical modalities have the potential to complement traditional therapy; however, it is crucial to seek guidance from a proficient healthcare professional. Presented here is a detailed evaluation of the possible therapeutic contributions of several medical systems in the treatment of ovarian cancer:

Ayurveda, a traditional comprehensive healing system with its roots in India, is founded upon the principle of achieving equilibrium in bodily systems using dietary practices, herbal remedies, and yogic breathing techniques. Throughout history, a diverse range of *Ayurvedic* methodologies and therapeutic substances have been employed to address a multitude of health ailments. Over time, much scientific study has been conducted to find out the efficacy of these methods in treating diverse medical diseases. Provided herein is a comprehensive summary of study findings about the *Ayush* systems[63]:

6.1 *Ayurveda*[64-66]

6.1.1 Arthritis

The Journal of Clinical Rheumatology in 2011, published a paper stating the randomized controlled trial that was conducted for assessing the potential therapeutic advantages of *Ayurvedic* medicines in treating rheumatoid arthritis, as compared to methotrexate.

6.1.2 Diabetes

The Journal of Traditional and Complementary Medicine 2016 released a study that demonstrated the effectiveness of several *Ayurvedic* remedies in regulating blood glucose levels.

6.2 *Yoga*[67]

6.2.1 Mental Health

Numerous research has demonstrated the potential advantages of using *yoga* as a therapeutic intervention for lowering symptoms related to anxiety, depression and post-traumatic stress disorder. This assertion is substantiated by a systematic review published in the Journal of Clinical Psychology in 2013.

6.2.2 Chronic Pain

In 2017, a comprehensive evaluation and meta-analysis was published in the Cochrane database of systematic reviews. The findings provided strong evidence that supports the recommendation of *Yoga* as an effective measure for people with chronic non-specific lower back pain.

6.3 Naturopathy[68]

6.3.1 Hypertension

In 2008, the Journal of Alternative and Complementary Medicine released a study that presented findings on the possible advantages of naturopathic therapy for individuals with chronic hypertension. The study explored the efficacy of various interventions such as dietary modifications, physical exercise, and relaxation techniques in the management of this condition.

6.4 Unani[69]

6.4.1 Vitiligo

The effects of specific *Unani* preparations on vitiligo have been subject to investigation, as evidenced by a study published in the Ancient Science of Life magazine in 2015. This study examined the possible advantages of *Unani* treatment in addressing the dermatological ailment.

6.5 *Siddha*[70]

The limited number of global studies on *Siddha* medicine can be attributed to its regional peculiarity predominantly concentrated in South India. Nevertheless, there have been discussions in regional periodicals regarding the possible advantages of *Siddha* remedies in addressing other ailments, including skin disorders and respiratory ailments.

6.6 Homoeopathy[71]

6.6.1 Upper Respiratory Tract Infections

With reference to a study that was published in Multidisciplinary Respiratory Medicine Journal 2016, it was suggested that the use of a homoeopathic syrup could potentially lead to a reduction in the severity of cough and viscosity of sputum.

6.6.2 Allergic Rhinitis

The American Journal of Rhinology and Allergy released a study in 2016 that provided evidence indicating a potential advantage of homoeopathy in the treatment of allergic rhinitis.

It is noteworthy to mention that several studies provide support for the effectiveness of *Ayush* therapies, while others have yielded equivocal findings or expressed criticism. In the subsequent paragraphs, we shall endeavour to delve more into the elaborate details of these medical systems.

6.7 *Ayurvedic*

The *Ayurvedic* portrayal of cancer pathophysiology incorporates traditional concepts that have been modified to suit modern situations. The topic of the first theme revolves around the interactions among various systems. Despite some differences among the *Vaidyas*, they together employed established concepts to conceptualize the pathophysiology of cancer. These included *Sapta dhatu* (seven body tissues), *Agni* (metabolic vigour) and *Tridosha* theory. The identification of the *nidana*, or causal variables, holds significant importance in the evaluation and management of patients within the *Ayurvedic* theoretical framework[72].

6.8 *Ayurvedic* Concept of Cancer

- The *Charaka* and *Sushruta Samhitas*, which are recognized as prominent *Ayurvedic* texts, refer to cancer as a form of swelling that can be categorized as either inflammatory or non-inflammatory. Additionally, these texts use the terms *Granthi* to describe a little neoplasm and *Arbuda* to describe a big neoplasm. *Ayurvedic* literature outlines three body-control systems, namely the nerve system (referred to as *Vata* or Air), the artery system (*Kapha* or water and the venous system (*Pitta* or Air). These systems work together to facilitate the proper functioning of the human body. One or two of the three biological systems that are dysregulated in benign tumours (*Vataja, Pittaja,* or *Kaphaja*) do not pose significant harm as the body continues to make efforts to regulate these systems. The inability of the three primary physiological systems to effectively coordinate with each other results in the occurrence of tissue damage in malignant tumours (known as *Tri-dosaja*), ultimately leading to a state of sickness that is fatal[73].
- The field of Indian *Ayurvedic* pharmacology is widely recognized and held in high regard due to its notable therapeutic benefits. The efficacy of phytochemicals sourced from Indian *Ayurvedic* shops in targeting ovarian cancer receptors can be effectively assessed by the application of bioinformatics and cheminformatics methodologies. Current research indicates that the cancer testis antigen family of POTE plays a key role in the progression and dissemination of malignant ovarian cancer. Especially, it has been noticed that POTEE paralog exhibits hypermethylation in ovarian cancer. The research aimed to explore the potential anticancer effectiveness of Indian *Ayurvedic* remedies against the ovarian cancer growth target receptor POTEE through in silico analysis. A screening process was conducted on the structures of 100 phytochemicals obtained from 11 *Ayurvedic* stores, utilizing ADME criteria. The most promising phytochemicals were then further analyzed using molecular docking and commerce analysis. A total of six phytochemicals exhibiting notable affinity for target receptors, referred to as POTEE, were selected for further investigation. These phytochemicals were subjected to a comprehensive replica exchange molecular dynamics simulation, spanning a duration of 50 nanoseconds. The affinities of six phytochemicals, namely Deodarin, Hematoxylin, Quercetin, Cedeodarin, Taxifolin and Matairesinol were assessed about POTEE. The determined affinities were 8.1, 7.7, 7.9, 8.0, and 7.7 kcal/spook, respectively. The assessment yielded a Root Mean Square Deviation value of zero. The phytochemicals found in *Asparagus racemosus* and *Cedrus deodara* have exhibited notable inhibitory action on ovarian cancer cell proliferation. This is evidenced by their ability to suppress the marker POTEE[74-76].

6.8.1 Ashwagandha

Ashwagandha, an ancient medicinal plant, holds significant importance in *Ayurvedic* medicine. Alternative appellations for this botanical specimen encompass Indian ginseng and Winter cherry. *Ashwagandha* is an indigenous shrub in India or North Africa and is characterized by its golden blossoms. Ashwagandha exhibits anti-cancer properties, which not only impede the advancement of cancer but also aid in managing the stress endured by cancer patients due to the various medications and therapies they undergo. With the use of ashwagandha, blood glucose levels are decreased. The substance exhibits anti-carcinogenic characteristics. One of the effects of this intervention is a reduction in cortisol levels. The reduction of stress and anxiety is also observed.

6.8.2 Shatavari (Asparagus racemosus)

Shatavari is widely used in *Ayurvedic* remedies to enhance immune function. The utilization of this specific kind of asparagus plant has been a longstanding practice in *Ayurvedic* medicine in India[77]. The product is accessible in several formulations, including tablets, powders, and liquid essences[78]. The improvement of female reproductive health, the alleviation of menopausal symptoms, and the impact of antioxidants are established with this plant[79].

6.8.3 Suvarna-Sutshekhar-Ras

An extensive study has been undertaken in cancer treatment. Based on available data, it possesses anti-cancer properties that contribute to the regeneration and renewal of a certain aspect of the human body. The *Bhringaraja*, scientifically called *Eclipta alba* is a subject of interest in sufficient quantity.

- *Shuddha parade* – Purified mercury
- *Shuddha gandhaka* – Purified sulphur
- *Swarna bhasma* – Gold calx
- *Roupya bhasma* – Silver calx
- *Suddha suhaga* – Purified borax
- *Saunth* – *Zingiber officinale nigrum*
- *Maricha* – Piper
- *Pippali* – Herb seeds of *Piper longum*
- *Datura* – *Datura*
- *Tamra bhasma* – Copper calx
- *Elaichi* – *Elettaria cardamomum*
- *Dalchini* – *Cinnamomum zeylanicum*
- *Tejpatta* – *Cinnamomum tamala*
- *Nagakesara* – *Mesua ferrea*
- *Shanka bhasma* – Conch shell calx

6.8.4 Suvarna parpati

An *Ayurvedic* combination developed from:

- *Shuddha parad* – Purified mercury
- *Shudh gandhaka* – Purified sulphur
- *Swarna bhasma* – Gold calx

7. *Ayurveda* Maintenance Treatment

Approximately seventy to eighty per cent of female individuals diagnosed with epithelial OC experience a disease recurrence even after taking initial platinum-based doublet chemotherapy and later a successful surgical procedure. The two instances of recurrent ovarian cancer were treated by utilization of AMT, involving the administration of medications containing herbal and herbomineral components. The regimen was adhered to for three years, during which the outcomes of Platinum Free Interval (PFI) and Progression-Free Survival (PFS) were documented[80-81].

Rasayana Chikitsa, a therapeutic aspect within *Ayurveda*, encompasses medicines that include immune-stimulant and immune-modulator qualities, hence facilitating the enhancement of immunological function. A therapeutic approach for the management of ROC has been outlined, involving the integration of anticancer pharmaceuticals with the primary botanicals and minerals found in *Rasayana*[82]. The primary objectives of therapy in the context of advanced cancer should be focused on the preservation of quality of life, palliation of cancer symptoms, and potential extension of life expectancy. A remarkable driving factor exists for the scholarly inquiry to prioritize the exploration of contemporary maintenance interventions for ROC[83]. Consequently, an examination was conducted to explore the potential of AMT in conjunction with the Rasayana properties in the herbs and the minerals used in the ZINCA 30 regimen. Within the realm of *Ayurveda*, *Rasayana* medications encompass herbal or herbomineral compositions, as well as singular botanical entities, which are employed to rejuvenate an individual or facilitate the realization of their utmost capabilities. The primary objective of such interventions

is to proactively avert the occurrence of ailments and counteract the degenerative mechanisms that underlie their manifestation. The most likely mechanism is the immune system stimulation, suppression of free radicals, the improvement of cellular detoxification, the repair of damaged, non-dividing cells, the start of cell division, and the activation of damaged, dividing tissues to self-renew and replenish by repopulating damaged or mutated cells[84]. ZINCA 30 formulation consists *of Jasad Bhasma* (an *Ayurveda* preparation), powdered *Curcuma amada* (*Amra Haridra*), and *Indukanth Kwatham* tablets were prescribed due to their recognized safety and efficacy in cancer treatment. *Rasashashtra*, a significant component of *Ayurvedic* pharmaceutical literature, encompasses the bio-absorbable *Rasayana* formulation referred to as *Jasad bhasma* (JB)[85]. The bioactivity and safety investigations of the JBs have been extensively studied and documented in the previous study[86]. The substance comprises macro, micro, and nanoparticles,[87] which have been manufactured following the guidelines provided by the Indian *Ayurvedic* Formulary[88-90], In the study, the efficacy of JB, a zinc-based preparation, was examined as a potential second-line therapy using SKOV3 and ES2 cell lines for resistant ovarian cancer[91]. *Amra Haridra* filed in *Ayurvedic* Pharmacopoeia of India[92], is a botanical variety of turmeric that has been acknowledged for its therapeutic attributes in combating cancer, particularly ovarian cancer. This particular plant is *Curcuma amada* Roxb, commonly called mango ginger. It targets mainly the NF-κB pathway in the SKOV3ip1 and HeyA8 human ovarian cancer cell lines[93-95]. *Indukant kwatham* (IK) has been found to have an impact on alternative therapies for ovarian cysts, intra-abdominal systems, and benign and malignant ovarian tumours called *Raktaja-Gulma*[96-100]. The progression-free survival noticed was 28 and 45 months respectively in the research. It is important to note that the ZINCA-30 regimen employed in the study did not include platinum-based agents. No adverse events were observed or documented for the entire duration of the treatment term. Consequently, the potential role of the AMT ZINCA-30, a regimen not reliant on platinum, could be considered in post-standard-of-care maintenance therapy. This treatment approach may contribute to an increase in PFI, thereby potentially resulting in a superior Overall Survival (OS) outcome devoid of any untoward events or incidents. Moreover, there has been a suggestion that the utilization of ZINCA-30, along with *Ayurvedic* maintenance therapy, may present a promising substitute for platinum-based treatments to enhance progression-free survival among individuals experiencing recurrent ovarian cancer[101].

8. Homeopathy

The primary therapeutic interventions encompass the administration of *lachesis*, specifically *Lachesis Mutus* 30C, which is a homoeopathic dilution derived from the original *Lachesis Mutus* that has been shown to mitigate symptoms of menopausal hot flashes. *Kreosote* is a homoeopathic remedy that is commercially available in different dilutions and is utilized for the treatment of profuse haemorrhaging. Moreover, it is employed for the treatment of nocturnal enuresis. Three chemical compounds, namely *ars. alb, aurum mur*, and *nat mur*, are being discussed. The utilization of *belladonna calcarea, sepia, lyco, apis,* and *iodium*[102] has been observed in the context of the right ovary. *Lachesis, Lillium, Kali Carb, Stramonium*, and *Naja* have been suggested as potential remedies for addressing issues related to the left ovary. Conium has demonstrated efficacy in the management of chronic patients. Chronic cases encompass symptoms such as ovarian hardness and the administration of *Apis mellifica*[103]. *Apis mellifica* is commonly employed for the treatment of minor burns characterized by pronounced erythema, oedema, and discomfort. Ice-cold compresses are employed as a means of alleviating discomfort. If it is clinically required, the patient should promptly seek treatment in an emergency care centre. The individual on his body's right side, experiences a sensation of stinging pain, accompanied by a reduced volume of urine and a lack of thirst, referred to as *lachesis*. The sensation of pain on the body's left side is intensified to the point of extreme discomfort, to the extent that even the slightest contact with clothing causes significant distress. In chronic circumstances where the patient experiences relief from hot fomentation, it is advisable to try the following homoeopathic remedies for hardness on the left side: *Thuja, Aurum muriaticum natronatum, Platina, Graphites, Pulsatilla, Colocynthis*, and *Ferrum phosphoricum*. *Apis mellifica* is a medicinal

substance employed for the treatment of right-sided dropsy; a condition characterized by the fluid accumulation in the ovary leading to its enlargement and sporadic formation of purulent discharge. Iodine: This intervention can be considered for addressing symptoms such as a sensation of pressure, pain, or the presence of fluid accumulation behind the right ovary (Table 1).

9. *Siddha*

Siddha, sometimes referred to as *Siddha Vaidya* or *Siddha* system is one of the oldest traditional systems of medicine practiced mostly in Southern India, especially Tamil Nadu. The method is thought to have started over 5000 years ago. The word "*Siddha*" is derived from the Tamil word "Siddhi", which signifies accomplishment. It has roots that date back thousands of years and is closely related to *Ayurveda* in some aspects. Siddhu means "perfection" or "an object to be attained". The three humours (doshas) - *Vata, Pitta* and *Kapha* are the key principles in *Siddha* that are termed *Vatham, Pitham,* and *Kapham*, respectively and the imbalance in these causes' disease for which, *Siddha* focuses on restoring this balance.

The main components of *Siddha* treatments include[105]:

9.1 Herbal Medicines

A significant proportion of *Siddha* remedies are derived from botanical sources. The entities may consist of individual botanicals or intricate combinations of multiple herbs. Illustrative instances encompass the use of neem, turmeric, black pepper, and several other indigenous botanical species.

9.2 Metal and Mineral Preparations

Siddha medicine is characterized by its distinctive practice of combining metals and minerals into therapeutic concoctions, known as "Bhasmas" and "Chenduram". These products have undergone certain processing methods to ensure their suitability for internal consumption. The substances undergo multiple purification processes and are frequently blended with botanical constituents.

9.3 Diet and Lifestyle

Like *Ayurveda*, *Siddha* lays considerable emphasis on diet and lifestyle. Dietary advice and limits are determined depending on the individual's constitution and the specific characteristics of their disease.

9.4 Detoxification

The *Siddha* tradition places emphasis on the detoxification of the body, particularly as a preliminary step prior to commencing any form of treatment. The process of detoxification is commonly referred to as "*Panchakarma*" in *Ayurveda*, however, in *Siddha* medicine it is known as "*Suthi Marunthu*".

9.5 *Yoga* and Meditation

Spiritual practices, such as *yoga* and meditation, are widely recognized as essential for the preservation of well-being and are frequently recommended as integral components of a comprehensive therapeutic strategy.

9.6 Massage and Physical Therapies

A range of massage techniques incorporating the use of therapeutic oils and poultices are frequently employed, typically as components of the detoxification regimen

Table 1. List of homoeopathic medicines for the treatment of ovarian cancer[104]

Homeopathic remedy	Diseased condition
Alumen 200 (od)	Tumor of ovaries with chronic constipation.
Aurum ars. (tds)	Uterine cancer, there was an observed increase in sexual desire. Ovarian inflammation, also known as oophoritis, refers to the pathological condition characterized by the inflammation of the ovaries. Excessive, frequent, or absent menstruation.
Colocynthis (tds)	Cystic tumour of the ovary.
Palladium met. (tds)	Tumours of the ovary.
Lachesis 200 (hs)	Neoplasm or malignancy affecting the left ovary or bilateral ovaries. The sensation of pain in the uterine region tends to intensify before the onset of menstruation and thereafter diminishes during the menstrual period.

or for the targeted management of certain health conditions.

9.6.1 Alchemy

One intriguing facet of *Siddha* pertains to its incorporation of alchemy and the pursuit of spiritual achievements. Certain practitioners of the *Siddha* tradition engage in the exploration of these profound dimensions, with a specific emphasis on the transformation of substances and the attainment of spiritual enlightenment.

9.6.2 Varma Therapy

The therapeutic approach of *Siddha* discussed here pertains to the identification and stimulation of key sites known as *varmams* within the human body. These *varmams* bear some resemblance to the acupuncture points utilized in Traditional Chinese Medicine. The manipulation of these spots might be employed for the treatment of many diseases.

Although there is currently a wide range of anticancer drugs available, the achievement of effective cancer control remains elusive. There exists a perpetual imperative to develop enhanced and more efficacious pharmaceutical interventions for combating the problem of cancer. The therapeutic strategy of the *Siddha* system is founded upon the consideration of the patient's body types and the pathophysiology of the condition. The commencement of treatment often occurs upon the recognition of a humoural imbalance, followed by the implementation of purifying therapies and the adoption of a health-conscious lifestyle to sustain the treatment. Subsequently, throughout the implementation of a dietary regimen, pharmaceuticals are employed to restore equilibrium to the individuals' disrupted humoral balance, ameliorate their physiological state, and augment their overall well-being.

Based on *Siddha* literature, the treatment of ulcers and tumours such as *Nakkaranai, Putru, Pilavai, Kiranthi,* and *Pun* involves the utilization of the Cauterization technique, which employs several tools including the *Aazhisootukaruvi* and *Pottusootukaruvi*[106,107]. Natural products were widely recognized as a dependable means of source for the treatment of non-communicable illnesses such as cancer. In recent years, there has been a significant surge in the scientific community's attention to phytochemicals sourced from plants, which possess notable anticancer characteristics. This treatment utilizes natural plant compounds that have the potential to eradicate or impede malignant cells. Plants at high Himalayan altitudes have been recognized long ago as customary sources of health and general well-being for the local inhabitants[108]. Plants inhabiting higher elevations are exposed to a multitude of challenging conditions, including elevated levels of carcinogenic UV radiation, physiological drought, desiccation, and severe winds. The primary classifications of anticancer drugs, such as *vinca alkaloids, taxanes, camptothecins*, and *epipodophyllotoxins,* are sourced from botanical origins and are presently included in numerous prevalent anticancer treatment protocols[109-112].

10. *Unani*[113]

The *Unani* system is rooted in Greco-Arabic traditions and centres on the four senses of humour (*Akhlat*): Blood (*Dam*), Yellow bile (*Safrā*') Phlegm (*Balgham*) and Black bile (*Saudā*'). It is postulated that the occurrence of disease is attributed to an imbalance in the humoral constituents. The principal objective of *Unani* treatments is to reestablish the equilibrium of these humors to reinstate well-being. The *Unani* system utilizes several primary modes of treatment.

10.1 Regimental Therapy (*Ilaj-bil-Tadbeer*)

This involves procedures to detoxify and rejuvenate the body.

Examples include:

- Venesection or bloodletting (*Fasd*)
- Cupping (*Hijama*)
- Sweating (*Takmeed*)
- Diuresis (*Idrar*)
- Massage (*Dalk*, *Malish*)
- Emesis (*Qai*)
- Leech therapy (*Taleeq*)

10.2 Dietotherapy (*Ilaj-bil-Ghiza*)

The practice encompasses the prescription of tailored dietary plans or the modification of existing diets to facilitate the management and amelioration of various medical conditions. The utilization of diet in *Unani* medicine can serve as both a therapeutic intervention and a preventive strategy.

10.3 Pharmacotherapy (*Ilaj-bil-Dawa*)

This modality utilizes pharmacological substances, predominantly derived from botanical sources, although substances derived from animal and mineral origins are also utilized. The process of drug selection is predicated upon the temperament and attributes of the pharmaceuticals, which are carefully chosen to mitigate the effects of the imbalanced humour that underlies the manifestation of the disease.

10.4 Single Drugs (*Mufradat*)

Single-ingredient drugs are typically composed of herbs, minerals, or other natural substances.

10.5 Compound Formulations (*Murakkabat*)

These are formulations made of multiple ingredients, such as decoctions, syrups, tablets, and powders.

10.6 Surgery (*Ilaj-bil-Yad*)

This technique is employed in cases where there is a necessity to extract an organ or rectify structural irregularities. Although *Unani*'s literature does provide descriptions of diverse surgical techniques, it is no worthier than the majority of surgical procedures performed in current practice adhere to modern surgical practices.

The importance of prevention, which involves maintaining the body's balance, is also emphasized in *Unani* medicine. *Unani* medicine provides guidance on six fundamental prerequisites (known as *Asbab-e-Sitta Zarooriya*) for promoting health. These prerequisites encompass various aspects such as air quality, dietary habits, mental activity, rest, sleep patterns, and proper excretion and retention processes.

The term "*Sartan*" refers to the pathological condition known as cancer in *Unani*. Galen (129–199 AD), Rhazes (854-925 AD), Abulcasis (936-1013 AD) and Avicenna (980-1037 AD) were renowned *Unani* physicians who possessed knowledge of cancer[114]. Based on extant historical documentation, it can be ascertained that Galen (Jlins) holds the distinction of being the initial individual to methodically delineate several types of growths, encompassing cancerous formations. The individual agreed with Hippocrates' foundational hypothesis regarding the origin of cancer, which posited that an overabundance of black bile serves as the underlying cause of the disease. The IC_{50} value fraction of ethyl acetate obtained from the methanolic extract of *Lespedeza cuneata* was found to be 77.25 ± 2.05 µg/mL during in vitro investigations focused on exploring the anti-cancer activity of Korean medicinal plants. This fraction exhibited a cell-poisoning effect on A2780 human ovarian carcinoma cells[114]. The activity of anti-ovarian cancer from dichloromethane extract of *Brachylaena rotundata* leaves is shown in the OVCAR-5 (Ovarian cancer cell line) bearing an IC_{50} value of 19.95 µg/ml[115]. The ethanolic extract from the roots of *Gomphocarpus fruticosus was* reported to possess anti-ovarian cancer activity, as evidenced by its IC_{50} value of 3.72 g/ml in the OVCAR-3 cell line. Dichloromethane-methanolic extract of the entire *Drimia robusta* plant exhibits anti-ovarian cancer action, with a 1.05 g/ml IC_{50} value in the OVCAR-3 cell line. Following treatment for 24 and 48 hours, the methanolic extract derived from *Pelargonium acraeum* exhibited limited cytotoxic effects shown by IC_{50} values 10 and 60gm/mL in the PA1 ovarian cancer cell line. Furthermore, the OVCAR-3 cell line exhibited enhanced anti-ovarian cancer activity with the lowest IC_{50} value of 6.92 g/ml when treated with the aqueous extract derived from this particular plant. The triterpenoid molecule known as Asiatic acid was obtained through extraction from *Centella asiatica*. Subsequent analysis revealed its activity against SKOV3 and OVCAR-3 cell lines indicating its potential as an anti-ovarian cancer agent.

Recent studies have generated significant interest among researchers in exploring the potential properties of quercetin on ovarian cancer. Numerous experimental types of research have been carried out to gain a better knowledge of the potential effects of quercetin on the apoptotic process in mice with ovarian cancer through intrinsic and caspase-dependent pathways of mitochondrial processes. It has been observed that Quercetin has the potential to induce endoplasmic reticulum stress in ovarian cancer cells, which may lead to cell death mediated by mitochondria. It has been observed that quercetin induces endoplasmic reticulum stress in ovarian cancer cells, which may lead to cell death mediated by mitochondria. Further research is needed to get a comprehensive knowledge of the mechanisms via which it acts against ovarian cancer. Quercetin exhibits potential synergistic effects, rendering it a prospective therapeutic modality for ovarian cancer, particularly when administered concomitantly with other chemo-preventive agents.

Integrative medicine is characterized by its inclusive approach to therapeutic interventions, wherein complementary and alternative therapies are seamlessly integrated with standard medical techniques. Integrative medicine aims to deliver holistic care by addressing all facets of an individual's well-being, including their physical, emotional, mental, social, and spiritual dimensions. The main goal is to establish a healthcare model that is complete and centred around the needs of patients, placing a strong emphasis on the promotion of wellness and prevention of sickness, while also incorporating effective disease management strategies.

Ayurvedic medicinal agents which are clinically proven anti-cancerous.

Numerous *Ayurvedic* therapeutic substances have been investigated for their prospective anti-neoplastic capabilities. The following drugs have been extensively investigated for their potential efficacy in combating ovarian cancer or cancer in a broader context. It is noteworthy to acknowledge that although these medications have demonstrated potential in preclinical investigations, encompassing in vitro and animal models, substantial clinical data in human subjects remains insufficient for a significant number of these agents. It is imperative to seek guidance from a healthcare practitioner before utilizing these substances for therapeutic intentions.

10.6.1 Curcumin (from Turmeric, Curcuma longa)[116,,117]

Mode of Action: Curcumin (Figure 3) has been shown to modulate multiple cell signalling pathways comprising NF-κB, STAT3, Nrf2, ROS, and others. Its anti-inflammatory and antioxidant properties might play a role in the inhibition of cancer cell growth. It may reduce apoptosis in cancer cells and induce cell cycle arrest.

10.6.2 Withanolides (from Ashwagandha, Withania somnifera)[118]

There are multiple with anolides, so the structure varies.

Mode of Action: Withanolides (Figure 4) can induce apoptosis in cancer cells and ROS production leading to mitochondrial dysfunction. It might also inhibit metastasis and angiogenesis by affecting various signalling pathways.

10.6.3 Nimbolide (from Neem, Azadirachta indica)[119]

Mode of Action: Nimbolide (Figure 5) induces apoptosis in cancer cells, inhibits angiogenesis, and suppresses inflammatory pathways. It might also interfere with molecules that are essential for cancer cell migration and invasion.

10.6.4 Quercetin[120]

Quercetin is found in many fruits, vegetables, and grains. *Ayurveda* and other traditional medicine systems use quercetin-containing herbs for their therapeutic advantages. The positive effects of *Ayurvedic* therapy may be due to quercetin-rich herbs.

Ayurveda uses quercetin-containing plants and their derivatives, but not isolated substances. *Emblica officinalis* (Amla) contains quercetin and is used in *Ayurveda* for its many benefits.

Quercetin has antioxidant, anti-histaminic, anti-viral, anti-inflammatory anti-cancer and cardiovascular benefits.

Mode of Action: Quercetin (Figure 6) can modulate various signalling pathways in cancer cells, potentially

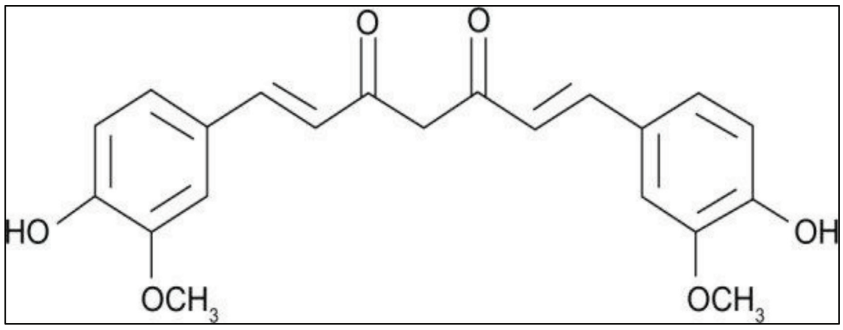


Figure 3. Chemical structure of curcumin.

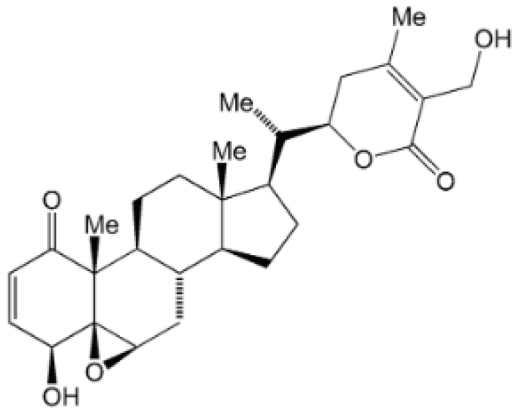


Figure 4. Chemical structure of Withaferin A.

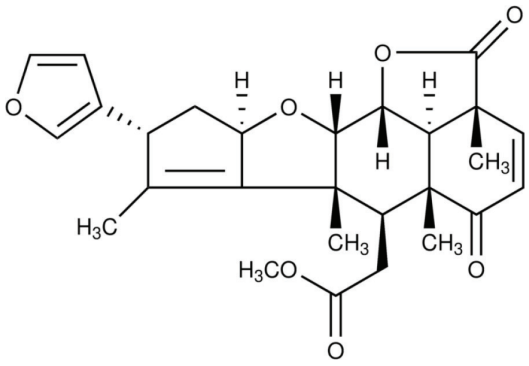


Figure 5. Chemical structure of Nimbolide.

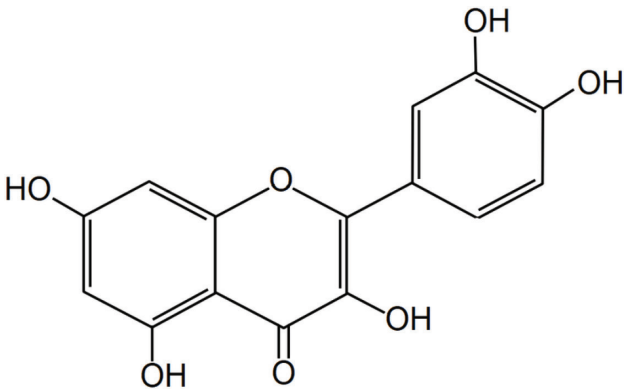


Figure 6. Chemical structure of Quercetin.

inhibiting their growth and inducing apoptosis (programmed cell death).

10.6.5 Asiatic Acid[120]

Asiatic acid (Figure 7) is derived from *Centella asiatica* (*Gotukola*) and has pentacyclic triterpenoid moiety. It is commonly referred to in *Ayurveda* as "*Mandukaparni*" or "Brahmi" (though the term "*Brahmi*" can also refer to *Bacopa monnieri*, another important *Ayurvedic* herb), and has been utilized for centuries for its wide range of therapeutic properties.

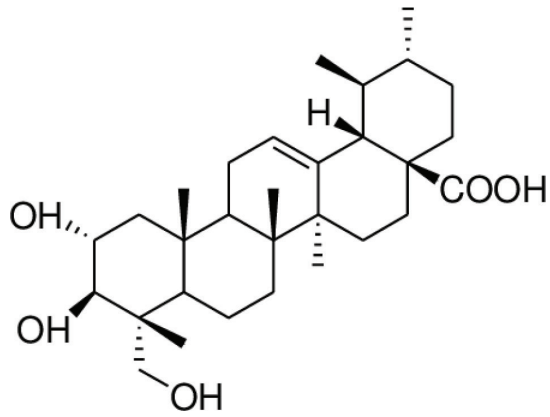


Figure 7. Chemical structure of Asiatic acid.

Asiatic acid has wound healing activity and improves skin health, anti-inflammatory and antioxidant, neuroprotective, anti-cancer, hepatoprotective, and anti-diabetic properties.

10.6.5.1 Mode of Action

Asiatic acid has demonstrated anti-proliferative and apoptotic (inducing programmed cell death) effects on various cancer cell lines. It modulates multiple signalling pathways in the progression of cancer.

11. Discussion

The *Ayush* system, comprising *Yoga* and naturopathy, *Ayurveda*, *Unani*, *Siddha* and Homoeopathy, represents a comprehensive framework of traditional and complementary medicine. This system encompasses a wide array of natural medicines, lifestyle practices, and dietary recommendations. While the *Ayush* methods exhibit potential in offering adjunctive care for a diverse array of medical conditions, it is imperative to emphasize that they should not be regarded as the primary modality of treatment for grave ailments such as ovarian cancer. Conventional therapeutic modalities, such as surgical intervention and chemotherapeutic regimens, are commonly employed as the primary therapeutic approaches in ovarian cancer management. In this comprehensive analysis, we present an overview of diverse *Ayush* methodologies and interventions that hold potential for implementation in the realm of supportive care (Table 2).

12. Future Perspective

12.1 Personalized Medicine Approach

Future strategies should focus on personalized medicine by integrating *Ayush* (*Ayurveda*, *Yoga*, *Unani*, *Siddha*, and Homeopathy) practices tailored to individual patient profiles. This can include customized herbal formulations, dietary recommendations, and lifestyle modifications based on *Ayurvedic* principles like *Prakriti* (body constitution).

12.2 Integrative Oncology Centres

Establishing integrative oncology centres that combine conventional cancer treatments with *Ayush* therapies. These centres can facilitate collaboration between oncologists and *Ayush* practitioners to develop holistic treatment plans.

12.3 Evidence-based Research

Increasing investment in research to provide robust clinical evidence for the efficacy of *Ayush* interventions in ovarian cancer. This includes randomized controlled trials, observational studies, and meta-analyses to validate the safety and effectiveness of these treatments.

12.4 Herbal and Nutraceutical Development

Focus on the development of standardized herbal extracts and nutraceuticals derived from *Ayush* systems. Research on compounds like curcumin, *ashwagandha*, and *triphala* for their anti-cancer properties and potential to enhance the efficacy of conventional therapies.

12.5 Mind-body Interventions

Incorporating mind-body interventions such as *yoga*, meditation, and *pranayama* (breathing exercises) as

Table 2. Overview of available treatments in *Ayush*

Treatment Component	Description	*Ayush* Medicines/Practices
Ayurveda	*Ayurveda* may focus on dietary modifications and the use of specific herbs and herbal formulations. Some herbs with potential anticancer properties may be recommended, such as Ashwagandha and Turmeric. Panchakarma, a detoxification and purification procedure, is sometimes used to help improve overall health. *Ayurvedic* practitioners may also emphasize stress reduction techniques and *yoga*.	Herbs and herbal formulations - Dietary recommendations – • *Ashwagandha* • *Shatavari (Asparagus Racemosus)* • *Suvarna-Parpati* etc., *-Rasayana Chikitsa*
Yoga	*Yoga* may be recommended as a complementary practice to improve overall well-being, reduce stress, and enhance physical fitness. Specific *yoga* asanas (postures) and pranayama (breathing exercises) may be suggested to support a patient's general health during cancer treatment.	*Yoga asanas* (postures) - *Pranayama* (breathing exercises)
Homeopathy	Homeopathy utilizes highly diluted substances to stimulate the healing response of the body. It cannot be used as the primary treatment for ovarian cancer patients. It may be used for the management of symptoms to improve their quality of life.	Homeopathic remedies for symptom management and some natural products used to treat OC like • Lachesis, • *Belladonna calcarea*, sepia, lyco, apis, and iodium etc.,
Siddha	One of the traditional medical practices is known as *Siddha* medicine, sometimes referred to as *Siddha* Vaidya or *Siddha* system, and is largely practised in Tamilnadu and south-indian regions. "*Siddha*" has an earmarked history of 5000 years and is derived from the Tamil word "Siddhi," which signifies accomplishment.	Vinca alkaloids, Taxanes, Camptothecins, and Epipodophyllotoxins,
Unani	The *Unani* system of medicine incorporates a vast array of plants (*herbs*) for therapeutic purposes. These plants are believed to balance four humours (*Akhlat*) of the body – yellow bile (*Safrā*), blood (*Dam*), black bile (*Saudā'*) and phlegm (*Balgham*) as per *Unani* philosophy, which is essential for maintaining health.	Regimental Therapy (*Ilaj-bil-Tadbeer*); Dietotherapy (*Ilaj-bil-Ghiza*); Pharmacotherapy (*Ilaj-bil-Dawa*); Surgery (*Ilaj-bil-Yad*)

adjunct therapies. These practices can help manage stress, improve quality of life, and potentially influence cancer progression through psychoneuroimmunological pathways.

12.6 Traditional Knowledge and Modern Science Synergy

Creating platforms for the synergy of traditional knowledge with modern science. Collaborative efforts between *Ayush* practitioners and biomedical researchers can lead to innovative treatment modalities and a deeper understanding of cancer biology from an integrative perspective.

12.7 Patient Education and Empowerment

Develop comprehensive patient education programs that inform patients about the benefits and limitations of *Ayush* therapies. Empowering patients to make informed decisions about integrating these practices into their cancer treatment plans.

12.8 Policy Support and Regulation

Advocacy for policy support and regulatory frameworks that facilitate the integration of *Ayush* therapies in mainstream cancer treatment. Ensuring quality control, safety, and standardization of *Ayush* practices and products.

12.9 Holistic Rehabilitation Programs

Designing holistic rehabilitation programs for ovarian cancer survivors that incorporate *Ayush* principles. These programs can address physical, emotional, and spiritual well-being, promoting long-term health and preventing recurrence.

12.10 Global Collaborations

Promoting global collaborations and knowledge exchange between countries practising traditional medicine and those with advanced oncology research. Such collaborations can enhance the global understanding and acceptance of integrative approaches in cancer care.

12.11 Public Health Initiatives

Implementing public health initiatives that promote preventive measures based on *Ayush* principles, such as diet, lifestyle modifications, and early screening, to reduce the incidence and improve the early detection of ovarian cancer.

By integrating these future perspectives, *Ayush* systems can contribute significantly to the holistic management and treatment of ovarian cancer, potentially improving patient outcomes and quality of life.

13. Conclusion

The advantages of this treatment include its short-term duration, cost-effectiveness, and ability to maintain a negative status of premalignancy over the long term, all without the need for surgical intervention. The employment of botanical remedies for the management of ovarian cancer presents itself as a seemingly evident trajectory. Despite the widespread utilization of synthetic pharmaceuticals for the management of diverse medical conditions, a substantial majority, exceeding 75% of the populace, persists in depending on conventional remedies to fulfil their fundamental healthcare needs. Further research on this subject withstands a huge advancement in efficacy for the development of efficacious anticancer medications and enhancing knowledge on the mechanisms of action. *Rasayana Chikitsa* and *Ayurvedic* maintenance therapy plays a key role in the *Ayurvedic* approach to the treatment of obsessive-compulsive disorder. These therapeutic modalities are integral components of this field of study. The optimization of treatment outcomes can be achieved through enhanced engagement and cooperation between medical researchers and *Ayush* practitioners.

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