**MASTER'S THESIS**

# Assessment of curcumin's potential in suppressing ovarian cancer: an in vitro study

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**February 2024**

# Assessment of curcumin's potential in suppressing ovarian cancer: an in vitro study

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A thesis submitted in partial fulfillment of the requirement for the degree of Master of Science

December 2023

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December 2023

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## 국문 초록

난소암은 전 세계적으로 두 번째로 흔한 부인암으로 치사율이 높다. 2020년 한 해에만 31만 3959명의 신규 환자가 발생하였고 이중 20만 7252명이 사망하였다. 난소암의 정확한 원인은 아직 알려지지 않았지만 몇 가지 식별 가능한 위험 인자가 확인되었다. 난소암은 나이가 들수록 위험도가 높아지는데, 주로 폐경기를 겪은 여성들에게 영향을 미친다. 난소암의 가장 흔한 증상 중 하나는 지속적이고 설명할 수 없는 골반 또는 복통으로, 둔하고 아픈 불편함에서 날카롭고 심한 통증까지 다양하다. 난소암의 치료 방법은 다양한 치료 옵션 및 조직 유형에 따라 복잡하다. 종래의 접근 방식, 특히 백금 계 약물의 투여 방법을 내성 문제가 있어 환자의 70-80%에서 재발된다. 한편, 강황 (*Curcuma longa*)으로부터 추출된 curcumin 식물 유래 화합물은 특별한 부작용이 없어 암 치료 효과가 뛰어나다. Curcumin은 암 발병과 관련된 복잡한 신호 전달 경로를 조절함으로써 난소암을 포함한 다양한 암에 대해 주목할 만한 효과를 나타냈다. 난소암에서 curcumin은 종양 발생을 감소시키고 방사선 화학 요법의 효능을 증가시킨다. 그러나 난소암에서 curcumin의 항암 활성을 뒷받침하는 정확한 작용기작은 여전히 밝혀지지 않았다.

이러한 것에 배경으로 하여, 이 논문의 연구 목표는 (i) 공개 영역에서 검색된 문헌 자료를 바탕으로 난소암 치료에서 curcumin의 역할에 대한 포괄적인 검토와 (ii) 인간 난소암 세포주인 Caov-3 및 SNU-8에서 curcumin에 의해 유발된 세포독성 잠재력 및 세포사멸 메커니즘에 대한 조사이다.

첫째, 우리는 PubMed, Scopus, ScienceDirect 및 ClinicalTrials.gov와 같은 데이터베이스에서 검색된 데이터를 기반으로 난소암 치료에서 curcumin의 역할에 대한 포괄적으로 검토하였다. 본 종설에서 정리한 정보는 난소암에 대한 curcumin 효과를 조사하는 연구자들에게 도움이 될 것이다.

검토 후, 난소암 세포주에 대한 curcumin의 영향을 조사하기 위한 실험을

수행했다. Caov-3 및 SNU-8 세포를 24시간 동안 여러 농도의 curcumin(3, 6, 12, 24 및 48 μM)으로 처리하고 MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) 분석을 수행하여 세포 생존력을 평가했다. Curcumin은 용량 의존적 방식으로 두 세포의 생존력을 감소시켰다. 특히 Caov-3 세포는 SNU-8의 IC50이 25.81μM인 것과 비교하여 22.24μM의 IC50으로 입증되어 높은 민감도를 보였다. Colony 생성 분석에서는 Caov-3 및 SNU-8 세포에서 colony 생성 능력이 용량이 증가함에 따라 억제력이 높아졌다. Caov-3 세포는 24 μM에서 증식을 완전히 멈춘 반면, SNU-8 세포는 최소 집락 수로 생존하였다. 유세포 분석에서는 용량 의존적 효과와 함께 두 세포주 모두에서 curcumin에 의해 유도된 G0/G1기 세포 주기가 정지되었다. 이러한 사실은 quantitative reverse transcription-polymerase chain reaction에 의한 유전자 발현 분석을 통해 세포 주기 관련 유전자인 CDK4 및 CCND1의 용량 의존적 하향 조절을 입증하였다. 또한, 세포자멸사 분석에서는 세포자멸사 세포가 용량 의존적으로 증가되었다며 Caov-3 및 SNU-8 세포주에서 세포자멸사를 유도할 수 있는 curcumin의 잠재력이 확인되었다.

본 연구에서 인간 난소암 세포주 Caov-3와 SNU-8에서 세포자멸사를 유도하는 curcumin의 능력을 확인하였지만, in vitro 실험에 의존하였다는 점을 감안할 때 세포자멸사 경로 관련 유전자의 추가 검사 확인 실험이 추가로 필요하다. 난소암에서 curcumin의 효능과 안전성을 종합적으로 평가하기 위해서는 Xenograft나 Orthotopic mouse와 같은 동물 모델을 이용한 in vivo 후속 연구가 필요하다. 자가포식과 같은 경로와의 crosstalk를 포함한 세포자멸사 작용기전에 대한 연구를 통해 난소암의 표적 치료제로서의 curcumin의 완전한 잠재력을 규명할 수 있을 것이다.

키워드: 난소암, 커큐민, 항암, 종양학, 식물화학물질

**ABSTRACT**

Ovarian cancer is the second most common gynecological cancer worldwide, with a high fatality rate. In 2020 alone, it accounted for 313,959 new cases, resulting in 207,252 deaths. Although the exact causes of ovarian cancer are still unknown, several discernible risk factors have been identified. The risk of ovarian cancer increases with age, mostly affecting women who have gone through menopause. One of the most common symptoms of ovarian cancer is persistent, unexplained pelvic or abdominal pain, which can range from dull, achy discomfort to sharp, severe pain. The treatment for ovarian cancer is complex due to the various histological subtypes and limited therapeutic options. Conventional approaches, notably platinum-based drugs, grapple with resistance issues, contributing to relapse in a substantial 70-80% of patients. On the other hand, plant-derived compounds, exemplified by curcumin extracted from turmeric (*Curcuma longa*), present a promising way in cancer treatment, offering potential efficacy without accompanying harmful side effects. Curcumin has exhibited notable effectiveness across diverse cancers, including ovarian cancer, by modulating intricate signaling pathways related to the cancer pathogenesis. In ovarian cancer, curcumin reduces tumorigenesis and increases the efficacy of radio chemotherapy. However, the precise mechanism underlying curcumin's anticancer activity in ovarian cancer remains elusive. With this backdrop, the study objectives include (i) a comprehensive review of curcumin's role in ovarian cancer treatment based on existing literature in the public domain and (ii) an examination of the cytotoxic potential and mechanism of cell death instigated by curcumin in Caov-3 and SNU-8, human ovarian cancer cell lines. First, we conducted a comprehensive review of the role of curcumin in treating ovarian cancer based on the available literature data retrieved from databases (PubMed, Scopus, ScienceDirect, and ClinicalTrials.gov). The information summarized in this review will be helpful to researchers investigating the effect of curcumin on ovarian cancer. Following our review, we performed experiments to examine the effects of curcumin on ovarian cancer cell lines. Caov-3 and SNU-8 cells were treated with varying concentrations of curcumin (3, 6, 12, 24, and 48 μM) for 24

hours, and an MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay was performed to assess the cell viability. Curcumin reduced the viability of both cells in a dose-dependent manner. In particular, Caov-3 cells showed high sensitivity, evidenced by an IC50 of 22.24 μM compared to SNU-8's IC50 of 25.81 μM. Clonogenic assays further indicate a dose-dependent suppression of clonogenic ability in Caov-3 and SNU-8 cells. Caov-3 cells ceased proliferation entirely at 24 μM, while SNU-8 cells exhibited survival with the minimum number of colonies. Flow cytometry analysis highlights G0/G1 phase cell cycle arrest induced by curcumin in both cell lines, with dose-dependent effects. Gene expression analysis by quantitative reverse transcription-polymerase chain reaction corroborates these findings, demonstrating the dose-dependent downregulation of cell cycle-related genes, CDK4 and CCND1. Further, apoptosis assays underscore a dose-dependent increase in apoptotic cells, affirming curcumin's potential to induce apoptosis in Caov-3 and SNU-8 cell lines. While our study confirms curcumin's ability to induce apoptosis in human ovarian cancer cell lines Caov-3 and SNU-8, additional examination of apoptosis pathway-related genes is essential for confirmation, given the reliance on in vitro experiments. To comprehensively assess curcumin's efficacy and safety in ovarian cancer, future investigations, prioritizing in vivo studies with animal models like Xenograft or Orthotopic mice, are imperative. A thorough exploration of apoptosis mechanisms, including crosstalk with pathways like autophagy, is key to unlocking curcumin's full potential as a targeted therapy for ovarian cancer.

**Keywords**: ovarian cancer, curcumin, anticancer, oncology, phytochemicals

# I. INTRODUCTION

Ovarian cancer is the second most prevalent gynecological malignancy globally, surpassed only by cervical cancer. It is distinguished by its substantial mortality rate among gynecological malignancies. In 2020 alone, ovarian cancer accounted for 313,959 newly diagnosed cases and claimed the lives of 207,252 individuals (Sung et al., 2021). These statistics emphasize the pressing imperative for comprehensive research endeavors and the development of innovative therapeutic approaches. Advanced-stage ovarian cancer poses formidable challenges due to its limited treatment modalities and diminished prospects for a favorable prognosis. This complexity is underscored by its diverse histological subtypes comprising epithelial ovarian cancers, including serous, endometrioid, mucinous, and clear cell variants (Gaona-Luviano et al., 2020). It also highlights the multifaceted nature of the disease. Conventional treatment of ovarian cancer heavily relies upon platinum-based chemotherapeutic agents, often in combination with paclitaxel or the anti-angiogenic drug bevacizumab. While initially efficacious, the emergence of resistance poses substantial hurdles, particularly for bevacizumab, leading to disease relapse or progression in 70-80% of patients' post-initial therapy (Mai et al., 2022). Additionally, anticancer agents have general side effects, such as fatigue, diarrhea, loss of appetite, and lymphopenia (S. Ghosh, 2019).

In this scenario, many studies have demonstrated a rise in the use of plant-based bioactive compounds to treat various human diseases, including cancer (Redkar & Jolly, 2003). The rhizomes of turmeric (*Curcuma longa*) contain an important bioactive compound known as curcumin, and it has a long history of use in pharmaceutical products. It is widely regarded as a safe and viable nutritional supplement with no harmful side effects (Tomeh et al., 2019, Moniruzzaman et al., 2021; Sureshbabu et al., 2023). Curcumin is used to treat various health conditions, including inflammation-related diseases (Du et al., 2023; Ruiz de Porras et al., 2023; Subramaniyan et al., 2023; Usmani et al., 2023), cardiovascular diseases (Ghaeini Hesarooeyeh et al., 2023), neurodegenerative diseases (Kuang et al., 2023; Phukan et al., 2023; Seady et al., 2023; Tuong et al., 2023), liver diseases (Harakeh et al., 2023; Molani-Gol et al.,

2023), diabetes ( Hassan et al., 2023; Rahimi et al., 2023), metal toxicity (Cengiz et al., 2023; Maghool et al., 2023; Smirnova et al., 2023) and, most importantly, several cancer types, including breast (Besasie et al., 2023; Joshi et al., 2023; Ahmadi et al., 2023; M Huang et al., 2023; Jafari & Namazi, 2023; Mushtaq et al., 2023), colorectal (Ge et al., 2023; Jain et al., 2023; Li et al., 2023), lung (Wu et al., 2021; Tang et al., 2022), prostate (Termini et al., 2020; Javed et al., 2021; Hashemi et al., 2022), pancreatic (Nagaraju et al., 2019; Pang et al., 2023), bladder (Piwowarczyk et al., 2020; Pourhanifeh, Mottaghi, et al., 2020; Fan et al., 2023), and liver (Shelash Al-Hawary et al., 2023; Srinivas et al., 2023) cancers. The available evidence shows that cancer cells are characterized by deregulated signaling pathways associated with proliferation, apoptosis, and angiogenesis. Curcumin effectively modulates various signaling pathways and molecular targets related to the progress of different types of cancers (Hussain et al., 2023; Zhao et al., 2023). In ovarian cancer, curcumin can act as an anticancer agent via various molecular pathways by reducing tumorigenesis, increasing the effectiveness of radio-chemotherapy, and minimizing adverse effects on normal cells (Pourhanifeh, Darvish, et al., 2020). However, the detailed mechanism governing curcumin's anticancer activity in ovarian cancer has not yet been well characterized.

With this background, the objectives of the present study were: (i) reviewing the role of curcumin in treating ovarian cancer based on the available literature in the public domain, (ii) studying the cytotoxic potential and mechanism of cell death initiated by curcumin on Caov-3 and SNU-8, human ovarian cancer cell lines.

# II. LITERATURE REVIEW

This chapter provides a literature review on the current status of ovarian cancer, with a specific focus on the challenges it poses, available treatment options, and the potential role of curcumin as a therapeutic agent. All the literature data were retrieved from databases such as PubMed, Scopus, ScienceDirect, and ClinicalTrials.gov.

## 2.1 A concise overview of ovarian cancer, including its current status, common symptoms, and stages

Ovarian cancer is a global health issue, ranking eighth in worldwide cancer incidence at 3.4% and the fifth most lethal cancer in women, with a mortality rate of 4.7%. Annually, over 300,000 women are diagnosed with ovarian cancer, and about 152,000 lose their lives to the disease (Sung et al., 2021). Epithelial ovarian cancer is particularly devastating, being the leading cause of gynecologic cancer-related deaths in the United States and the fifth most common cause of cancer mortality among women. Notably, about 75% of cases are diagnosed in advanced stages, and as a result, less than half of patients survive five years after diagnosis, with a 40% survival rate for stage III and a 20% survival rate for stage IV (Torre et al., 2018). In South Korea, ovarian cancer represents 2.5% of all female cancer cases, with an incidence rate of 11.4 per 100,000 women. Ovarian cancer is most common in women aged 40 to 60, with those in their 40s at 20.7%, those in their 50s at 29.7%, and those in their 60s at 18.8%. Ovarian cancer also ranks fourth among cancers diagnosed in girls under 14. Survival rates for ovarian cancer have gradually improved, with a 5.2% increase in the 5-year survival rate from 58.9% in 2000 to 64.1% in 2015. However, early detection methods and effective treatments remain critical due to the lack of specific screening, late-stage diagnoses, and over 60% of patients presenting with stage III or higher (Korea Central Cancer Registry, 2022). Ovarian cancer is often called the "silent killer" due to its asymptomatic early stages, contributing to late-stage diagnoses and poor outcomes (Jacobs et al., 2016). These statistics emphasize the urgent need for better early detection and more effective treatment.

Common symptoms of ovarian cancer often include persistent, unexplained abdominal or pelvic pain, which can range from dull, achy discomfort to sharp, severe pain. Women may also experience persistent bloating, accompanied by a sensation of fullness or difficulty in eating. Ovarian cancer can lead to changes in bowel or bladder habits, such as frequent urination or constipation. Unexplained, prolonged fatigue and significant weight loss are also concerning symptoms, particularly in the advanced stages of the disease (Orr & Edwards, 2018). It is crucial for women to pay attention to their bodies and report any unusual or persistent symptoms to their healthcare providers, as early detection can significantly improve the prognosis.

The precise causes of ovarian cancer remain elusive, but several identifiable risk factors have been recognized. Ovarian cancer risk rises with age, predominantly affecting postmenopausal women. Inherited genetic mutations like breast cancer type 1 susceptibility protein (BRCA1) and breast cancer type 2 susceptibility protein (BRCA2) significantly heighten the likelihood of developing ovarian cancer, and a family history of ovarian or breast cancer can also elevate one's risk (Lancaster et al., 2015). Reproductive factors, including nulliparity or delayed childbirth, may increase the risk, as can the long-term use of hormone replacement therapy, particularly estrogen alone or combined with progesterone (Piombino et al., 2020). Understanding the stage of ovarian cancer is crucial in determining the most suitable treatment strategy, which may include surgery, chemotherapy, targeted therapy, and, in some cases, hormonal therapy. Ovarian cancer is classified into different stages, typically ranging from stage I (Early) to stage IV (Advanced), based on the extent of the disease. The stages of ovarian cancer (Menon et al., 2018) are as follows:

Stage I: Cancer is confined to one or both ovaries.

Stage II: Cancer has spread beyond the ovaries but is still within the pelvis.

Stage III: Cancer has extended into the abdomen or lymph nodes.

Stage IV: Cancer has metastasized to distant sites, such as the liver, lungs, or other organs.

**2.2 Mechanisms, pathophysiology, and molecular alterations in ovarian cancer**

Understanding the pathophysiology of ovarian cancer involves exploring the molecular alterations that underlie the development and progression of the disease. The molecular landscape of ovarian cancer is a complex web of genetic alterations that impact the disease's progression and treatment outcomes. In order to unravel the nuanced nature of this malignancy, it is imperative to delve into the fundamental molecular alterations that are intricately associated with ovarian cancer. One of the most well-known molecular alterations associated with ovarian cancer is mutations in the BRCA1 and BRCA2 genes (Kuchenbaecker et al., 2017). These genetic mutations significantly contribute to ovarian cancer, as women with these mutations have a significantly higher risk of developing the disease. In addition to BRCA mutations, homologous recombination deficiency (HRD) is a common feature in many ovarian cancers, particularly high-grade serous ovarian cancer. HRD includes alterations in genes involved in homologous recombination, DNA repair, and maintenance of genomic stability. This deficiency is often linked to sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors, which have become an important part of ovarian cancer treatment (Vergote et al., 2022). Tumor protein 53 (TP53) is a tumor suppressor gene frequently mutated in high-grade serous ovarian cancer (HGSC). These TP53 mutations play a significant role in the disease, as they are associated with genomic instability, uncontrolled cell division, and resistance to chemotherapy (Silwal-Pandit et al., 2017). In contrast to TP53 mutations in HGSC, low-grade serous ovarian cancer (LGSC) is characterized by mutations in the mitogen-activated protein kinase (MAPK) pathway, particularly in genes like kirsten rat sarcoma viral oncogene homolog (KRAS) and B-raf proto-oncogene (BRAF). This distinction in mutation profiles is less common in HGSC (Hendrikse et al., 2023).

Moving beyond genetic alterations, hormone receptor status, such as estrogen and progesterone receptors, can vary in ovarian cancer subtypes (Modugno et al., 2012). This variation in receptor status is important, as some tumors may be hormone-receptor positive,

making them potentially responsive to hormonal therapy. Adding another layer to the complexity of ovarian cancer, these cancers can exhibit microsatellite instability (MSI) and mismatch repair deficiency (dMMR), which are associated with defects in deoxyribonucleic acid (DNA) repair mechanisms (Roudko et al., 2021). These defects offer an avenue for targeted treatments, particularly through immunotherapy in some cases. Further expanding our understanding, tumor mutational burden (TMB) measures the number of mutations in the DNA of cancer cells (H. Wang et al., 2022). It can help predict the response to immunotherapy in some ovarian cancer patients.

Ovarian cancer is a complex disease with various subtypes, and molecular alterations can differ between these subtypes. This diversity highlights the need for tailored approaches to diagnosis and treatment. For example, clear cell and mucinous ovarian cancers have distinct molecular profiles. Understanding these molecular alterations is crucial for clinical decision-making. Considering these genetic and molecular characteristics is essential for creating personalized treatment strategies. For instance, patients with BRCA mutations are more likely to respond to PARP inhibitors, which can be used for maintenance therapy after initial treatment. Moreover, patients with LGSC are treated differently due to its distinct molecular profile and lower chemosensitivity compared to HGSC (Moujaber et al., 2022). Additionally, molecular testing is becoming increasingly important for guiding treatment decisions. By leveraging this genetic knowledge, healthcare providers can identify patients more likely to benefit from specific targeted therapies or immunotherapy. It underscores the growing role of molecular analysis in clinical trials, where patients are often enrolled based on specific molecular markers.

### 2.3 Management and treatment options for ovarian cancer and side effects

Management and treatment options for ovarian cancer encompass a diverse range of approaches designed to balance effectiveness with improving patients' quality of life. However, ovarian cancer presents significant challenges, particularly in cases of drug resistance, where

traditional chemotherapy agents like cisplatin face resistance. In response to this resistance, researchers are actively exploring strategies to combat it. These strategies include extending platinum-free intervals (Sambasivan, 2022; Gilbert et al., 2023), adopting non-platinum cytotoxic agents (Tomao et al., 2017; Dockery et al., 2019), and investigating molecularly targeted therapies like PARP inhibitors and immunotherapies. These efforts reflect the ongoing battle against ovarian cancer and the resistance posed by chemotherapy agents.

In the spectrum of targeted therapies utilized in the treatment of ovarian cancer, one encounters agents designed to inhibit DNA repair enzymes (such as PARP inhibitors), compounds that disrupt angiogenesis (e.g., bevacizumab), and pharmacological interventions exploiting DNA repair deficiencies (HRD-targeting agents) (Grunewald & Ledermann, 2017). These therapeutic modalities offer promise for enhanced disease management in the context of ovarian cancer. However, the field faces a unique challenge due to the "cold tumor" phenotype, characterized by a low tumor mutational burden (TMB), which refers to the number of mutations in a tumor's DNA. The presence of this cold tumor phenotype underscores the critical need for personalized immunotherapy approaches. Molecular profiling is essential in cancer care, assessing key factors like TMB, which indicates cancer aggressiveness and potential immunotherapy response. Furthermore, programmed cell death protein 1 (PD-1) on immune cells and programmed death-ligand 1 (PD-L1) on cancer cells guide immunotherapy choices. HRD reveals DNA repair issues, shaping drug options like PARP inhibitors. Neoantigen heterogeneity considers diverse abnormal proteins that influence personalized therapies. Tumor-infiltrating lymphocytes (TILs) offer insights into immune system interactions, crucial for tailored immunotherapy strategies (Yang et al., 2020). These assessments inform and enhance the precision of cancer diagnosis and therapeutic approaches, playing a crucial role in understanding the cancer's immunogenicity and the complex tumor microenvironment. Effective patient stratification based on these biomarkers is pivotal for tailoring treatment approaches to individual needs.

Clinical trials are at the forefront of these efforts, encompassing many therapies. They

emphasize the importance of personalized treatment approaches and the promise of innovative strategies, such as dendritic cell-based vaccines and combination therapies involving immune checkpoint inhibitors (ICIs) and chemotherapy. Additionally, the roles of tumor-associated macrophages (TAMs) and autophagy modulation are under investigation, offering potential avenues for enhancing treatment responses (Morand et al., 2021).

In the ongoing battle against ovarian cancer and the challenges posed by chemotherapy resistance, key insights highlight the intricate nature of this disease and the persistent efforts to revolutionize treatment modalities. These strategies encompass a diverse range of approaches, from investigating emerging therapies to leveraging the potential of natural compounds and advanced drug delivery systems. Notably, advanced nanoparticle drug delivery systems offer innovative solutions for controlled and targeted drug release, thereby substantially enhancing treatment efficacy (Beyene et al., 2021; Wu et al., 2023). Despite these promising advancements, significant hurdles remain, including late-stage diagnoses, aggressive metastasis, and disparities in healthcare access. The path forward necessitates sustained commitment to research, funding, and collaborative efforts to comprehend and address the complexities of ovarian cancer. Through the integration of existing medications, researchers aspire to formulate more effective treatment protocols, ultimately striving to improve outcomes for individuals affected by ovarian cancer.

### 2.4 Phytochemicals in cancer prevention

Emerging research explores the potential connection between dietary factors and ovarian cancer, with a specific focus on phytochemicals. Phytochemicals, non-nutritive compounds found in plants, fall into five major groups: phenolics, carotenoids, organosulfur compounds, nitrogen-containing compounds, and alkaloids. They have garnered significant attention due to their potential health benefits, including cancer prevention (Ranjan et al., 2019). In this context, the investigation of phytochemicals derived from natural sources such as grapes, turmeric, black pepper, green tea, and ginger has gained significant traction in medical research

(Yoo et al., 2018; Kumar et al., 2023) and drug development (Katiyar et al., 2012; Dutt et al., 2018; Huneif et al., 2023). Phytochemicals have emerged as potent agents in cancer prevention, targeting key molecular factors involved in the initiation and progression of various cancers. Additionally, the use of these natural compounds holds promise in sensitizing cancer cells to conventional chemotherapy, notably cisplatin, by targeting key resistance-related pathways (Farrand et al., 2014). The synergistic action of phytochemicals with chemotherapy not only presents an innovative approach to reduce chemotherapy dosages but also holds promise in mitigating associated toxicities. This multifaceted strategy has the potential to amplify treatment efficacy while concurrently improving the overall well-being of patients (Rizeq et al., 2020).

Phytochemicals have received attention for their potential role in reducing the risk of ovarian cancer due to their anticancer properties. Among these compounds, polyphenols like resveratrol have shown promise in experimental studies, indicating their potential to mitigate inflammation, reduce drug resistance, and limit carcinogenesis in ovarian cancer cells (Ferraresi et al., 2021). Similarly, catechins found in green tea and terpenoids like lycopene in various fruits and vegetables have demonstrated potential for ovarian cancer prevention and inhibiting tumor metastasis (Xu et al., 2019; Sicard et al., 2021). Furthermore, thiols such as isothiocyanates (ITCs) and indole-3-carbinol (I3C) found in cruciferous vegetables offer potential by reducing ovarian cancer risk, inducing apoptosis, blocking metastasis, and increasing chemotherapy sensitivity (Taylor-Harding et al., 2012; Wei et al., 2021). However, it is essential to acknowledge the need for further epidemiological research to substantiate these promising findings and establish their role in preventing ovarian cancer. Understanding the complex interplay between phytochemicals and ovarian cancer risk offers the potential for developing novel strategies for prevention and treatment.

**2.5 Curcumin – a potential bioactive natural agent for cancer treatment**

Curcumin is a natural compound derived from turmeric (*Curcuma longa*) with promising anticancer properties. Its chemical structure consists of two aromatic ring structures adorned with hydroxy and methoxy groups, interconnected by a seven-carbon chain featuring an α, β-unsaturated β-diketone moiety. Commercial curcumin typically contains three curcuminoids: bisdemethoxycurcumin (about 5%), demethoxycurcumin (around 18%), and diferuloylmethane (approximately 77%) (Sharifi-Rad et al., 2020). Curcumin exhibits keto-enol tautomerism, existing in two structural forms with distinct properties. The keto form prevails in neutral or acidic environments, while the enol form is more prominent in alkaline conditions. Its ionization properties make it less water-soluble in neutral or acidic pH but soluble in alkali, ethanol, methanol, and various organic solvents. The yellow color of curcumin is due to multiple methoxy groups within the chemical composition of diferuloylmethane, contributing to the specific pharmacological and biological behaviors of curcuminoids, including bisdemethoxycurcumin, demethoxycurcumin, and cyclocurcumin (Abd El-Hack et al., 2021; Racz et al., 2022). With its rich pharmacological profile, curcumin has exhibited its potential as a multifaceted agent in the prevention and treatment of cancer. Numerous studies highlight its well-tolerated, safe, and biocompatible characteristics, further reinforcing its suitability for therapeutic use (Soleimani et al., 2018). Curcumin possesses significant anticancer potential by improving the effectiveness of conventional chemotherapy drugs, bolstering their ability to combat cancer, and making cancer cells more responsive. Its multifaceted activity in cancer can be attributed to its ability to impede tumorigenesis and enhance the effectiveness of radio-chemotherapy (Giordano & Tommonaro, 2019).

However, despite these promising attributes, the administration of curcumin via the oral route has encountered challenges related to its poor biodistribution. Even with high oral dosages, clinical studies have revealed that only minute amounts of curcumin are detected in the bloodstream (Cas & Ghidoni, 2019). This is primarily due to the extensive physiological transformations that curcumin undergoes as it traverses the liver and gut. To address these

challenges, curcumin nanoformulations employing nanotechnology enhance the therapeutic potential of this hydrophobic bioactive compound (Moniruzzaman & Min, 2020; Karthikeyan et al., 2021). Techniques like ionic gelation and antisolvent precipitation address challenges such as low water solubility and poor bioavailability. These nano-range formulations exhibit improved biological and pharmacological benefits, promising enhanced efficacy over conventional curcumin. They offer solutions for optimizing therapeutic applications, potentially improving bioavailability and overall effectiveness in treating various conditions. Nanoencapsulation emerges as a key solution, showing significant advantages over traditional forms for enhancing curcumin's therapeutic outcomes (Karthikeyan et al., 2020; Bapat et al., 2023).

**2.6 Curcumin and its multifaceted activity in ovarian cancer prevention and treatment**

In the intricate realm of cancer modulation, curcumin plays a crucial role in coordinating and regulating a series of molecular events **(Figure 1)**. Curcumin’s significance lies in upregulating pro-apoptotic proteins, such as tumor protein 53 (TP53) and B-cell lymphoma 2-associated X protein (BAX), which are essential for its anti-cancer activity. This ability to induce apoptosis involves activating TP53 while downregulating key components of the phosphoinositide 3-kinase-protein kinase B-mammalian target of rapamycin (PI3K/Akt/Mtor) pathway, vital for cancer cell survival. Curcumin directly activates TP53, contributing to DNA repair and the induction of apoptosis (He et al., 2019; Borges et al., 2020; Tu et al., 2020; Khan et al., 2020; Yu et al., 2020; Han et al., 2021). In addition to its effects on apoptosis, curcumin also interferes with the activity of nuclear factor-kappa B (NF-κB), a pro-inflammatory transcription factor that regulates the expression of genes involved in cancer progression and inflammation (Wang et al., 2018; Zhu et al., 2020; Li et al., 2021; Zhang et al., 2019, 2022). This modulation of various pathways, often hyperactivated in cancer cells, underscores curcumin's diverse effects. Matrix metalloproteinases (MMPs) are another target for curcumin (Hassan & Daghestani, 2012; Kumar et al., 2012; Wroński et al., 2022). These enzymes are

often overexpressed in tumor infiltration and play a role in tumor angiogenesis by degrading the extracellular matrix. In brain tumors, curcumin has been shown to downregulate MMP9 expression by inhibiting the binding of NF-κB and AP-1 to the DNA promoter domain (Dhandapani et al., 2007). It also reduces the activity of MMP2, which is involved in tumor invasion, and activates Caspase-3 to initiate cell death (Namkaew et al., 2018). Furthermore, curcumin's impact on cyclin D1, a regulator of cell cycle progression, is significant, as high levels of cyclin D1 are associated with cancer development. Curcumin inhibits cyclin D1 by suppressing NF-κB. Additionally, it promotes the activity of molecules such as cyclin-dependent kinase inhibitor 1 (p21) and tissue inhibitor of metalloproteinases 1 (TIMP1), which control the cell cycle, trigger cell death, and inhibit tumor growth (Mukhopadhyay et al., 2002; Choudhuri et al., 2005). Furthermore, curcumin suppresses anti-apoptotic proteins like B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma-extra-large (Bcl-xL) (Shakor et al., 2015; Kian et al., 2020; Singh et al., 2022), cleaves PARP to affect DNA repair (Xue et al., 2014; Molla et al., 2021; Zhou et al., 2021), induces phosphatidylserine translocation signifying apoptotic cell death (Mackenzie et al., 2008), activates autophagy (Chen et al., 2019; Kong et al., 2020; Tang et al., 2021; Li et al., 2022), and generates cytotoxic reactive oxygen species (ROS) (Wang et al., 2019; Liang et al., 2021; Wu et al., 2022; Liu et al., 2023).

Emerging evidence has identified non-coding RNAs as key targets of curcumin in cancer therapy (Liu et al., 2019; Yang et al., 2020; Shabgah et al., 2021; Hayakawa et al., 2022; Li et al., 2022; Si et al., 2023). Among these, circular RNAs (circRNAs) have garnered considerable attention due to their roles in cancer progression and their potential as diagnostic and therapeutic biomarkers (Chen & Shan, 2021). Several circRNAs have been associated with ovarian cancer, with some promoting proliferation and metastasis while others act as tumor suppressors (Liu et al., 2022). Notably, circ-PLEKHM3, derived from the pleckstrin homology domain containing M3 (PLEKHM3) gene, is downregulated in ovarian cancer and exhibits inhibitory effects on cell growth and metastasis (Cammarata et al., 2022). One of the mechanisms through which circRNAs exert their influence is by acting as microRNA (miRNA)

sponges, indirectly regulating the expression of downstream genes. miRNAs have been identified as crucial players in ovarian cancer development and are modulated by curcumin (Zhao et al., 2014). Curcumin's multifaceted actions extend to its influence on miRNAs. For example, miRNA-194-5p is downregulated in gastric cancer, while curcumin treatment upregulates it, suppressing tumor growth. Moreover, curcumin regulates circ_0056618 in gastric cells, influencing cell proliferation, migration, invasion, apoptosis, and cell cycle arrest (Li et al., 2021).

The preceding studies on curcumin and ovarian cancer have offered pioneering insights and ignited hope for its future promise as a therapeutic agent. These investigations have unveiled the multifaceted mechanisms through which curcumin exerts its influence, from its capacity as a natural DNA methyltransferase (DNMT) inhibitor (Jiang et al., 2015; Maugeri et al., 2018) to its potential as an epigenetic therapy for ovarian cancer (Ming et al., 2022; Al-Moghrabi et al., 2023). Moreover, research has elucidated intricate molecular mechanisms involving focal-adhesion kinase (FAK) and its disruption by curcumin, offering a potential strategy to curtail cancer cell invasiveness ( Chen et al., 2013; Choe et al., 2018). Additionally, curcumin's multifaceted impact on ovarian cancer is underscored by the inhibition of integrin recycling through rab-coupling protein (RCP) (Link et al., 2013; Choe et al., 2018; Guo et al., 2018; Fabianowska-Majewska et al., 2021). Furthermore, innovative combination therapy approaches, integrating curcumin with DNMT inhibitors such as DAC (5-Aza-2'-deoxycytidine) (Hosokawa et al., 2021), hold promise in targeting multiple pathways, including the notorious Wnt/β-catenin signaling pathway, thereby enhancing therapeutic outcomes in ovarian cancer treatment (Ghasemi et al., 2019).

While curcumin faces certain challenges, including low water solubility, hydrolysis in aqueous solutions, and limited bioavailability, researchers actively endeavor to modify its molecular structure to overcome these obstacles. Among the groundbreaking findings is the discovery of WZ10, a curcumin derivative with remarkable inhibitory activity against ovarian cancer cells, surpassing its parent compound (Zheng et al., 2022). However, it is crucial to

emphasize that further rigorous research and clinical trials are imperative to validate its efficacy across various cancer types and establish its safety profile for clinical application.

The convergence of innovative molecular insights and curcumin represents a dynamic shift in the ovarian cancer treatment landscape. These studies underscore the immense potential of curcumin and its derivatives as formidable contenders in the quest for more effective, targeted, and less toxic therapies. While challenges persist, the future holds promise, and continued research endeavors will undoubtedly unveil further groundbreaking discoveries on the path to conquering ovarian cancer.

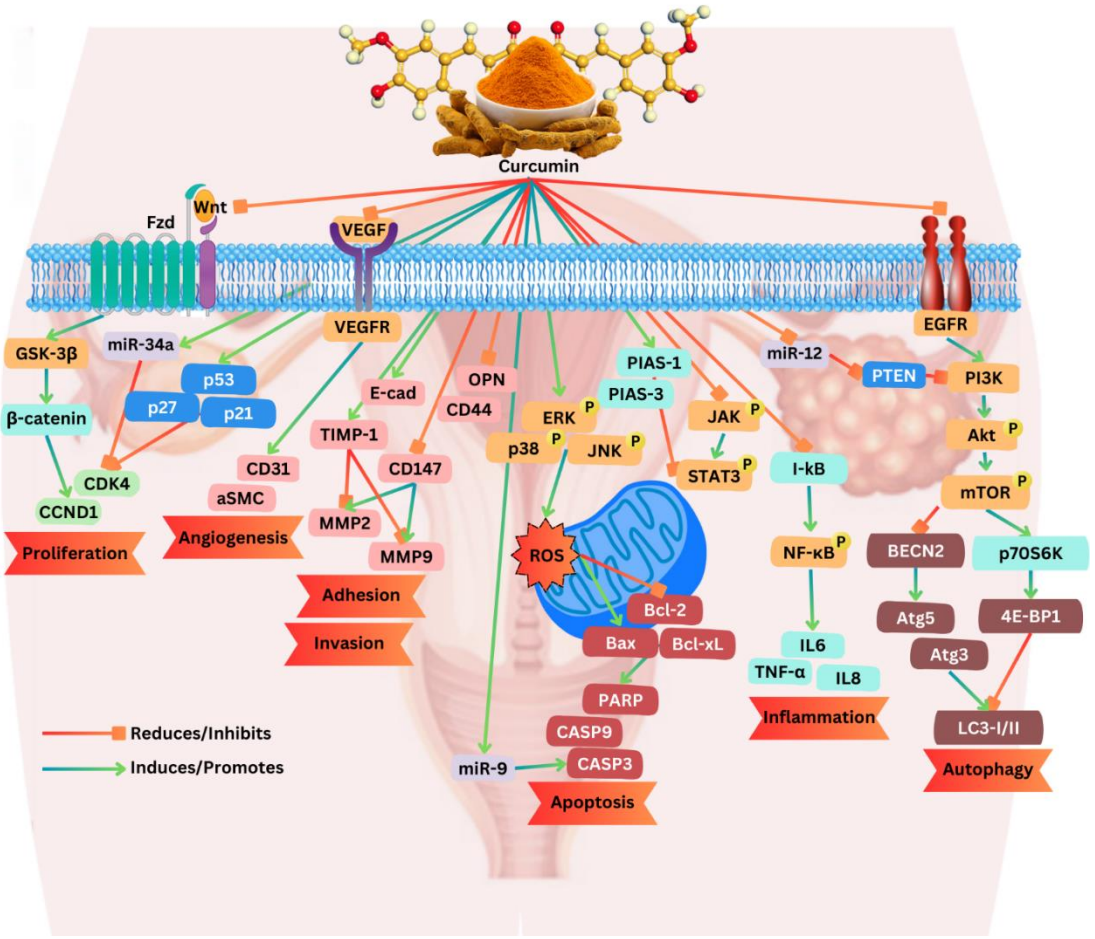


**Figure 1.** Schematic illustration of the effects and anticancer mechanism of curcumin on ovarian cancer. In this figure, molecular targets linked to ovarian cancer pathways are color-coded to highlight curcumin's impact. Curcumin regulates crucial targets, upregulating tumor suppressor proteins (p53, PTEN, p21, p27 - blue), modulating apoptosis regulators (Bax, Bcl-2, Bcl-xL, CASP3, CASP9, PARP - red), inhibiting cell cycle regulators (CDK4, CCND1 - green), and influencing signal transduction pathways (PI3K, Akt, mTOR, NF-κB, JAK, STAT3, EGFR, VEGF, GSK-3β, p38, JNK, ERK - orange). Additionally, curcumin exhibits anti-metastatic effects through factors like CD44, CD31, CD147, MMP2, MMP9, OPN, TIMP-1, RCP, aSMC (pink). It suppresses inflammation via β-catenin, IL8, IL6, PIAS-1/3, I-Kb, TNF-α, p70S6K (light blue), induces autophagy-related proteins LC3-I/II, BECN2, Atg3, Atg5, 4E-BP1 (brown), and influences microRNA expression (miRNA-9, miRNA-12, miRNA-34a - violet).

### 2.7 The effect of curcumin on ovarian cancer cell lines; In vitro studies

In vitro studies have comprehensively explored curcumin's impact on ovarian cancer, including its effects on apoptosis, cell cycle regulation, autophagy, metastasis, inflammation, chemotherapy drug resistance, and epigenetic modifications (**Table 1**). These studies provide a comprehensive summary, including specific molecular targets and the ovarian cancer cell models employed in each investigation. In these studies, involving specific ovarian cancer cell lines, curcumin has been shown to induce apoptosis by affecting specific molecular targets. poorly-differentiated ovarian papillary serous cyst-adenocarcinoma, curcumin preconditioning demonstrated the downregulation of anti-apoptotic proteins (Bcl-2, and Bcl-XL) and the upregulation of apoptotic proteins (pro-caspase-3, p53, and Bax). This led to a significant suppression of cell growth and the induction of apoptosis (Shi et al., 2006). Similarly, a study by Dan et al. reported similar outcomes in SKOV3 human ovarian cancer cell line with epithelial-like morphology. In this study, as the concentration of curcumin increased, the ratio of phosphorylated AKT (p-AKT) to total AKT decreased dose-dependently, resulting in a marked increase in cytotoxicity. This suggests that curcumin's impact on SKOV3 cells involves the downregulation of p-AKT and subsequent cytotoxic effects, highlighting its potential in combating ovarian cancer (Dan et al., 2021).

In A2780 cell line that was established from an ovarian endometroid adenocarcinoma tumor in an untreated patient, curcumin time-dependently upregulated caspase-3, inhibiting tumor growth (L.-D. Zheng et al., 2006). Furthermore, when curcumin was combined with triptolide in SKOV3 tumor cells, they arrested the cell cycle at the S-phase and G2 transition, demonstrating a potent capacity to induce apoptosis (Liu et al., 2018). The impact of curcumin on autophagy in ovarian cancer cells is complex and context-dependent. It can induce protective autophagy, potentially shielding cancer cells from death. However, when curcumin is combined with autophagy inhibitors, it enhances the sensitivity of cancer cells to curcumin treatment (Liu et al., 2019). Curcumin inhibits ovarian cancer metastasis by targeting specific molecular targets related to cell invasion, adhesion, and angiogenesis. These targets include

matrix metalloproteinases (MMPs) (Seyed Hosseini et al., 2023), E-Cadherin (E-Cad) (Trillsch et al., 2016), and vascular endothelial growth factor (VEGF) (Fu et al., 2015).

Moreover, curcumin's anti-inflammatory effects are achieved by inhibiting the activity and production of inflammatory factors such as NF-κB, tumor necrosis factor-alpha (TNFα), interleukin-6 (IL-6), and interleukin-8 (IL-8) (J. H. Seo et al., 2010). These anti-inflammatory actions are attributed to its modulation of various signaling pathways and cytokines. In another in vitro study, curcumin's antioxidant properties were spotlighted, particularly in the context of NF-κB activity. By acting as an antioxidant, curcumin can suppress NF-κB activity that depends on lysophosphatidic acid (LPA), a lipid mediator, in SKOV3 cells. This interference ultimately curtails the proliferation of SKOV3 cells, emphasizing curcumin's role in modulating cell signaling pathways connected to cancer cell proliferation, with implications for anti-cancer therapies (Saunders et al., 2010).

Curcumin also combats multidrug resistance (MDR) in ovarian cancer cells through various mechanisms. It can reverse membrane transporter-mediated MDR and inhibit DNA repair pathways. This enables it to sensitize cancer cells to chemotherapy drugs such as paclitaxel and cisplatin by downregulating proteins linked to drug resistance (Y. Wei et al., 2017). In fact, in cisplatin-resistant A2780 ovarian cancer cells, prior treatment with curcumin not only reduced the expression and transcriptional activity of β-catenin but also lowered the levels of pro-survival proteins, namely Bcl-XL and Mcl-1. This highlights the efficacy of curcumin to sensitize cisplatin-resistant cells to chemotherapy (Yallapu et al., 2010; Cacciola et al., 2023).

In addition to its direct effects, curcumin's anti-cancer properties, associated with DNA methylation and miRNA regulation, play a significant role in its potential as a therapeutic agent. It has been shown that demethylate gene promoters, such as SFRP5, effectively inhibit the Wnt/β-catenin signaling pathway (Su et al., 2010). Curcumin can also upregulate specific miRNAs, like miR-9, miR-124, and miR-551a, influencing the expression of genes involved in cancer progression and drug resistance (Li et al., 2012; Du & Sha, 2017). This

comprehensive approach extends to in vitro studies, where both curcumin alone and curcumin in combination with paclitaxel were tested on ovarian cancer cell lines SKOV3 and A2780. The study found that a pairing of curcumin and paclitaxel had a synergistic effect, inhibiting cell growth and promoting apoptosis. This effect was associated with changes in miR-9-5p and breast cancer type 1 (BRCA1) expression. This heightened uptake translated into enhanced cytotoxicity and anti-cancer effects, suggesting a promising strategy for combining curcumin with paclitaxel to boost the drug's tumor cell targeting and cytotoxicity (Liu et al., 2023).

Given the inherent limitation of poor bioavailability, efforts are being made to enhance the solubility of curcumin. Xu et al. pioneered the development of novel niosomes loaded with curcumin. They employed a non-ionic surfactant mixture of polysorbatum 80, sorbitan monooleate, and poloxamer 188 in a specific ratio (3:1:1) to encapsulate curcumin. This niosome system significantly improved the stability and solubility of curcumin, addressing its poor in vivo performance. In in vitro testing, the curcumin-niosome system displayed improved cytotoxicity and induced a higher apoptotic rate in ovarian cancer A2780 cells than freely dispersed curcumin (Xu et al., 2016). Moreover, Seyed Hosseini et al. conducted a study on dendrosomal nanocurcumin (DNC) in ovarian cancer treatment, revealing promising outcomes. DNC exhibited superior efficacy compared to free curcumin, suggesting enhanced water solubility and cellular entry facilitated by dendrosomes as a carrier. In combination with oxaliplatin, DNC demonstrated a synergistic impact on ovarian carcinoma cell viability, outperforming individual treatments (Seyed Hosseini et al., 2019, 2023). In combating MDR in ovarian cancer, a promising strategy involves a nano drug-loading system leveraging curcumin. The approach utilizes poly(lactic-co-glycolic acid) (PLGA)-phospholipid hybrid nanodrugs with a core-shell structure. The PLGA core carries poorly water-soluble curcumin, while the hydrophilic outer shell enhances circulation and evades immune recognition. Curcumin, known for inhibiting MDR-associated transporters, is encapsulated in the nano carrier alongside paclitaxel. This dual drug-loaded system aims to enhance chemotherapy efficacy, increase drug concentrations in tumor cells, and minimize

toxic effects on normal tissues, emphasizing the role of targeted drug delivery in overcoming MDR in ovarian cancer (Liu et al., 2016).

Collectively, curcumin exerts concentration-dependent effects on various specific molecular pathways and genes in ovarian cancer cells. These effects encompass the modulation of apoptotic regulators (e.g., Bcl-2, Bcl-xL, p53, Bax, and caspases), inhibition of pro-survival and inflammatory pathways (e.g., NF-κB, Akt, STAT3, JAK-1, JAK-2, PIAS-3, and SOCS-3), activation of stress-responsive signaling (e.g., AMPK, p38 MAPK, and FOXO1), alterations in redox balance (ROS, glutathione), and the regulation of microRNAs (e.g., miR-9). Across a broad range of concentrations, curcumin's multifaceted actions result in decreased cell proliferation, increased apoptosis, reduced cell migration, and attenuated inflammation. Notably, recent advancements in nanodrug delivery systems have opened new avenues in optimizing curcumin's therapeutic potential for ovarian cancer. Nano formulations, such as DNC and PLGA-core carries, have demonstrated superior efficacy compared to free curcumin. These findings underscore the versatile and promising therapeutic potential of curcumin for combating ovarian cancer by targeting numerous pathways and genes, making it a subject of great interest in ongoing research and clinical investigations.

**Table 1.** The summary of in vitro studies investigated the effects and molecular targets of curcumin on ovarian cancer.

| S.No | Cell lines | Dose and duration | Curcumin's effects and molecular targets | References |
|---|---|---|---|---|
| 1 | Ho-8910 | 10 - 40 μM, 24 and 48 hours | Downregulation of anti-apoptotic proteins (Bcl-2, Bcl-XL), Upregulation of apoptotic proteins (pro-caspase-3, p53, and Bax). | Shi et al., 2006 |
| 2 | A2780 | 10 - 50 μmol/L, 6 and 24 hours | Upregulation of caspase-3, contributing to the inhibition of tumor growth. | Zheng et al., 2006 |
| 3 | A2780CP (Cisplatin-resistance) | 2.5 - 40 μM, 6 and 48 hours | Reduction of β-catenin, Bcl-XL, and Mcl-1 in cisplatin-resistant cells, enhancing sensitivity to chemotherapy. | Yallapu et al., 2010 |
| 4 | OVCAR3 | 0 - 25 μM, 24 hours | Anti-inflammatory effects through NF-κB, TNFα, IL-6, and IL-8 inhibition. | Seo et al., 2010 |
| 5 | SKOV3 | 1, 5, 10, 20 μM, 6 – 72 hours | Suppression of NF-κB activity via antioxidant properties, leading to decreased proliferation of cells. | Saunders et al., 2010 |
| 6 | COC1/DDP (Cisplatin-resistance) | Various concentrations, 48 hours | Elevated curcumin levels enhance growth inhibition and apoptosis, with synergistic effects alongside cisplatin and paclitaxel. Down-regulation of PI3KCA mRNA suggests a potential mechanism for increased apoptosis. | Lin et al., 2012 |
| 7 | A2780, $A2780^{cisR}$ (Cisplatin-resistance), and $A2780^{ZD0473R}$ (ZD0473-resistance) | 1.1 – 17.63 μM, 1.34 – 21.41 μM, 1.35 – 21.52 μM, 72 hours | LH4 synergizes in A2780 cells regardless of sequence, with pre-treatment improving platinum sensitivity, especially in $A2780^{cisR}$. Chemosensitization involves reducing oxidative stress, increasing Pt-DNA binding in A2780, and modulating NF-κB, FA/BRCA pathway, and apoptosis. | Arzuman et al., 2014 |
| 8 | A2780 | 1.5 - 25 μM (Curcumin and curcumin-loaded niosomes), 24 hours | Improved curcumin solubility and cytotoxicity with the niosome system. Enhanced cellular uptake, increased cytotoxicity, cell cycle arrest, and higher apoptosis rates. | Xu et al., 2016 |

| | | | | |
|---|---|---|---|---|
| 9 | A2780, and A2780/ADM (Adriamycin-resistance) | Various concentrations (Nanocurcumin, 24 hours | Overcomes MDR in tumor cells.<br>Elevates paclitaxel concentration within tumor cells.<br>Improves antitumor activity in combination with taxol.<br>Reduction in P-gp content.<br>Targets mechanisms associated with drug resistance. | Liu et al., 2016 |
| 10 | MDAH 2774, SKOV3, and PA1 | 0, 3, 10, 30, and 90 μM, 24 and 48 hours | Apoptosis induction in cells is concentration- and time-dependent, correlating with increased cytosolic $Ca^{2+}$ levels.<br>Inhibition of SERCA activity leads to cytosolic $Ca^{2+}$ flux.<br>Suppression of SERCA activity without affecting protein expression. | Seo et al., 2016 |
| 11 | SKOV3 | 5 – 160 μM (Demethoxycurcumin), 12, 24, 36, and 48 hours | Inhibits cell proliferation, induces apoptosis, inactivates IRS2/PI3K/Akt pathway, and up-regulates miR-551a.<br>MiR-551a targets IRS2. | Du & Sha, 2017 |
| 12 | SKOV3 | 6.62 μg/mL (Nanocurcumin) | Cell cycle arrest at S-phase and G2 transition, inducing apoptosis when combined with triptolide. | Liu et al., 2018 |
| 13 | SKOV3 | 250 nM, 500 nM, 750 nM, 1000 nM, and 2000 nM (Nanocurcumin), 72 hours | Synergistic anticancer effect when combined with folic acid decorated BSA nanoparticles with difluorinated curcumin.<br>Folate receptor-mediated targeted uptake.<br>Induction of apoptosis. | Gawde et al., 2018 |
| 14 | SKOV3, and OVCAR3 | 5 – 55 μM (Nanocurcumin), 24, 48, and 72 hours | Higher cell death than curcumin alone, enhanced apoptosis in both cell lines, and greatest overall impact.<br>Combined effect on long non-coding RNA expression in both cell lines. | Seyed Hosseini et al., 2019 |
| 15 | SKOV3, and A2780 | 0, 10, 20, and 40 μM, 24, 48, and 72 hours | Reduction in cell viability, induction of apoptotic cell death, induction of protective autophagy, enhanced apoptosis by inhibiting autophagy, and direct association with the AKT/mTOR/p70S6K pathway. | Zhao et al., 2019 |
| 16 | SKOV3 | 0 μM, 40 μM, and 80 μM, 4 hours | Downregulation of p-AKT, resulting in cytotoxicity | Dan et al., 2021 |

| | | | | |
|---|---|---|---|---|
| 17 | SKOV3, and A2780 | SKOV3: 0, 10, 20, 40 μM; A2780: 0, 7.5, 15, 30 μM, 48 hours | Reduced cell viability, induced apoptotic cell death, activated protective autophagy, enhanced apoptosis with autophagy inhibitors and LC3B knockdown, directly linked to the AKT/mTOR/p70S6K pathway. | Liu et al., 2023 |
| 18 | SKOV3, and OVCAR3 | SKOV3: 10 μM (Nanocurcumin), 24, 48, and 72 hours; OVCAR3: 5 μM (Nanocurcumin), 24, 48, and 72 hours | Targeting MMPs inhibits ovarian cancer metastasis. Dendrosomal nanocurcumin maximizes cell death and synergizes with oxaliplatin for growth inhibition. Differential expression of MMP-2 and MMP-9 observed. | Seyed Hosseini et al., 2023 |
| 19 | SKOV3, SKOV3/Txr (Taxol-resistant), MDAH2774, and 2774/Txr (Taxol-resistant) | 0 – 60 μM, 72 hours | Reduced cell viability and increased apoptosis in taxol-resistant ovarian cancer cells. SNIP1 upregulation downregulates pro-survival genes (Bcl-2 and Mcl-1), inhibiting NFκB activity through the EGR1/SNIP1 axis. Key components: NF-κB pathway, SNIP1, EGR1, Bcl-2, and Mcl-1. | Huang et al., 2023 |
| 20 | SKOV3 | 10 μM, 24 hours | Enhanced MPP inhibition reduces NF-κB DNA binding, suppressing downstream genes (COX2, MMP-9, iNOS). Lower proinflammatory cytokines, NO levels, and increased IκB concentration indicate NF-κB pathway suppression. Reinforced inhibitory effects on NF-κB DNA binding, proinflammatory cytokines (IL-1β, IL-6, TNF-α), and COX2 gene expression. | Nourbakhsh et al., 2023 |

S.No: Serial Number, μM: micro molar, μmol/L: micromoles per liter, mM: millimolar, Bcl-2: B-cell lymphoma 2, Bcl-XL: B-cell lymphoma-extra-large, pro-caspase-3: Precursor form of caspase-3, p53: Tumor protein p53, Bax: Bcl-2-associated X protein, NF-κB: Nuclear Factor-kappa B, TNFα: Tumor Necrosis Factor-alpha, IL-6: Interleukin-6, IL-8: Interleukin-8, PI3KCA: Phosphoinositide 3-kinase catalytic subunit, cisplatin: A chemotherapy drug, paclitaxel: A chemotherapy drug, FA/BRCA pathway: Fanconi Anemia/Breast Cancer gene pathway, SERCA: Sarco/Endoplasmic Reticulum Calcium ATPase, IRS2: Insulin Receptor

Substrate 2, MMP-2 - Matrix Metalloproteinase-2, MMP-9: Matrix Metalloproteinase-9, miR-551a: microRNA-551a, G2: Gap 2 (phase of the cell cycle), $Ca^{2+}$: Calcium ion, P-gp: P-glycoprotein, MDR: Multidrug Resistance, OSE: Ovarian Surface Epithelial cells, EGR1: Early Growth Response 1, SNIP1: Smad Nuclear Interacting Protein 1, COX2: Cyclooxygenase-2, iNOS: Inducible Nitric Oxide Synthase, NO: Nitric Oxide.

**2.8 The effect of curcumin on ovarian cancer and on ovarian-related diseases in animal models; In vivo studies**

In animal models, curcumin demonstrates a broad spectrum of effects, encompassing the inhibition of cancer cell proliferation, modulation of hormone levels, reduction of oxidative stress, and mitigation of inflammatory processes. This review delves into the significant implications of curcumin in the context of ovarian health and disease management, drawing insights from diverse animal studies that collectively underscore the multifaceted benefits of this natural remedy (**Tables 2 and 3**). Curcumin's impact has undergone extensive investigation in various cancer models, including ovarian cancer, through animal studies. Notably recognized for its antioxidant properties, curcumin possesses the potential to exert influence over critical biological processes associated with cancer development. Through a series of in vivo experiments, curcumin has consistently demonstrated its capacity to impede cellular proliferation, hinder angiogenesis, disrupt cell cycle progression in tumor cells, and induce apoptosis in diverse cancer types.

In a study reported by Sahin et al., researchers investigated the impact of daily dietary curcumin intake on the development and progression of spontaneous ovarian cancer in a unique animal model – hens, where ovarian cancer naturally occurs. The results revealed a remarkable reduction in ovarian cancer incidence and tumor growth with curcumin supplementation. Ovarian cancer occurred in 39% of the control hens. However, in hens given 25.8 mg/day and 53.0 mg/day of curcumin, the incidence dropped to 27% and 17%, respectively, indicating a significant dose-dependent effect. Furthermore, curcumin intake inhibited key signaling pathways, such as the NF-κB and STAT3 pathways associated with cancer development. It also induced the antioxidant pathway involving nuclear factor erythroid 2 (NFE2) and heme oxygenase 1 in ovarian tissues. Importantly, genetic analysis showed fewer mutations in ovarian tumors from curcumin-fed animals, particularly in the Ras family genes, including KRAS, NRAS, and HRAS. These findings suggest that daily curcumin intake holds promise as a potent and dose-dependent strategy for reducing the risk and growth of

spontaneous ovarian cancer, positioning curcumin as a potential chemopreventive agent in the fight against this disease (Sahin et al., 2018). Furthermore, in the realm of ovarian cancer treatment, concurrent delivery of curcumin and paclitaxel through specialized nanocarriers demonstrates a powerful synergy. This synergy manifests robust anti-cancer effects on chemosensitive human ovarian cancer cells (SKOV3) and their multi-drug resistant counterparts (SKOV3-TR30) when tested in vitro. Additionally, these nanocarriers showcase compelling anti-tumor efficacy in ovarian tumor-bearing nude mice, providing hope for innovative treatment approaches in the fight against ovarian cancer (Zhao et al., 2019). Additionally, dihydroartemisinin (DHA) with curcumin significantly inhibited tumor growth in xenograft nude mice without causing obvious toxicity (Zhao et al., 2017). In a SKOV3 xenograft animal model, polyacetal-based polycurcumin demonstrated significant antitumor activity, with mice treated showing a remarkable 68% reduction in tumor growth compared to the control group. Tumor burden decreased from 1.57 g to 0.49 g, highlighting the potent tumor growth inhibition ability of polycurcumin (Tang et al., 2010). Moreover, in experiments using mice with multidrug-resistant ovarian cancer, curcumin treatment alone and in combination with docetaxel significantly reduced tumor growth by 47% and 58%, respectively. In SKOV3 tumor-bearing mice, curcumin and paclitaxel in nanoemulsion down-regulated drug resistance-related proteins. In various ovarian cancer models, curcumin, particularly when combined with docetaxel, reduced tumor growth and suppressed proliferation and blood vessel formation while increasing tumor cell apoptosis. These results indicate the potential of curcumin to enhance the treatment of ovarian cancer, including drug-resistant forms (Lin et al., 2007). In a study reported by Sandhiutami et al., researchers aimed to improve the bioavailability of curcumin in the treatment of ovarian cancer. In this study, curcumin was encapsulated within chitosan-sodium tripolyphosphate nanoparticles. Notably, these nanocurcumin particles significantly increased plasma concentrations by 20-fold compared to free curcumin. Furthermore, nanocurcumin enhanced the anticancer effects of cisplatin against ovarian cancer in rats by reducing the expressions of PI3K, JAK, STAT3, and Akt

phosphorylation (Sandhiutami et al., 2021). In a parallel investigation, Ganta et al. conducted a study focused on evaluating the synergistic effects of curcumin and paclitaxel (PTX) when administered in nanoemulsion to mice harboring SKOV3 tumors. Curcumin pretreatment reduced intestinal P-glycoprotein (Pgp) and cytochrome P450 3A2 (CYP3A2) levels. When PTX was administered in nanoemulsion to curcumin-pretreated mice, it significantly improved PTX's oral bioavailability, increasing plasma levels by 4.1-fold and PTX accumulation in tumor tissue by 3.2-fold. This combination also demonstrated enhanced anti-tumor activity without inducing acute toxicity, suggesting its potential to improve oral bioavailability and therapeutic efficacy in ovarian adenocarcinoma (Ganta et al., 2010).

Additionally, curcumin has favorable effects on ovarian-related diseases, likely attributable to its anti-inflammatory, anti-apoptotic, and antioxidant properties. In a mouse model of autoimmune ovarian disease, curcumin treatment alleviated the reduction in oocytes in metaphases I and II and has been found to exert anti-apoptotic effects in ovarian tissues. In mice with D-galactose-induced premature ovarian failure (POF), curcumin reduced the apoptosis of granulosa cells and the expression of proteins associated with apoptosis (Abuelezz et al., 2020a). Building on the positive outcomes in the mouse model of autoimmune ovarian disease, another compelling study investigated the effects of curcumin in a POF mouse model. In this study, mice received a daily intraperitoneal injection of 100 mg/kg of curcumin for 42 days. Curcumin increased progesterone and estrogen levels while reducing follicle-stimulating hormone (FSH) levels and luteinizing hormone (LH). This suggests that curcumin has a positive impact on hormonal balance. Moreover, it elevated the levels of superoxide dismutase (SOD), a potent antioxidant enzyme, while decreasing levels of malondialdehyde (MDA), a marker of oxidative stress. The expression of senescence-associated protein P16, 8-hydroxy-2'-deoxyguanosine (8-OhdG), 4-Hydroxynonenal (4-HNE), and nitrotyrosine (NTY) decreased, indicating its anti-aging and anti-oxidative properties. Simultaneously, anti-Müllerian hormone (AMH) expression increased, showing potential benefits for fertility. Furthermore, apoptosis in granulosa cells was reduced, and there were increased protein levels

of p-Akt, Nrf2, and HO-1, suggesting anti-apoptotic and anti-inflammatory effects. Cleaved caspase-3 and -9 protein expression levels decreased, underscoring curcumin's role in reducing cell death (Yan et al., 2018). In a rat model of ovarian ischemia–reperfusion injury, rats were treated with curcumin at 200 mg/kg via intraperitoneal injection, with varying durations of ischemia and reperfusion. In the 2-hour ischemia and 2-hour reperfusion group, curcumin did not significantly affect oxidative and histological parameters. However, the ovary histological grade was significantly higher in the control and curcumin groups compared to the sham group. Similarly, curcumin did not affect oxidative parameters in the 4-hour ischemia and 4-hour reperfusion group. The ovary histological grade was significantly higher in the control and curcumin groups compared to the sham group, indicating potential protective effects (Eser et al., 2015). Comparing curcumin and nanocurcumin in the same rat model of ovarian ischemia–reperfusion injury revealed that nanocurcumin treatment significantly improved outcomes. The nanocurcumin group exhibited superior antioxidant defense and lower levels of oxidative stress markers, emphasizing the dose-dependent and formulation-specific effects of curcumin (Behroozi-Lak et al., 2018). In a study involving CBA female mice with immune disease in the ovaries, mice were administered curcumin at a dose of 100 μg/g via intragastric administration four times a week. Curcumin treatment significantly improved oocyte development, particularly in metaphases I and II, compared to immunized mice. The treatment also reduced apoptosis and necrosis in immune-related tissues. Additionally, the percentage of blood stab neutrophils decreased, demonstrating the potential benefits of this dose and administration regimen (Alekseyeva et al., 2011). Moreover, in a study using female Kunming mice induced with ovarian oxidative stress, mice received various doses of curcumin (0, 100, 150, or 200 mg/kg) daily via intragastric administration for 21 days. In mice exposed to sodium arsenite-induced ovarian oxidative stress, all doses of curcumin effectively reduced the levels of ROS and malondialdehyde (MDA), indicating a decrease in oxidative stress. Furthermore, curcumin increased the levels of superoxide dismutase (SOD), suggesting enhanced antioxidant capacity. The treatment also reduced the number of atretic follicles, indicating an

improvement in ovarian health with the potential dose-dependent response (Wang et al., 2017). Collectively, these studies underscore the potential therapeutic benefits of curcumin in managing various ovarian diseases and conditions. Curcumin's multifaceted effects, including antioxidant, anti-apoptotic, and anti-inflammatory actions, make it a promising natural remedy for promoting ovarian health and mitigating the impact of ovarian diseases, with doses and duration playing a critical role in achieving these benefits.

In the quest to manage ovarian diseases and disorders, the extensive body of evidence presented in animal studies underscores the immense potential of curcumin. With its capacity to regulate hormone balance, reduce oxidative stress, and mitigate inflammation and apoptosis, curcumin is a versatile and promising natural remedy for ovarian health, including the potential management of ovarian cancer. Whether it's alleviating premature ovarian failure, protecting against ischemia-reperfusion injury, or enhancing the bioavailability of curcumin through innovative nanoparticle formulations, the findings from these studies point towards a brighter future in the fight against ovarian-related diseases. While these animal models have provided compelling insights, further research and clinical investigations are warranted to fully understand the mechanisms at play and optimize the use of curcumin in real-world applications.

**Table 2.** The effect of curcumin on ovarian cancer in various in vivo models: insights into dosages, duration, administration routes, molecular targets, and effects.

| S.No | In vivo model | Dose, duration, and route of administration | Curcumin's effects and molecular targets | Reference |
|---|---|---|---|---|
| 1 | Orthotopic murine model | 500 mg/kg for 5 weeks, p.o. | Reduced tumor growth and drug resistance when combined with docetaxel.<br>Suppressed proliferation and angiogenesis. | Lin et al., 2007 |
| 2 | Athymic nude mouse xenograft | 100 mg/kg (Polyacetal-based polycurcumin) for 48 hours, TE | 68% reduction in tumor growth. | Tang et al., 2010 |
| 3 | Murine model | 50 mg/kg for 3 days, p.o. | Improved oral bioavailability of paclitaxel.<br>Enhanced anti-tumor activity. | Ganta et al., 2010 |
| 4 | Nude mouse xenograft | 20 mg/kg for 5 weeks, p.o. | Significant tumor growth inhibition when combined with dihydroartemisinin without obvious toxicity. | Zhao et al., 2017 |
| 5 | Hen model | 25.8 mg/day, 53.0 mg/day for 12 months, p.o. | 31% reduction in ovarian cancer incidence.<br>Reduction in tumor sizes and the number of tumors.<br>Inhibition of NF-κB and STAT3 signaling pathways.<br>Induction of the nuclear factor erythroid 2/heme oxygenase 1 antioxidant pathway.<br>Fewer KRAS and HRAS mutations in ovarian tumors. | Sahin et al., 2018 |
| 6 | Nude mouse xenograft | 10 mg/kg for 10 days, p.o. | Synergistic anti-cancer effects with paclitaxel.<br>Reverses the resistance of paclitaxel to increase antitumor activity. | Zhao et al., 2019 |
| 7 | Sprague Dawley rats | 500 mg/kg (Curcumin or nanocurcumin), single dose, p.o. | Comparable pharmacokinetic parameters in plasma and organs, except for ovaries.<br>Higher curcumin levels in plasma, liver, kidney, and colon.<br>3.6 times higher curcumin concentrations in ovaries for nanocurcumin. | Arozal et al., 2019 |
| 8 | Xenogeneic nude mouse model | 5 mg/kg, every day for 20-25 days, p.o. | Specifically targets the tumor microenvironment in the MC38 murine colon cancer model.<br>Promotes the induction of tumor | Hayakawa et al., 2020 |

| | | | | |
|---|---|---|---|---|
| | | | antigen-specific T cells.<br>Restores the activity of DCs in tumor tissues.<br>Inhibits the STAT3 transcription activity in $CD11c^+$ DCs.<br>Modulates the expression of immune-related markers on DCs, such as CD83 and PD-L1. | |
| 9 | Wistar rats with DMBA-induced ovarian cancer | 100 mg/kg BW (Free curcumin and nanocurcumin) every day for 4 weeks. | Significant reduction in ovarian tumor volume and weight.<br>Downregulation of Ki67, TGF-β, PI3K, and Akt phosphorylation.<br>Reduction in JAK expression, STAT3 phosphorylation, and IL-6 concentrations.<br>Inhibition of proliferation through downregulation of PI3K/Akt and JAK/STAT3 signaling pathways. | Sandhiutami et al., 2021 |
| 10 | Wistar rats with DMBA-induced ovarian cancer | 100 mg/kg BW (Free curcumin or nanocurcumin) daily for 4 weeks. | Nanocurcumin combined with cisplatin alleviates kidney function markers and haematological abnormalities.<br>Decreased plasma urea, creatinine, and NGAL levels.<br>Increased glutathione activities, reduced lipid peroxidation, and decreased plasma TNF-α.<br>Antioxidant and anti-inflammatory effects. | Louisa et al., 2023 |

S.No: Serial Number, mg: milligrams, kg: kilograms, µg/g: micrograms per gram, i.v.: Intravenous (referring to administration directly into a vein), p.o.: Per os (referring to oral administration), NF-κb: Nuclear factor-kappa B, STAT3: Signal transducer and activator of transcription 3, KRAS and HRAS: Kirsten and Harvey rat sarcoma viral oncogene homolog, MC38: Murine colon carcinoma cell line, DCs: dendritic cells, DMBA: 7,12-Dimethylbenz[a]anthracene, BW: Body weight, TGF-β: Transforming growth factor beta, PI3K: Phosphoinositide 3-Kinase, Akt: Protein kinase B, JAK: Janus kinase, IL-6: Interleukin 6, NGAL: Neutrophil gelatinase-associated lipocalin, TNF-α: Tumor necrosis factor alpha.

**Table 3.** The impact of curcumin on ovarian function in various in vivo models: insights into dosages, duration, administration routes, molecular targets, and effects.

| S.No | In vivo model | Dose, duration, and route of administration | Curcumin's effects and molecular targets | Reference |
|---|---|---|---|---|
| 1 | CBA mice | 100 µg/g, i.g. | Improved oocyte development.<br>Reduced apoptosis and necrosis in immune-related tissues. | Alekseyeva et al., 2011 |
| 2 | Wistar albino rats | 200 mg/kg for 2 or 4 hours, i.p. | Potential protective effects against ovarian ischemia–reperfusion injury. | Eser et al., 2015 |
| 3 | Kunming mice | 0, 100, 150, or 200 mg/kg for 21 days, i.g. | Reduced oxidative stress.<br>Increased antioxidant capacity.<br>Decreased atretic follicles. | Wang et al., 2017 |
| 4 | C57BL/6 female mice | 100 mg/kg for 42 days, i.p. | Improved hormonal balance.<br>Enhanced antioxidant capacity.<br>Anti-aging effects.<br>Reduced apoptosis in granulosa cells. | Yan et al., 2018b |
| 5 | Wistar rats | 100 mg/kg (free curcumin) and 1 mg/kg (nanocurcumin) for 2.5 or 3 hours, i.p. | Superior antioxidant defense and reduced oxidative stress with nanocurcumin. | Behroozi-Lak et al., 2018 |
| 6 | Wistar rats | 50 mg/kg, 100 mg/kg, 200 mg/kg (nanocurcumin) for 15 days, p.o. | Alleviated oocyte reduction and anti-apoptotic effects.<br>Reduced sex hormone disturbances in PCOS.<br>Improved oxidative stress markers and decreased elevated TNF-α levels.<br>Restored PI3K/AKT/mTOR levels.<br>Alleviated insulin resistance, improved β-cell function, and preserved islet integrity.<br>Normalized sex hormonal levels. | Abuelezz et al., 2020b |
| 7 | Rat model | 200 mg/kg for 2 weeks. | Ovarioprotective effects.<br>Down-regulation of serum testosterone.<br>Restoration of IR.<br>Inhibition of inflammatory cell infiltration in ovarian tissues.<br>Decreased expression of IRS1, PI3K, AKT.<br>Increased expression of GLUT4 and PTEN. | Zheng et al., 2022 |

S.No: Serial Number, mg: milligrams, kg: kilograms, µg/g: micrograms per gram, i.g.: Intragastric (referring to administration through the stomach), i.p.: Intraperitoneal (referring to administration into the peritoneal cavity), p.o.: Per os (referring to oral administration), PCOS: Polycystic Ovary Syndrome, TNF-α: Tumor Necrosis Factor-alpha, PI3K/AKT/mTOR: Phosphoinositide 3-kinase/Protein kinase B/Mammalian target of rapamycin, IRS1: Insulin Receptor Substrate 1, GLUT4: Glucose Transporter 4, PTEN: Phosphatase and Tensin Homolog, IR: Insulin Resistance.

### 2.9 Human clinical studies

The growing interest in turmeric supplements has led to pre-clinical studies, both in vitro and in vivo, examining curcumin's potential in various areas. Its benefits, particularly in cancer prevention and treatment, have piqued interest and prompted clinical trials. Curcumin has shown the ability to reduce inflammation, making it a candidate for managing diseases with inflammatory components. It has also demonstrated promise in limiting cancer proliferation and progression, leading to clinical trials focused on its effects on cancer treatment. Clinical trials have explored a wide range of cancer types, such as prostate cancer (Suzuki et al., 2006; Hejazi et al., 2013, 2016; Choi et al., 2019; Saadipoor et al., 2019), breast cancer (Ryan et al., 2013; Miller, 2018; Ryan Wolf et al., 2018; Kalluru et al., 2020), colorectal cancer (Carroll et al., 2011; Gunther et al., 2017; Cruz-Correa et al., 2018; Howells et al., 2019), multiple myeloma (Vadhan-Raj, 2009; Golombick et al., 2009, 2012; Santosa et al., 2019), head and neck cancer (Khafif et al., 1998; Delavarian et al., 2019; Arun et al., 2020), gynecologic cancers (J. V Joshi et al., 2011; Tuyaerts et al., 2019; Purbadi et al., 2020), pancreatic cancer (Dhillon et al., 2008; Parsons et al., 2016), gastric cancer (A. K. Srivastava et al., 2014), thyroid cancer (Farhadi et al., 2018), bladder cancer (Sandoughdaran et al., 2021), and solid tumors of various types (Giovanni, 2012; Panahi, Saadat, Beiraghdar, & Sahebkar, 2014; Panahi, Saadat, Beiraghdar, Nouzari, et al., 2014; Belcaro et al., 2014; Chaiworramukkul et al., 2022). These trials collectively underscore the broad applicability of curcumin.

The objectives of these trials often centered around mitigating treatment-related side effects, addressing concerns such as oxidative stress, urinary symptoms, and radiation-induced toxicity. For example, in prostate cancer trials, researchers examined the impact of curcumin on these factors (Hejazi et al., 2016). Similarly, breast cancer trials explored various outcomes, such as radiation-induced dermatitis, inflammatory biomarkers, pain management, quality of life, and response rates to chemotherapy (Ryan et al., 2013; Miller, 2018; Ryan Wolf et al., 2018). Curcumin is well-tolerated in normal tissues, as demonstrated in studies with colorectal cancer patients. Notably, it can achieve therapeutic levels in colorectal tissue with limited

systemic distribution, offering potential benefits for colorectal cancer treatment (Garcea et al., 2005). In a study conducted between January 2007 and May 2008 involving 14 patients with advanced or metastatic breast cancer, the feasibility of combining docetaxel and curcumin was investigated. Patients received docetaxel according to established guidelines, with six dose levels of curcumin tested, determining a maximum tolerated dose of 6,000 mg/d. Notably, dose-limiting toxicities (DLTs) were observed at the highest curcumin dose level (8,000 mg/d), including grade III diarrhea. Hematological toxicities were mainly neutropenia and leucopenia, which typically resolved within 15 days post-treatment, and non-hematological toxicities were generally limited. Tumor marker analyses demonstrated significant reductions in carcinoembryonic antigen (CEA) and vascular endothelial growth factor (VEGF) levels, supporting potential antiangiogenic effects. Among the evaluable patients with measurable lesions, no progressive disease was observed, with five achieving partial responses and three showing stable disease according to response evaluation criteria in solid tumors (RECIST) criteria. Additionally, some patients exhibited remarkable biological responses with substantial reductions in tumor markers, including one patient who achieved a complete histological response. These findings suggested the promise of combining docetaxel and curcumin for the treatment of advanced breast cancer patients, prompting further investigation in a phase II trial (Bayet-Robert et al., 2010).

It's important to note that only a minimum number of cancer studies were randomized controlled trials, and the trials' size and duration varied significantly, highlighting the challenges and variations in curcumin research for cancer. Despite the limited clinical evidence, there is a discrepancy between clinical research and real-world usage, emphasizing the need for caution in integrating curcumin supplements into cancer care (Parsons et al., 2016). Currently, there are no ongoing pilot studies listed on ClinicalTrials.gov that aim to evaluate the potential therapeutic advantages of curcumin supplementation for individuals diagnosed with primary epithelial ovarian cancer. In summary, while curcumin has shown potential in pre-clinical studies, the limited number of clinical trials and their focus on symptom

management rather than disease progression underscore the need for further research and evidence-based practices in utilizing curcumin in cancer treatment. Careful consideration, rigorous evaluation, and ongoing research are essential in harnessing curcumin's potential for cancer patients.

### 2.10 Safety of curcumin

In recent years, curcuminoid-enriched turmeric supplements, particularly those containing 98% curcuminoid-enriched extracts, have gained popularity in western medicine. These supplements have been widely touted in the media as potential remedies for various health conditions, including osteoarthritis and cancer. Epidemiological studies have revealed their use among individuals with different health issues. For example, about one-third of rheumatoid arthritis patients have reported using turmeric supplements (Skiba et al., 2020), and nearly a quarter of women with breast cancer incorporate them into their health regimens (Panknin et al., 2021; Silver et al., 2022).

While curcumin has been deemed safe based on preclinical and clinical assessments and has received "Generally Recognized as Safe" (GRAS) status from the US Food and Drug Administration (FDA) (S. C. Gupta et al., 2013), it has not yet gained approval for cancer therapy. This lack of approval raises important questions about the potential benefits and risks of curcumin. To address this gap in knowledge, further clinical and in vivo investigations are necessary to provide substantial evidence for its effectiveness in cancer treatment. Additionally, it is essential to determine optimal dosages for both natural curcuminoids and synthetic analogs. Regarding safety, most clinical trials involving curcumin have reported mild side effects, with common adverse events such as mild gastrointestinal symptoms (diarrhea, abdominal pain, flatulence, yellow stools, dyspepsia, nausea, vomiting, GI distress, and constipation). These side effects were generally manageable and posed no significant health risk. Serious side effects were rare but have been observed in specific cases, including worsened cachexia and muscle wasting in a pancreatic cancer trial (Parsons et al., 2016) and

an increased incidence of acute kidney injury in patients undergoing elective abdominal aortic aneurysm repair (Garg et al., 2018). It is crucial to highlight that curcumin lacks approval from the Food and Drug Administration (FDA) as a drug for any specific medical condition. Instead, it is primarily available as a dietary supplement, and its use in clinical trials is investigational, focused on exploring potential therapeutic effects. While curcumin has shown promise in the treatment of inflammatory (Schneider et al., 2015; Serhan et al., 2019; Edwards et al., 2017, 2020) and obesity-related conditions (Campbell et al., 2019; Kuszewski et al., 2020; T. M. Panknin et al., 2023), as well as osteoarthritis (Panahi, Rahimnia, et al., 2014; Gupte et al., 2019; Atabaki et al., 2020; Calderón-Pérez et al., 2021), additional well-designed and well-funded studies are needed to establish best practices for its clinical use. The safety and efficacy of curcumin can vary depending on the specific context and condition being treated, underscoring the importance of consulting healthcare professionals before using it, especially in the context of specific medical conditions or treatments.

# III. MATERIALS AND METHODS

This chapter provides information about the materials and methods used to study the cytotoxic potential and mechanism of cell death initiated by curcumin on human ovarian cancer cells. The experimental design for assessing curcumin's effect on ovarian cancer cells consisted of following systematic and multidimensional experiments. Ovarian cancer cell lines were treated with varying concentrations of curcumin, and then cell viability, long-term proliferation (Colony formation), cell cycle progression, gene expression, and apoptosis were assessed by MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) and clonogenic assays, flow cytometry, quantitative reverse transcription-polymerase chain reaction (qRT-PCR), and Annexin V binding staining, respectively (refer to **Figure 2**). To ensure the reliability of the experimental data, each assay was performed in triplicate, and all the experiments were repeated at least three times. Statistical analysis was employed to determine the significance of observed differences, providing a reliable quantitative basis for the study's conclusions.

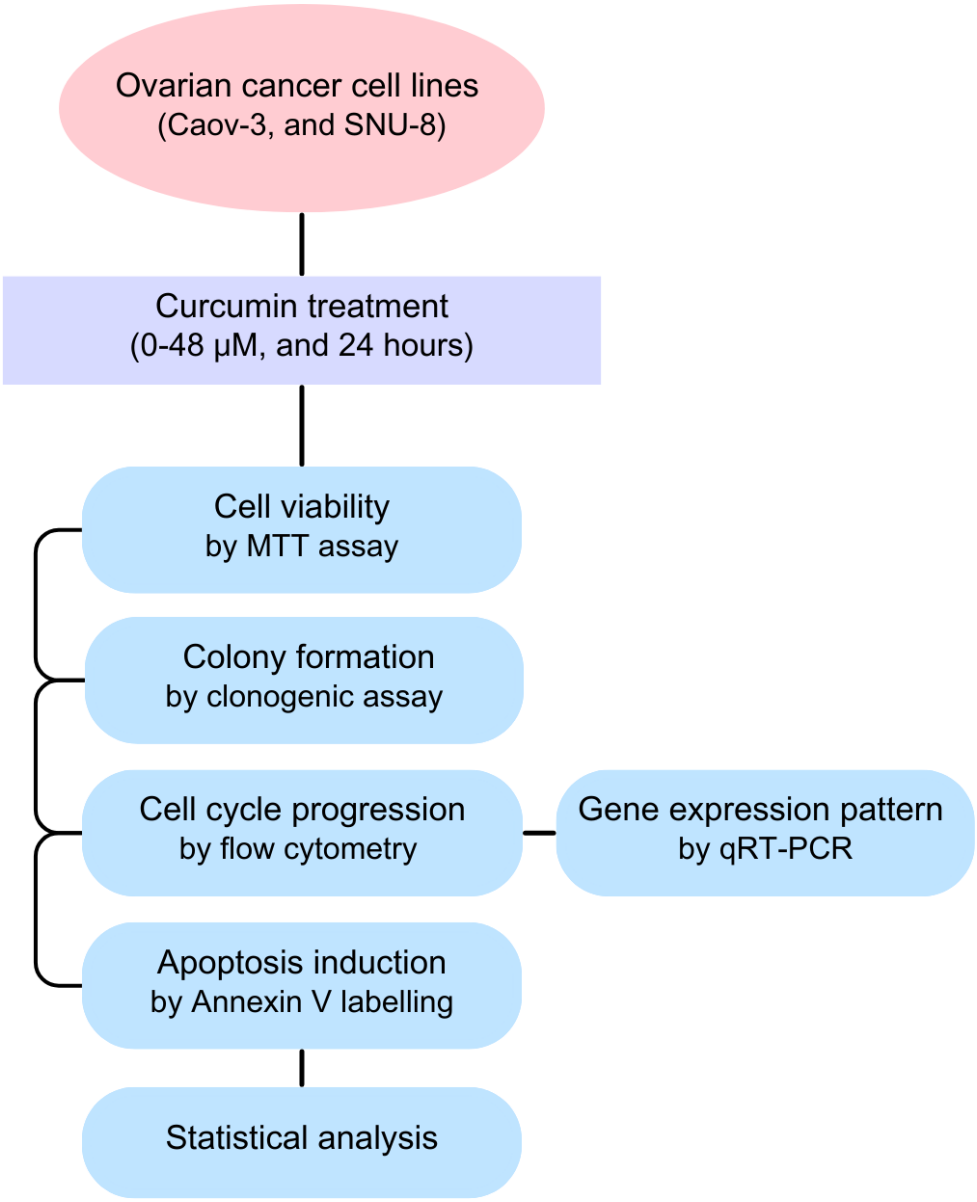


**Figure 2.** Schematic diagram of the experimental design. Diagram illustrates the experimental design for investigating the cytotoxic potential and underlying mechanism of cell death induced by curcumin on human ovarian cancer cells, with a specific focus on Caov-3 and SNU-8 cell lines.

### 3.1 Chemicals and reagents

Unless otherwise stated, chemicals and laboratory wares were purchased from Sigma Chemical Co. (St. Louis, MO, USA), and Samchun Pure Chemical Co., Ltd. (Seoul, South Korea). The culture media and all medium supplements used in this research were sourced from WelGENE Inc. (Daegu, South Korea).

### 3.2 Cell culture

The Caov-3 (Cat. #30075) and SNU-8 (Cat. #00008) ovarian cancer cell lines were obtained from the Korean Cell Line Bank (Seoul, South Korea). The following procedures were adhered to: Upon receipt, frozen stocks were prepared and regularly thawed in small aliquots to minimize culture and passaging effects. Distinct complete media formulations were employed to meet the specific nutritional needs of each cell line. Caov-3 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) (Cat. #LM001-5), while SNU-8 cells were cultivated in Roswell Park Memorial Institute 1640 (RPMI 1640) (Cat. #LM011-01), chosen based on known preferences for optimal growth and maintenance. The culture media were supplemented with 10% fetal bovine serum (Cat. #S001-07) to provide vital growth factors and nutrients. Additionally, 1% penicillin-streptomycin (Cat. #LS202-02) was added to maintain a sterile culture environment and prevent bacterial contamination. Cells were incubated in a controlled environment at a constant temperature of 37°C in a humidified incubator with 5% $CO_2$. Routine testing for mycoplasma contamination was conducted using the MycoBlue Mycoplasma Detector kit (Cat. #D101-01, Vazyme Biotech Co., Ltd., Nanjing, China).

### 3.3 Cell viability assay

Cells were seeded at a density of $1 \times 10^3$ cells per well and cultured in 96-well plates. The plates were then placed in an incubator for 24 hours to facilitate cell adhesion and initiate growth. Following the 24-hour incubation, the culture medium was carefully aspirated from each well. Subsequently, cells were exposed to curcumin at various concentrations (3, 6, 12,

24, and 48 μM) dissolved in dimethyl sulfoxide (DMSO). These concentrations and treatment durations were selected based on prior research findings and our experimental objectives. The plates were returned to the incubator for an additional 24-hour period to allow the cells to respond to the curcumin treatment. This enabled the assessment of potential effects on cell viability and behavior. Cell viability was assessed using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, following the manufacturer's protocol (Cat. #M6494, Invitrogen Co., Carlsbad, CA, USA). To prepare the MTT reagent (12 mM), MTT powder was dissolved in phosphate-buffered saline (PBS). This reagent was added to each well, and the plates were incubated for 3 hours under standard cell culture conditions (37°C, 5% $CO_2$). MTT is used as a viability indicator due to its conversion by viable cells into formazan crystals, the quantity of which reflects the number of metabolically active cells. Following a 3-hour incubation period with the MTT reagent, the culture medium, along with the reagent, was carefully aspirated from each well. Subsequently, formazan crystals were dissolved by the addition of 100 μL of dimethyl sulfoxide (DMSO) to each well. The plates were gently agitated or swirled to guarantee the thorough dissolution of the formazan crystals. This dissolution process was conducted at room temperature for a duration of 15 minutes. Subsequently, absorbance at 540 nm was measured using a GloMax® Explorer Multimode Microplate Reader (Promega Corp., Madison, WI, USA). Measurements were taken in triplicate to ensure data consistency and minimize experimental variability.

**3.4 Colony formation assay**

Cells ($1 \times 10^3$ cells per well) were seeded into 6-well plates using aseptic techniques to ensure contamination-free handling. The plates were labeled to accurately track the experimental conditions. Subsequently, the cells were treated with curcumin at specified concentrations: 12 μM and 24 μM, with a treatment duration of 24 hours. After the curcumin treatment, the medium was gently aspirated, and the cells were carefully washed with PBS to eliminate any residual curcumin and cellular debris. This washing step was carried out gently to avoid

disturbing the adherent cells. Fresh, complete culture medium was then added to the plates to support cell growth and recovery. The plates were incubated for 2 weeks under controlled conditions. Following the 14-day incubation period, formed colonies were fixed by adding pre-chilled ethanol directly to the wells, with a fixation duration of 30 minutes to ensure proper cell fixation. After fixation, the colonies were stained with 1% crystal violet solution (Cat. #000C1828, Samchun Pure Chemical Co., Ltd., Seoul, South Korea). Care was taken to ensure an even distribution of the staining solution, and the staining process was allowed to proceed for an additional 20 minutes at room temperature. For colony analysis, the staining solution was removed, and the colonies were washed meticulously with PBS. This washing step was repeated two times to remove excess crystal violet and enhance the visibility of individual colonies. Finally, the colony counting process (foci containing > 50 cells) was conducted using a microscope at an optimal magnification. Additionally, photographic documentation of the counted colonies was undertaken.

**3.5 Cell cycle analysis**

In brief, cells were seeded at a density of $5 \times 10^5$ in a six-well plate. The cells were then subjected to a 24-hour treatment with curcumin at concentrations of 12 μM and 24 μM. Following this treatment period, the cells were harvested from the six-well plate and thoroughly washed with PBS. This washing step was crucial to eliminate any residual curcumin or culture medium that might interfere with subsequent analyses. To preserve the cells' structural integrity and DNA content, they were fixed in 75% ethanol at a low temperature of -21°C for a minimum of 1 hour. After fixation, the cells underwent two PBS washes to remove excess ethanol, ensuring accurate results in subsequent staining steps. For assessing cell cycle progression, the cells were stained using a propidium iodide solution (Cat. #5135, Tocris Bioscience, a Bio-Techne Brand, Bristol, United Kingdom). The staining solution was prepared at a concentration of 50 μg/mL in PBS. To minimize interference from RNA, RNase A (Cat. #EN053130, Thermo Scientific™, Waltham, MA, USA) at a

concentration of 50 μg/mL was included in the staining solution. The staining process took place during a 30-minute incubation period at room temperature in a dark. The stained cell samples, each representing a different treatment group, underwent flow cytometric analysis using the CytoFLEX research flow cytometer (Beckman Coulter, Brea, CA, USA). A minimum of 10,000 events were acquired for each sample. The flow cytometry data obtained were then processed and analyzed using FlowJo™ v10.8 Software (BD Life Sciences).

### 3.6 Quantitative reverse transcription-polymerase chain reaction (qRT-PCR)

Total RNA was extracted from Caov-3 and SNU-8 cells using FavorPrep™ Tri-RNA Reagent (Cat. #FATRR 001, FAVORGEN Biotech Corp., Pingtung, Taiwan), following the manufacturer's instructions. Subsequently, reverse transcription was performed with the iScript™ cDNA Synthesis Kit (Cat. #1708891, Bio-Rad Laboratories, Inc., Hercules, CA, USA). For qRT-PCR analysis, AccuPower® 2X GreenStar™ qPCR Master Mix (Cat. # K-6253, BIONEER Corp., Daejeon, South Korea) was utilized. The qPCR reactions were prepared using a standardized protocol, incorporating appropriate amounts of cDNA, primers, and master mix components. qRT-PCR experiments were conducted on the CFX Opus 96 Real-Time PCR System (Bio-Rad Laboratories, Inc., Hercules, CA, USA). Detailed information regarding the PCR primers used in this study can be found in **Supplementary table 1**, which provides sequences required for target amplification.

### 3.7 Apoptosis assay

The apoptosis of Caov-3 and SNU-8 cells was determined using the BD Pharmingen™ FITC Annexin V Apoptosis Detection Kit I (Cat. #556547, BD Biosciences, Franklin Lakes, NJ, USA). In brief, cells were seeded at a density of $5\times10^5$ in a six-well plate and incubated at 37°C in a humidified atmosphere containing 5% $CO_2$ for 24 hours. After this incubation period, the cells were treated with curcumin at specified concentrations (12 μM and 24 μM) for 24

hours. Following the treatment, the cells were harvested by trypsinization, gently washed with PBS to remove any residual curcumin, and then centrifuged at 220 g for 5 minutes. The cell pellet was resuspended in the provided 1x binding buffer containing Annexin V-FITC and propidium iodide solution. The cell suspension was gently mixed to ensure proper staining and then incubated for 15 minutes at room temperature (25°C) in the dark to allow Annexin V-FITC and propidium iodide to bind to the appropriate cellular components. After incubation, the stained cells were examined using the CytoFLEX research flow cytometer (Beckman Coulter, Brea, CA, USA) within 1 hour of staining. The flow cytometer settings were adjusted appropriately for FITC and propidium iodide fluorescence detection. Flow cytometry results, including the percentages of live, apoptotic, and necrotic cells, were analyzed using FlowJo™ v10.8 Software (BD Life Sciences). The data were obtained from at least three independent experiments.

### 3.8 Statistical analysis

The IC50 value was calculated using the online tool "Quest Graph™ IC50 Calculator" (AAT Bioquest, Inc., 4 Nov. 2023, https://www.aatbio.com/tools/IC50-calculator). The statistical analysis was performed in OriginPro 2023 software. Results were presented as the mean ± SEM. The data were statistically analyzed with Student's t-test, one-way ANOVA and followed by a post-hoc test, Bonferroni's and two-way ANOVA. Difference with p-values *p <0.05, **p <0.01, ***p <0.001 were considered statistically significant.

# IV. RESULTS

The present study aims to understand the curcumin anticancer mechanism in ovarian cancer. For this purpose, we have treated curcumin in human ovarian cancer cell lines and examined its anticancer effects. The experimental results are presented hereunder.

## 4.1 Cytotoxic effects of curcumin on Caov-3 and SNU-8 ovarian cancer cells

The cytotoxic effects of curcumin on Caov-3 and SNU-8 ovarian cancer cell lines were investigated using the MTT assay. This assay relies on converting the yellow tetrazolium salt MTT to purple formazan crystals by mitochondrial enzymes in metabolically active cells, enabling the quantification of cell viability. Both cell lines were treated with various curcumin concentrations ranging from 0 μM to 48 μM for 24 hours. The results revealed a significant reduction in cell viability with increasing curcumin concentrations (refer to **Figure 3**). At the highest concentration (48 μM), Caov-3 cell viability decreased to 29.68%, while SNU-8 cells exhibited a reduction to 21.28%, underscoring the potent inhibitory effects of curcumin on proliferation and survival. IC50 values were determined to assess the inhibitory potential of curcumin. SNU-8 cells displayed an IC50 of 25.81 μM, while Caov-3 cells were more sensitive, with an IC50 of 22.24 μM. The lower IC50 for Caov-3 indicates a higher sensitivity to curcumin's cytotoxic effects than SNU-8 cells. This dose-dependent inhibitory effect confirms the therapeutic potential of curcumin.

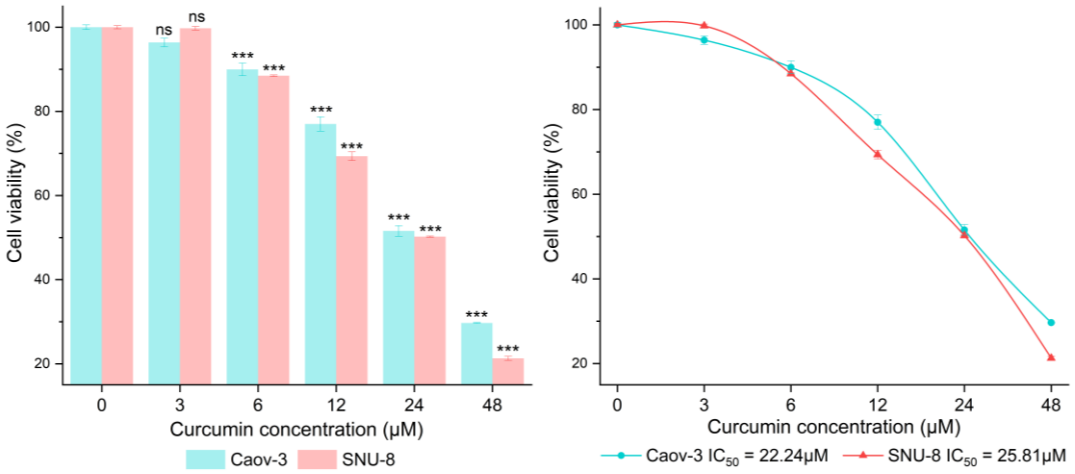


**Figure 3.** Cytotoxicity of curcumin on ovarian cancer cells. The figure illustrates the MTT assay results, showcasing the dose-dependent reduction in cell viability in both Caov-3 and SNU-8 ovarian cancer cells exposed to varying curcumin concentrations. SNU-8 cells exhibit an IC50 of 25.81 μM, while Caov-3 cells are more sensitive with an IC50 of 22.24 μM. Data, expressed as mean ± SEM, are representative of three independent experiments performed in triplicate. Statistical significance is denoted by "ns" for not significant, and ***$p < 0.001$ indicates a significant difference from the control.

### 4.2 Cell proliferation of ovarian cancer cells post-curcumin treatment

Clonogenic assays were conducted on Caov-3 and SNU-8 cells for 14 days to investigate curcumin's cytotoxic effects over an extended duration. The cells were treated with 12 and 24 μM concentrations of curcumin for 24 hours, revealing a dose-dependent inhibition of clonogenic ability in both cell lines. Increasing curcumin concentration led to a significant reduction in colony formation for both cell lines, highlighting its inhibitory effect on ovarian cancer cells (refer to **Figure 4**). In the case of Caov-3 cells, proliferation activity was arrested at 12 μM, with complete cessation observed at 24 μM. Similarly, SNU-8 cells exhibited a significant dose-dependent inhibition in proliferation activity. Notably, the colony formation ability of SNU-8 cells was profoundly impeded, although a minimal number of surviving colonies were identified after prolonged incubation, indicating slight variability between the cell lines. In the control group, both cell lines displayed robust colony formation, underscoring the substantial impact of curcumin on this process. These results illustrate the dose-dependent response, with higher concentrations (24 μM) exerting a more pronounced inhibitory effect, emphasizing a crucial aspect of curcumin's effectiveness.

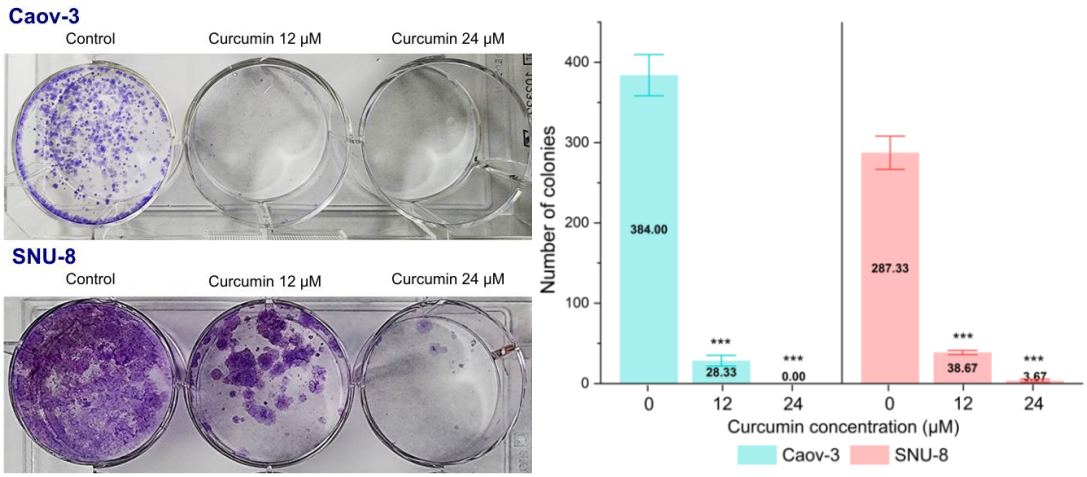


**Figure 4.** Inhibitory effect of curcumin on colony formation in ovarian cancer cells. The figure depicts clonogenic assay results for Caov-3 and SNU-8 cell lines, revealing the pronounced inhibitory effect of curcumin on colony formation. In Caov-3 cells, curcumin concentrations of 12 μM led to a significant reduction in colonies, with complete absence observed at 24 μM. Similarly, SNU-8 cells exhibited decreased colony formation with increasing curcumin concentrations, reaching a substantial decrease at the highest concentration of 24 μM. The absence of colonies at the highest concentration in Caov-3 cells underscores the robust inhibitory potential of curcumin. Data, expressed as mean ± SEM, are representative of three independent experiments performed in triplicate. Statistical significance is denoted by "ns" for not significant, and ***$p < 0.001$ indicates a significant difference from the control.

### 4.3 Curcumin effect on cell cycle progression in ovarian cancer cell lines

To elucidate the dose-dependent effect of curcumin on cell cycle progression, Caov-3, and SNU-8 cells were treated with 12 and 24 μM of curcumin for 24 hours. Cell cycle progression was analyzed using flow cytometry, revealing distinct effects on the cell cycle profiles of both cell lines. As shown in **Figure 5**, in SNU-8 cells, treatment with 12 μM curcumin induced a notable transition toward the G1 phase, encompassing 60.3% of the cell population, accompanied by a simultaneous increase in the S phase, constituting 21.7%. This trend intensified at 24 μM, with 62.1% of cells residing in the G1 phase and 28.7% in the S phase. Conversely, in Caov-3 cells, there was a notable reversion to G1 dominance, reaching 82.7% at 24 μM, as compared to 45.1% in the control group's G1 phase. These concentration-dependent effects underscore the regulatory influence of curcumin on the dynamic progression of the cell cycle.

In addition, the expression levels of CDK4 and CCND1, which are related genes on G1, were analyzed by qRT-PCR analysis. It revealed parallel responses across both cell lines (refer to **Figure 6 and 7**). In SNU-8 cells, the treatment of 12 μM curcumin resulted in a significant downregulation of CCND1, leading to a reduction in its expression, with a more pronounced effect observed at 24 μM. In the case of Caov-3 cells, the downregulation of CCND1 was subtler at 12 μM but became more prominent at 24 μM. Concomitantly, the expression of CDK4 mirrored a comparable trend of downregulation in both cell lines. Specifically, in SNU-8 cells, 12 μM curcumin induced a slight downregulation of CDK4, persisting at 24 μM. Meanwhile, in Caov-3 cells, CDK4 exhibited modest downregulation at 12 μM, intensifying at 24 μM.

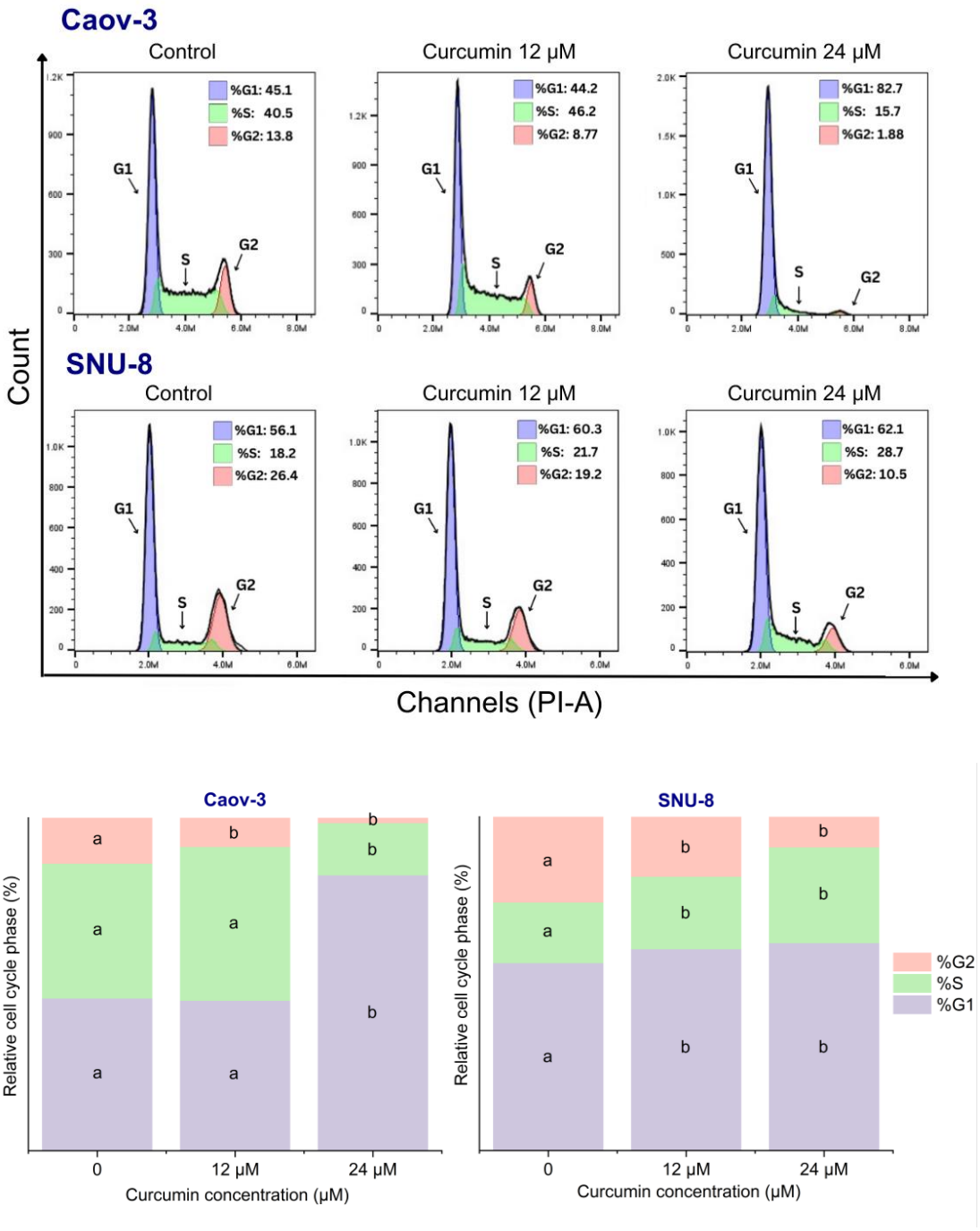


**Figure 5.** Curcumin differentially alters the cell cycle progression in ovarian cancer cells. The figure illustrates cell cycle analyses for SNU-8 and Caov-3 cell lines, highlighting curcumin's concentration-dependent effects. In SNU-8 cells, 12 μM induced a G1 phase increase to 60.3%, rising to 62.1% at 24 μM, with a concurrent S phase increase. Conversely, Caov-3 cells at 24 μM exhibited a notable G1 dominance at 82.7%, contrasting the control group's 45.1% G1 phase. Data, expressed as mean ± SEM, are representative of three independent experiments performed in triplicate. Statistical significance is indicated by dissimilar letters, denoting means that are significantly different.

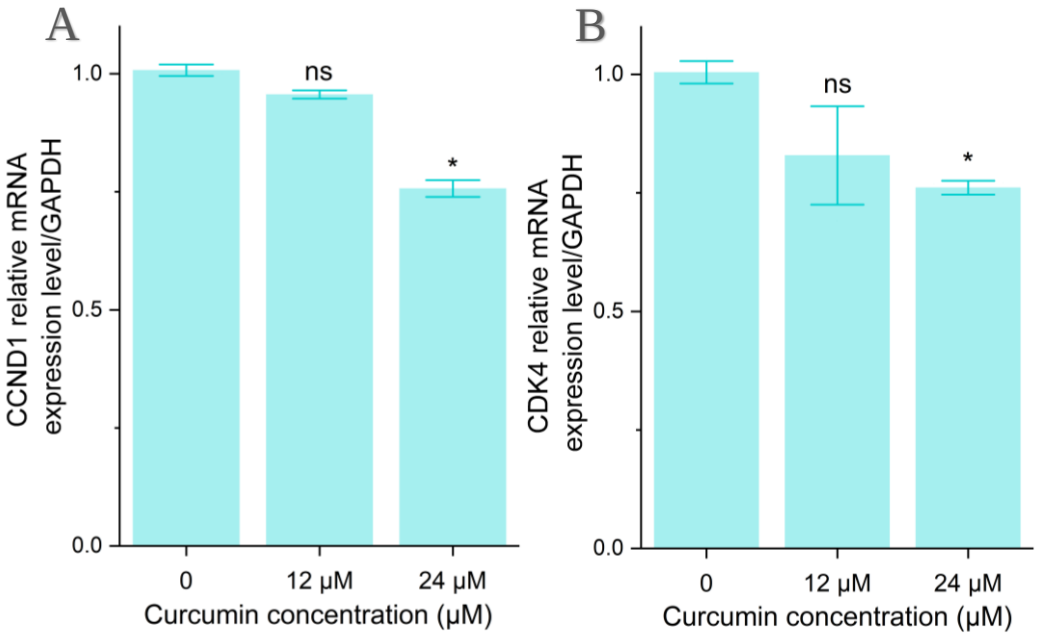


**Figure 6.** Curcumin effect on cell cycle-associated genes in Caov-3 ovarian cancer cells. The figure illustrates the dose-dependent effects of curcumin on cell cycle regulators in Caov-3 ovarian cancer cells by qRT-PCR analysis. At 12 μM, curcumin induces a subtle downregulation of CCND1 **(A)**, which becomes more pronounced at 24 μM. Concurrently, CDK4 **(B)** in Caov-3 cells exhibits a modest downregulation at 12 μM, intensifying at the higher concentration of 24 μM. Data, expressed as mean ± SEM, are representative of three independent experiments performed in triplicate. Statistical significance is denoted by "ns" for not significant, *$p < 0.05$, ***$p < 0.001$, indicating a significant difference from the control.

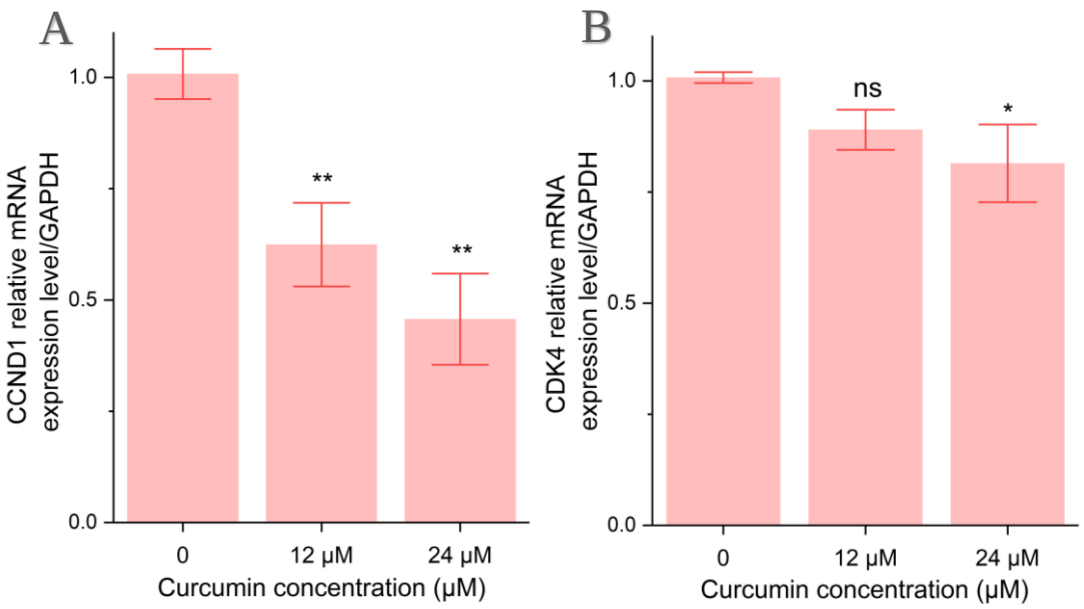


**Figure 7.** Curcumin effect on cell cycle-associated genes in SNU-8 ovarian cancer cells. The figure depicts the impact of curcumin on cell cycle-associated genes in SNU-8 ovarian cancer cells by qRT-PCR analysis. At 12 μM, curcumin significantly downregulates CCND1 **(A)** expression, intensifying at 24 μM. Additionally, curcumin moderately reduces CDK4 **(B)** expression at both concentrations. Data, presented as mean ± SEM, are representative of three independent experiments performed in triplicate. Statistical significance is denoted by "ns" for not significant, *$p < 0.05$, **$p < 0.01$, indicating a significant difference from the control.

### 4.4 Curcumin-induced apoptosis in ovarian cancer cells

Apoptotic effects of curcumin on ovarian cancer cells were assessed using Annexin V-FITC and propidium iodide (PI) staining, coupled with flow cytometry analysis. After a 24-hour exposure of both cell lines to curcumin at concentrations of 12 and 24 μM, a substantial increase in apoptotic cells was observed, suggesting a significant induction of apoptotic cell death. The dose-dependent effect of curcumin on apoptosis induction is illustrated in **Figure 8**. In comparison to the low baseline apoptotic rates observed in the control groups for both the Caov-3 and SNU-8 cell lines, the treatment of curcumin at concentrations of 12 μM and 24 μM resulted in a progressive increase in the percentage of apoptotic cells. Specifically, in the Caov-3 cell line, the apoptotic rate increased from 0.713% in the control group to 9.46% at 12 μM, peaking at 44.9% at the higher concentration of 24 μM. Similarly, in the SNU-8 cell line, the apoptotic rate rose from 0.626% in the control group to 7.73% at 12 μM, with a subsequent increase to 19.89% at the elevated concentration of 24 μM.

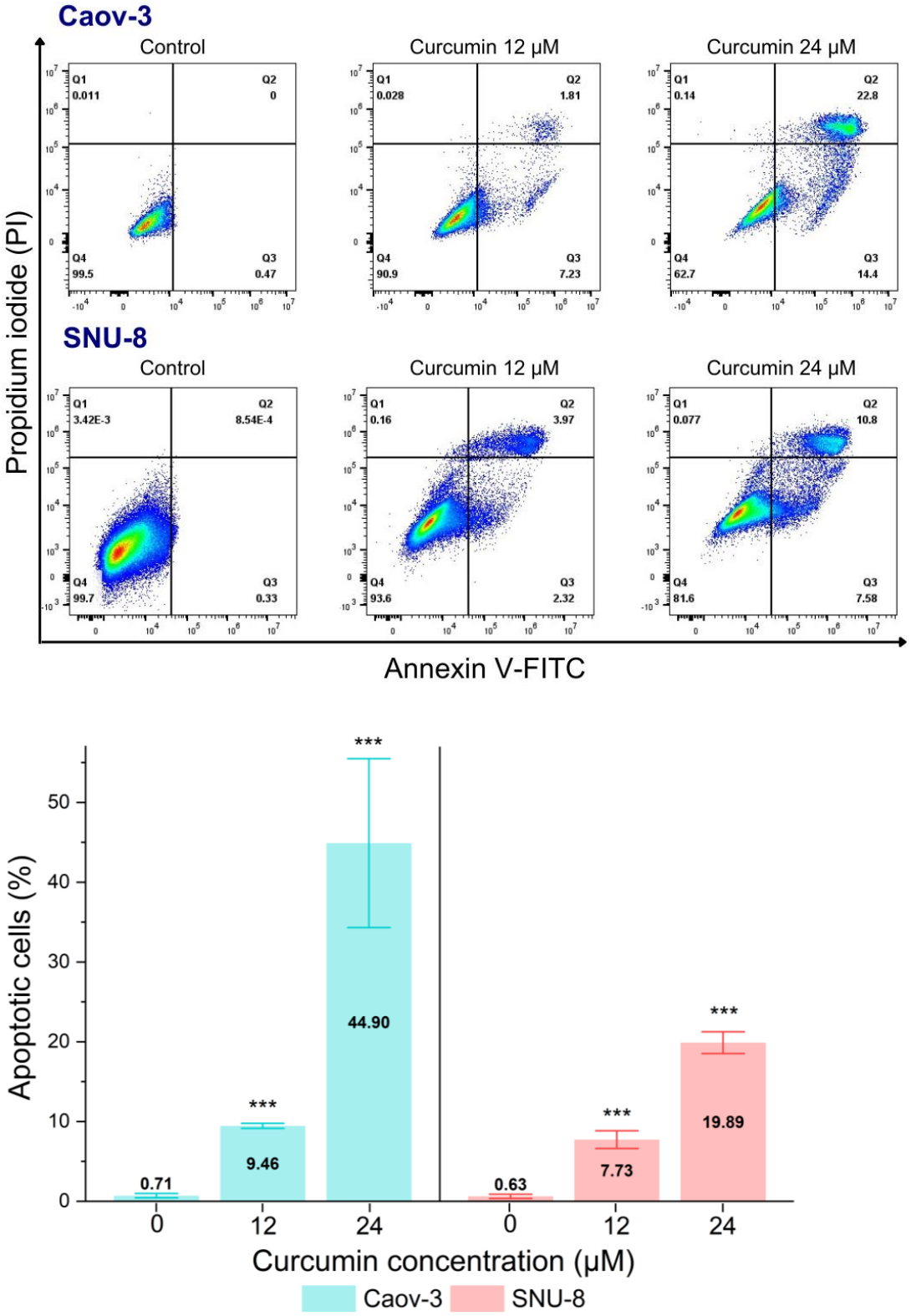


**Figure 8.** Dose-dependent induction of apoptosis by curcumin in ovarian cell lines. The figure portrays the apoptosis analysis data for Caov-3 and SNU-8 cell lines, demonstrating the concentration-dependent effect of curcumin on apoptosis induction. Control groups for both cell lines exhibit low baseline apoptotic rates, while the treatment of curcumin at

concentrations of 12 μM and 24 μM results in a progressive increase in the percentage of apoptotic cells. In the Caov-3 cell line, the apoptotic rate rises from 0.713% in the control to 9.46% at 12 μM and 44.9% at 24 μM. Similarly, in the SNU-8 cell line, the apoptotic rate increases from 0.626% in the control to 7.73% at 12 μM and 19.89% at 24 μM. Data, expressed as mean ± SEM, are representative of three independent experiments performed in triplicate. Statistical significance is denoted by ***$p < 0.001$, indicating a significant difference from the control.

# V. DISCUSSION

The persistent high mortality rates associated with ovarian cancer can be attributed to challenges in early detection and the emergence of chemo resistance during treatment (Lisio et al., 2019). Remarkably, the past decade has witnessed exponential progress in the treatment of ovarian cancer, marked by the introduction of numerous experimental targeted agents and the approval of new drugs. While these advancements offer promising opportunities, they also present challenges in selecting optimal agents, evaluating their efficacy, and determining the most effective treatment regimens to enhance patient outcomes. Over the decades, various histologic diagnoses have been grouped under the umbrella term "ovarian cancer" and treated uniformly. However, recent advancements in research have led to the identification of specific molecular markers associated with distinct histologies, enabling more precise diagnoses. Notably, the primary chemotherapeutic agents for ovarian, testicular, and colon cancer, namely cisplatin and oxaliplatin, are increasingly encountering resistance (Bukowski et al., 2020). To address this challenge, ongoing investigations explore the potential of combining these agents with other cytostatic drugs or novel molecular-targeted agents (Gupta et al., 2022).

In the realm of experimental findings, recent research has unveiled a noteworthy discovery regarding curcumin, a botanical polyphenol extracted from the rhizomes of *Curcuma longa*. The multifaceted attributes of curcumin, encompassing antimicrobial (Trigo-gutierrez et al., 2021), anti-inflammatory (Peng et al., 2021), immunomodulatory (Chamani et al., 2022), free radical scavenging (Calabrese et al., 2008), and antidiabetic activities (Den Hartogh et al., 2020), make it a compelling subject of study. Curcumin has emerged as a promising candidate, showcasing chemopreventive and anticarcinogenic properties in vivo (Zhang et al., 2015; Chikara et al., 2018) and elucidating cell-cycle and apoptosis-related molecular mechanisms in vitro (Koprowski et al., 2015; Gianfredi et al., 2017; Moawad et al., 2023). Curcumin has gained attention due to its low toxic side effects and promising anticancer effects (Tan & Norhaizan, 2019). Among the diverse cancer types studied, curcumin has exhibited noteworthy effects on breast, prostate, brain, lung, pancreatic, gastric, and ovarian

cancers (Meeran & Kumar Katiyar, 2008; Zhang et al., 2015; Barra et al., 2022; Fatemizadeh et al., 2022; Passos et al., 2023; Chen et al., 2023). Significantly, curcumin has exhibited substantial anticancer effects on various cancer cell lines, including breast (Wang et al., 2016), cervical (Zhang et al., 2023), lung (Zhu et al., 2021), and ovarian cancers (Bondì et al., 2017; Zhang et al., 2017; Dwivedi et al., 2018).

In light of the above facts, the objectives of the present study were: (i) reviewing the role of curcumin in treating ovarian cancer based on the available literature in the public domain, (ii) studying the cytotoxic potential and mechanism of cell death initiated by curcumin on Caov-3 and SNU-8, human ovarian cancer cell lines. We conducted a comprehensive review for the role of curcumin in treating ovarian cancer based on the available literature data retrieved from databases such as PubMed, Scopus, ScienceDirect, and ClinicalTrials.gov. Our review found that a comparative study of curcumin and curcumin nanoformulation's efficacy against ovarian cancers is sorely needed. Significant research gaps have also been identified due to limited clinical trials conducted to assess the safety and efficacy of curcumin or curcumin nanoformulations in humans. Eventually, still more research is required to completely understand the curcumin anticancer mechanism in ovarian cancer. Overall, the information we summarized in our review will be useful to researchers investigating curcumin's impact on ovarian cancer.

Following our review, we went on to conduct experiments to investigate the therapeutic benefits of curcumin on ovarian cancer cells, with a specific focus on two distinct cell lines: epithelial high-grade ovarian serous adenocarcinoma (Caov-3) and ovarian serous cystadenocarcinoma (SNU-8). Our exploration builds upon previous research demonstrating curcumin's inhibitory effects on tumor formation. SNU-8, a human ovarian cancer cell line derived from the ovary and characterized by the presence of ascites, was isolated from a 55-year-old Asian female. Its histopathology reveals cystadenocarcinoma with serous and papillary characteristics. In contrast, Caov-3, another human ovarian cancer cell line with an epithelial origin, was obtained in 1976 from a 54-year-old Caucasian woman diagnosed with

adenocarcinoma. The histopathology of Caov-3 reveals characteristics of adenocarcinoma, and the cells exhibit epithelial morphology. The demographic disparities between the two cell lines, SNU-8 originating from an Asian female and Caov-3 from a Caucasian woman, underscore the heterogeneity of ovarian cancer. This emphasizes the importance of considering demographic factors in experimental design. The unique features of SNU-8 and Caov-3, representing different histopathological types of ovarian cancer (Cystadenocarcinoma and adenocarcinoma, respectively), provide a valuable platform for testing curcumin. By examining its effects across diverse cancer subtypes, this study aims to contribute a more comprehensive understanding of curcumin's potential therapeutic impact on ovarian cancer.

We first assessed the cytotoxic effect of curcumin on ovarian cancer cell lines, Caov-3 and SNU-8. Cells were exposed to various concentrations of curcumin (0 μM, 3 μM, 6 μM, 12 μM, 24 μM, and 48 μM) over 24 hours. The results demonstrated a clear, dose-dependent reduction in cell viability. Notably, the calculated IC50 values indicated heightened sensitivity in Caov-3 cells (IC50 = 22.24 μM) compared to SNU-8 cells (IC50 = 25.81 μM). This observation aligns with findings from Pan et al., who reported a concentration-dependent decline in cell viability in Caov-3 cells. Specifically, exposure to 25 μM curcumin over 12, 24, 48, and 72 hours resulted in diminishing viability percentages of 88%, 58%, 27%, and 9%, respectively (Pan et al., 2008). In a parallel investigation, Guo et al. observed IC50 values for curcumin in Caov-3 and A2780 cells (18.43 ± 0.69 μM and 35.92 ± 3.77 μM, respectively) (Q. Guo et al., 2021). Further experiments were conducted using curcumin at the two indicated concentrations (12 and 24 μM) based on the results of this cytotoxicity study.

The clonogenic assay is widely used to examine the adhesion-independent cell proliferation of cancer cells. Therefore, we studied the curcumin’s inhibition on Caov-3 and SNU-8 cell proliferation by clonogenic assay. Over 14 days, cells were exposed to two distinct concentrations of curcumin (12 μM and 24 μM) for 24 hours. Our study revealed a dose-dependent suppression of clonogenic ability in Caov-3 and SNU-8 cell lines. Caov-3 cells exhibited a complete cessation of proliferation at 24 μM, following an initial pause at 12 μM.

Conversely, SNU-8 cells displayed a dose-dependent inhibition with surviving colonies, indicating a nuanced response to curcumin. Sun & Fang., performed a colony formation assay and found that curcumin treatment significantly inhibited the proliferation of ovarian cancer cells. Exposing SKOV3 and A2780 cells to curcumin (10 μM, 20 μM, and 40 μM) resulted in a dose-dependent inhibition on the colony-formation ability of the cells compared to the DMSO or control group (Sun & Fang, 2021).

Furthermore, our investigation illuminates curcumin's potential to induce cell cycle arrest in Caov-3 and SNU-8 cells, specifically at the G0/G1 phase. The concentration-dependent modulation of curcumin on cell cycle progression in these distinct cell lines serves as a central focus of our study. Notably, in SNU-8 cells, exposure to 12 μM curcumin prompts a shift towards the G1 phase, with a simultaneous increase in the S phase, indicative of a regulatory influence on cell cycle dynamics. This effect intensifies at 24 μM curcumin, emphasizing a concentration-dependent impact. Conversely, Caov-3 cells exhibit a significant reversion to G1 dominance at 24 μM, highlighting a distinct concentration-dependent regulatory effect compared to the control group. These concentration-dependent effects underscore the regulatory influence of curcumin on the dynamic progression of the cell cycle. These findings align with prior studies confirming curcumin's adeptness in inducing cell cycle arrest, particularly in the G1 phase (Li et al., 2022; Kim et al., 2023). Another investigation demonstrated that drug treatment for 24 hours led to a multi-phase cell cycle arrest. To elucidate distinctions in cell cycle distribution induced by curcumin and nanocurcumin, HCT116 colorectal carcinoma cells were synchronized in the G0, S, and G2/M phases. While both curcumin and nanocurcumin treatments resulted in a prolonged G0/G1 arrest in cells released from G0-phase synchronization, nanocurcumin exhibited distinctive cell cycle fluctuations, notably leading to a higher proportion of cells in the G2/M phase. This observation underscores the sustained and unique regulatory effects of these compounds on the cell cycle (Xu et al., 2023).

To elucidate the underlying mechanisms of curcumin's impact on cell cycle arrest, our

investigation focused on evaluating the expression patterns of key cell cycle-related genes, specifically cyclin-dependent kinase 4 (CDK4) and cyclin D1 (CCND1), through qRT-PCR analysis. Previously, Roy and Mukherjee documented curcumin's inhibitory effects on CCND1 and CDK4 expression, crucial for regulating the transition from G1 to S phase, providing valuable insights into its role in impeding G1-S phase cell cycle arrest in cervical cancer cells (Roy & Mukherjee, 2014). Within the SNU-8 cell line, a discernible reduction in CCND1 expression was observed at concentrations of 12 μM and 24 μM, while CDK4 exhibited a slight downregulation at these concentrations. Similarly, in the Caov-3 cell line, CCND1 expression decreased at 12 μM and 24 μM, accompanied by a modest downregulation of CDK4. The significance of Cyclin D1 as a pivotal regulatory protein orchestrating the G1 to S phase transition is underscored by its downregulation, suggesting a potential impediment to this transition and leading to cell cycle arrest. Furthermore, the observed downregulation of CDK4, a critical collaborator with Cyclin D1 in facilitating the G1 to S phase transition, indicates a disruption in this progression, further supporting the role of curcumin in inducing cell cycle arrest. Aligning with Mukhopadhyay et al.'s work, curcumin consistently reduces cyclin D1 across various cancer cell lines and selectively targets cyclin D2 and D3. Mechanistically, curcumin inhibits CDK4-mediated phosphorylation of the retinoblastoma protein, affecting cell cycle progression through transcriptional and post-transcriptional pathways (Mukhopadhyay et al., 2002b). Further, it is essential to study the specific impact of curcumin on crucial S phase regulators, including Cyclin E, Cyclin A, and CDK2. It will help to confirm the multi-phase cell cycle arrest mechanism of curcumin and support our findings.

Moreover, the concentration-dependent increase in apoptotic cells underscores curcumin's potential in coordinating programmed cell death in ovarian cancer cells. The treatment of curcumin at concentrations of 12 μM and 24 μM precipitates a progressive escalation in the percentage of apoptotic cells. In the Caov-3 cell line, apoptotic rates increase from 0.713% (control) to 9.46% (12 μM) and 44.9% (24 μM). Similarly, in the SNU-8 cell line, rates rise from 0.626% (control) to 7.73% (12 μM) and 19.89% (24 μM), consistent with

earlier observations (Srivastava et al., 2007). This study documented curcumin treatment (5, 10, and 20 μM) inducing dose- and time-dependent apoptosis in PC-3 human prostate cancer cells and dose-dependent apoptosis in LNCaP human prostate carcinoma cells at 48 hours. In a study by Yang et al., the combination of SKI-II and curcumin synergistically induced cell apoptosis in cultured ovarian cancer cells (Caov-3, SKOV3, and A2780). Particularly in Caov-3 cells, the apoptosis percentage following SKI-II (5 μM) plus curcumin (25 μM) treatment surged to 27%, in stark contrast to 9% after SKI-II treatment alone and 4% for curcumin monotherapy (Yang et al., 2012).

The effect of curcumin on ovarian cancer cells is predominantly associated with apoptotic pathways, underscoring its potential as a therapeutic agent for inducing programmed cell death. Curcumin effectively targets key signaling pathways, including NF-κB, AP-1, STAT3, and PI3K/Akt, disrupting oncogene transcription and hindering cellular proliferation and angiogenesis (Cimino et al., 2012; Jia et al., 2014; Fetoni et al., 2015; Tong et al., 2016). By inhibiting NF-κB activity, curcumin prevents the nuclear translocation of the p65 subunit, suppressing pro-inflammatory transcription (Shanmugam et al., 2015). The AP-1 pathway, associated with anti-apoptotic and pro-angiogenic genes, is downregulated by curcumin (Yao et al., 2015). In the STAT3 pathway, curcumin suppresses the expression of anti-apoptotic proteins, such as Bcl-2 and Bcl-xL (Singh & Aggarwal, 1995; Vadhan-Raj et al., 2007). Additionally, in lung cancer cells, curcumin exhibits proapoptotic activity by targeting the PI3K/Akt signaling pathway (Jin et al., 2015). Its effects extend to various cancer types, including B cell chronic lymphocytic leukemia (Anand et al., 2008; Ghosh et al., 2009), lung adenocarcinoma (Khan & Mukhtar, 2015), and acute monocytic leukemia (Yang et al., 2012), influencing caspase-3 and inhibiting Akt/mTOR/p70S6 signaling (Kuttan et al., 2007; Xue et al., 2014). Curcumin's modulation of EZH2 contributes to apoptosis in multiple myeloma cells (Jiang et al., 2021), and it upregulates microRNA-192-5p, associated with inducing apoptosis in non-small cell lung cancer cells (Jin et al., 2015). Curcumin's effect on cancer cells extends beyond apoptosis, involving intricate crosstalk with various signaling pathways. Notably, it

modulates critical cancer pathways, including MAPK/ERK (Zhang et al., 2012; Fang et al., 2018) and Wnt/β-Catenin (Vallée et al., 2019; Vallée, 2022), governing cell proliferation and fate determination. Furthermore, it exerts influence on the Notch signaling pathway (Zhao et al., 2018; Tandon et al., 2020), vital for cell differentiation, and selectively targets the Hedgehog pathway associated with cellular growth (Wang et al., 2017). In addition to its previously discussed interactions with STAT3, curcumin exhibits the potential to affect the JAK/STAT pathway (Porro et al., 2019; Ashrafizadeh et al., 2020), highlighting its nuanced and multifaceted role in impeding the progression of cancer.

Collectively, our study results confirm that curcumin induces cell death by apoptosis in human ovarian cancer cell lines Caov-3 and SNU-8. However, this study has notable limitations that merit attention. The mechanism of apoptosis induction in curcumin-treated ovarian cancer cells may need confirmation through the examination of apoptosis intrinsic and extrinsic pathway genes at the mRNA or protein level. Moreover, our results rely primarily on in vitro experiments. Therefore, additional studies are required to validate the in vitro analysis conducted in the current study. In particular, future investigations should prioritize in vivo studies using animal models, such as Xenograft or Orthotopic mouse models derived from ovarian cancer cells (e.g., Caov-3 and SNU-8), to assess the efficacy and safety of curcumin. Furthermore, a comprehensive exploration of apoptosis mechanisms, including the crosstalk between apoptosis and other pathways (e.g., autophagy), is essential to uncover the full potential of curcumin as a targeted therapy in ovarian cancer.

## VI. SUMMARY

The current investigation aims to comprehend the anticancer mechanism of curcumin in ovarian cancer. To achieve this, we treated human ovarian cancer cell lines, Caov-3 and SNU-8, with various curcumin concentrations and investigated curcumin's anticancer effects by examining cell viability, clonogenic potential, cell cycle alterations, and apoptosis induction. The primary findings are summarized below:

- To assess the effect of curcumin on cell viability, curcumin concentrations (3, 6, 12, 24, and 48 μM) were administered to Caov-3 and SNU-8 cell lines for 24 hours.
- MTT assay results revealed a dose-dependent reduction in cell viability. Caov-3 cells exhibited heightened sensitivity (IC50: 22.24 μM) compared to SNU-8 cells (IC50: 25.81 μM). The cytotoxicity assessment results guided further experiments using two curcumin concentrations (12 and 24 μM).
- Clonogenic ability was examined through colony formation assays conducted over 14 days with exposure to 12 μM and 24 μM of curcumin. A dose-dependent suppression of clonogenic ability was observed, with Caov-3 cells ceasing proliferation entirely at 24 μM, while SNU-8 cells exhibited survival with the minimum number of colonies.
- Flow cytometry analysis was done to investigate how curcumin affects the cell cycle progression. Following a 24-hour exposure to curcumin (12 and 24 μM), cells were subjected to staining with propidium iodide (PI) for subsequent cell cycle analysis.
- Curcumin showed the G0/G1 phase cell cycle arrest in a concentration-dependent manner on both cell lines. Caov-3 cells exhibited significant G1 reversion at 24 μM (82.7%), accompanied by reduced S (15.7%) and G2 (1.88%). SNU-8 cells displayed a shift toward G1 (12 μM: 60.3%, 24 μM: 62.1%) and increased S phase (12 μM: 21.7%, 24 μM: 28.7%), intensifying at 24 μM.
- Cyclin-dependent kinase 4 (CDK4) and cyclin D1 (CCND1) genes are related to the cell cycle. Therefore, following curcumin (12 and 24 μM) treatment, the expression patterns of these two genes were examined using qRT-PCR analysis.

- In the SNU-8 cell line, a noticeable reduction in CCND1 expression was observed, while CDK4 exhibited a slight downregulation. Similarly, in the Caov-3 cell line, CCND1 expression decreased, accompanied by a modest downregulation of CDK4. The observed effects on gene expression were dose-dependent, indicating that the effect of curcumin on cell cycle-related genes varied with the concentration used.
- Apoptosis assays using Annexin V-FITC and propidium iodide labeling demonstrated a concentration-dependent increase in apoptotic cells at 12 μM and 24 μM curcumin in both cell lines.
- In Caov-3, the apoptotic rate rose from 0.713% in the control to 9.46% at 12 μM and 44.9% at 24 μM. Similarly, in SNU-8, the apoptotic rate increased from 0.626% to 7.73% at 12 μM and 19.89% at 24 μM.
- Our study affirms curcumin's potential to induce apoptosis in human ovarian cancer cell lines Caov-3 and SNU-8. However, certain limitations exist, necessitating further validation by examining apoptosis pathway genes at mRNA or protein levels.
- It is crucial to note that our findings are based on in vitro experiments, requiring additional confirmation. Future studies should prioritize in vivo investigations using animal models, such as Xenograft or Orthotopic mouse models derived from ovarian cancer cells (e.g., Caov-3 and SNU-8), to establish curcumin's efficacy and safety.
- Unlocking curcumin's full potential as an ovarian cancer therapy requires a detailed exploration of apoptosis mechanisms and crosstalk with pathways like autophagy for comprehensive therapeutic benefits.
- Eventually, we conducted a comprehensive review of the role of curcumin in treating ovarian cancer, based on the available literature data retrieved from the public domain. It will be useful to researchers investigating the effect of curcumin on ovarian cancer.

## VII. 국문 요약

현재 연구는 난소암에서 curcumin의 항암 기전을 이해하는 것을 목표로 한다. 이를 위해 우리는 인간 난소암 세포주인 Caov-3 및 SNU-8에 다양한 curcumin 농도를 처리하고 세포 생존율, clonogenic 능력, 세포 주기 변화 및 apoptosis 유도를 조사하여 curcumin의 항암 효과를 조사하였다. 주요 결과는 아래와 같다:

- Curcumin이 세포 생존력에 미치는 영향을 평가하기 위해 Caov-3 및 SNU-8 세포주에 24시간 동안 curcumin 농도(3, 6, 12, 24 및 48 μM)를 투여했다.
- MTT 분석 결과 세포 생존율이 농도에 따라 감소함을 나타냈다. Caov-3 세포는 SNU-8 세포 (IC50: 25.81μM)에 비해 높은 민감도 (IC50: 22.24μM)를 보였다. 세포 독성 평가 결과에 따라 두 가지 curcumin 농도 (12 및 24 μM)를 사용하여 추가 실험을 진행했다.
- Clonogenic 능력은 12 μM 및 24 μM의 curcumin에 노출된 상태에서 14일 동안 진행된 colony 형성 분석을 통해 조사되었다. 농도에 따른 clonogenic 능력의 억제가 관찰되었으며, Caov-3 세포는 24 μM에서 증식을 완전히 중단하는 반면, SNU-8 세포는 최소한의 colonies 개수로 생존했다.
- Curcumin이 세포 주기 진행에 어떤 영향을 미치는지 조사하기 위해 유세포 분석을 실시하였다. 24시간 동안 curcumin (12 및 24 μM)에 노출된 후 세포 주기를 분석하기 위해 propidium iodide (PI)를 사용하여 세포를 염색했다.
- Curcumin은 두 세포주에서 농도 의존적인 방식으로 G0/G1기 세포 주기 정지를 보였다. Caov-3 세포는 24 μM에서 유의한 G1기 복귀를 보였으며(82.7%), S기 (15.7%) 및 G2기 (1.88%)가 감소했다. SNU-8 세포는 G1기(12 μM: 60.3%, 24 μM: 62.1%)로 이동하고 S기(12 μM: 21.7%, 24 μM: 28.7%)가 증가하여 24 μM에서 강화되었다.
- 세포 주기와 관련된 cyclin-dependent kinase 4 (CDK4) 및 cyclin D1 (CCND1)

유전자를 조사하기 위해 curcumin (12 및 24 μM) 처리 후 qRT-PCR 분석을 이용하여 이 두 유전자의 발현 양상을 살펴보았다.

- SNU-8 세포주에서는 CCND1 발현의 현저한 감소가 관찰된 반면, CDK4는 약간의 하향 조절을 보였다. 마찬가지로, Caov-3 세포주에서는 CCND1 발현이 감소하였으며, CDK4는 약간의 하향 조절을 나타냈다. 유전자 발현에 대한 관찰된 효과는 용량 의존적이었으며, 이는 세포 주기 관련 유전자에 대한 curcumin의 효과가 사용된 농도에 따라 다름을 나타낸다.
- Annexin V-FITC 및 propidium iodide labeling을 사용한 세포자멸사 분석에서는 두 세포주 모두에서 12μM 및 24μM curcumin에서 세포자멸사 세포의 농도 의존적 증가를 보여주었다.
- Caov-3에서 세포 사멸률은 대조군의 0.713%에서 12 μM에서 9.46%, 24 μM에서 44.9%로 증가하였다. 비슷하게, SNU-8에서도 세포 사멸률은 12 μM에서 0.626%에서 7.73%, 24 μM에서 19.89%로 증가하였다.
- 우리의 연구는 인간 난소암 세포주 Caov-3과 SNU-8에서 세포자멸사를 유도할 수 있는 curcumin의 가능성을 확인한다. 그러나 특정 한계가 존재하므로 mRNA 또는 단백질 수준에서 세포자멸 경로 유전자를 조사하여 추가 검증이 필요하다.
- 우리의 연구 결과는 in vitro 실험을 기반으로 하므로 추가 확인이 필요하다는 점에 유의해야 한다. 향후 연구에서는 동물 모델(예: 난소암 세포인 Caov-3 및 SNU-8에서 파생된 Xenograft 또는 Orthotopic 마우스 모델)을 사용하여 curcumin의 효능과 안전성을 확립하기 위해 in vivo 조사를 우선해야 한다.
- 난소암 치료제로서 curcumin의 전체 잠재력을 활용하기 위해서는 세포자멸사 메커니즘에 대한 상세한 조사와 포괄적인 치료 이득을 위한 자가포식과 같은 경로와의 상호작용에 대한 상세한 탐색이 필요하다.

- 최종적으로 공개 영역에서 검색된 가용한 문헌 자료를 바탕으로 난소암 치료에 있어 curcumin의 역할에 대한 종합적인 검토를 수행하였다. curcumin이 난소암에 미치는 영향을 조사하는 연구자들에게 유용할 것이다.

**Supplementary table 1.** Primer sequences employed in qRT-PCR experiments.

| Gene | Forward primer (5'-3') | Reverse primer (5'-3') |
|---|---|---|
| **GAPDH** | GGCCTCCAAGGAGTAAGACC | AGGGGTCTACATGGCAACTG |
| **CDK4** | ATGGCTACCTCTCGATATGAGC | CATTGGGGACTCTCACACTCT |
| **CCND1** | GCTGCGAAGTGGAAACCATC | CCTCCTTCTGCACACATTTGAA |

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## ACKNOWLEDGEMENTS

I wish to express my profound gratitude to Professor Min TaeSun, my esteemed supervisor, for the invaluable guidance, unwavering support, and insightful feedback provided throughout the entire trajectory of completing this master's thesis. Professor Min's expertise, encouragement, and unwavering dedication have played a pivotal role in shaping the course of this research.

I extend sincere appreciation to the esteemed members of my thesis committee, Professor Do KyoungTag and Professor Park JongEun, for their constructive comments and thoughtful suggestions. Their expert insights significantly elevated the quality of this work and substantially contributed to its refinement.

I am grateful to the Department of Animal Biotechnology, Bio-Resources Computing Research Center, Sustainable Agriculture Research Institute, and the Center for Research Facilities at Jeju National University for creating a supportive academic environment and providing access to vital resources, which played a crucial role in the successful completion of this research.

I would also like to express my gratitude to the Korean Government Scholarship Program (KGSP) for granting me the valuable opportunity to pursue higher education in Korea. Their unwavering support has been instrumental throughout the entirety of my degree.

Special appreciation is extended to the Animal Resource Utilization Laboratory for their invaluable assistance and cooperation. Deepest gratitude is expressed to the laboratory members, including Dr. Karthikeyan Adhimoolam, Mr. Kim Donghyun, Dr. Mohammad Moniruzzaman, Ms. Anjana Sureshbabu, Ms. Do Thi Cat Tuong, and Ms. Chin Sungyeon, for their unwavering support, love, and understanding throughout this academic journey. Their encouragement was indispensable in persevering through the challenges encountered.

Special thanks are extended to Dr. Karthikeyan Adhimoolam for his unwavering support and invaluable mentorship throughout the research process. His depth of knowledge, keen insights, and unwavering commitment significantly influenced the intellectual rigor of this thesis. Dr. Adhimoolam's guidance went beyond the academic realm, providing me with a

broader perspective on the implications of my research and its potential real-world applications. I am truly grateful for the countless hours Dr. Adhimoolam dedicated to discussing and refining the finer details of the study. His constructive feedback not only improved the quality of my work but also fostered my intellectual growth as a researcher.

Finally, I extend my gratitude to all the participants who generously contributed their time and insights to this study. This thesis is a culmination of the collective efforts and contributions of numerous individuals, and I sincerely appreciate the support received from each one of them.