

Effect of Oxysophocarpine on Proliferation and Invasion of Endometrial Cancer HEC-1-B Cells and Related Proteins

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Abstract: Endometrial cancer is one of the most common cancer of the female reproductive tract, which has been one of the primary causes of cancer related deaths and accounts for approximately 1/4 of these patients. In this paper, HEC-1 cell lines that are known to propagate endometrial cancer have been considered as potential sites of action for various therapeutic agents in an attempt to combat proliferation. Ancient Chinese remedies are by far the most recognized therapeutic method which have been found to relieve patients suffering from a tumor and also suppresses tumor growth. This study researches the effect of an injection formulation of the compound Kushen, which is a large oxysophocarpine-associated compound. In CKI- handled tumor cells, cellular proliferation through DNA synthesis and mobile differentiation seems to be a surprisingly modified mechanism. Cell cycle inhibition is seen to be one of the key mechanisms in CKI mediated tumor suppression in most instances. This is based on the fact that aggregates display certain 2-D specifications and dimerization of genes within the proposed mechanisms [10]. There is, nevertheless, little to no proof that oxysophocarpine, specifically in endometrial cells HEC-1B, inhibits the growth of most cancers' cells.

Keywords: Cancer, Tumor, Proliferation, HEC-1B Cells, Oxysophocarpine, Kushen, Anti-tumor

1. Introduction

Endometrial cancer is the seventh leading cause of cancer deaths, but its prevalence varies by country [49]. Despite the fact that mortality is higher in developed countries, risk factors are much less common, even though endometrial most cancers are less common [1, 39]. The situation is ten times worse in North America and Europe than in developing countries; in these areas, the most aggressive of cancers inhabit the vagina. After breast, lung, and colorectal cancers, this is the fourth most popular type of cancer in the world [49, 24]. The rate rises in tandem with the length of life expectancy [59]. Even after a hysterectomy, the risk of developing cancer of the reproductive tract continues to grow [37]. This increase is linked to problems of obesity and physical inactivity [59, 56]. After breast and colon cancers, endometrial cancer is the third most common cancer in

females in Flanders. Cervical, vaginal, and endometrial cancers occur at rates of 133, 208, and 1619 per 100,000 girls in the same region, respectively. Endometrial cancer affects 1.7 percent of women under the age of 75, according to figures [15]. In the United States, endometrial cancer is the eighth leading cause of cancer-related death in women [61]. Endometrial cancer kills approximately 9000 women in Europe per year. Endometrial cancer is predicted to become more common and cause further deaths in the coming years [81]. Endometrial carcinoma (EC) has become a widespread gynecological cancer in developed countries as a result of the increasing trend [26]. Over the last 20 years, China's EC situation has also worsened, and the death toll from EC has increased by more than a hundred percent [2]. Type I (endometrioid) EC is usually much less susceptible and

easily treatable. Type II EC, on the other hand, has non-endometrioid histology with a high rate of deep myometrial proliferation and lymph node metastasis, contributing to a poor prognosis and a high mortality rate. Endometrioid carcinoma is categorized into two subtypes or types: secretory carcinoma and villoglandular carcinoma [4]. Given that glycogen vacuoles are found in several tumor cells, the first one reflects the secreting endometrium, whereas the latter has a papillary developmental pattern of bland nuclei hit [83]. The separation of squamous epithelium is a typical feature of the acquisition of patients at high risk of death [61]. The development of pathways that attack EC would undoubtedly aid in the advancement of current therapies. The mechanism of EC cellular metastasis is difficult to understand. Matrix metalloproteinase (MMP) -2 and -9 play critical roles in this process by destabilizing the external matrix (ECM) [8]. MP-2 and -nine are also essential in EC metastasis and are linked to disease progression [74, 25].

2. Literature Review

2.1. Endometrial Cancer Pathogenesis

Pathogenesis is a term that applies to the examination of the disease at various levels, including people at risk,

etiologic causes, advanced and microscopic histopathology, and the study of pathogens. When we concentrate on “molecular pathogenesis,” we cannot ignore the importance of recognizing a disease at these stages. Instead, the best interpretation of the disorder is supplemented by a combination of molecular or genetic knowledge of the cause, which has a high probability of being converted into a defensive or therapeutic strategy. Endometrial cancer is the most prevalent gynecologic cancer in the United States of America, responsible for forty-one hundred new infections and 7,470 deaths per year [77]. Ovarian cancer is the most common cancer in gynecology and the sixth most common cause of cancer deaths in the United States. Endometrial cancer and ovarian cancer have similar age patterns and geographic distribution patterns. Each cancer is more prevalent during the perimenopausal years and decreases during menopause (Figure 1). Despite the fact that the costs of endometrial cancer drop significantly after the age of 65, the costs of ovarian cancer continue to increase when a woman is eighty years old. Endometrial and ovarian cancers are much less common in advanced and northern Europeans than in one-third of the world's population [17].

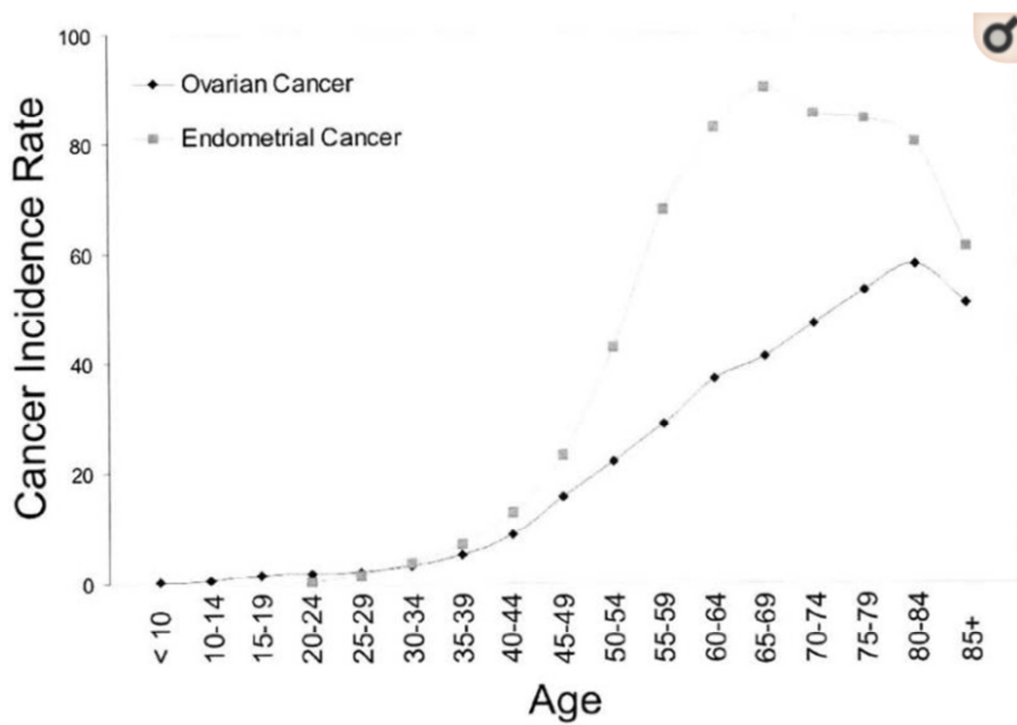


Figure 1. Age-Specific Cancer Incidence Rates are per 100,000 and are age-adjusted to the 2000 US Standard Population. Rates include all races and pertain to invasive cancers only. Adapted from Ries et al. (SEER, 2005).

Endometrial and ovarian cancer risk factors are linked to maternal factors such as higher birth rate, longer breastfeeding, and long-term oral contraceptive pill use. Past-due menstruation decreases the risk of all cancers of the female reproductive tract, while late menopause increases the risk of endometrial cancer but not ovarian cancer. These

practices may be integrated into an evolving variable that counts the number of ovulatory cycles or years of ovulation when the daily cycle time is considered. Ovulatory proliferation is specifically related to an increased risk of ovarian most cancers. While it is not well-known, puberty is often linked to an increased risk of endometrial cancer [43].

Table 1. (Cell types and their histologic description).

Type	Histologic description	Comments
Endometrioid	Resemblance to benign endometrial epithelium. Composed of tubular glands, lined by stratified or pseudostratified columnar cells. Nuclear pleomorphism is often mild to moderate.	
Serous	Forms complex papillary fronds covered by stratified, highly atypical epithelial cells that often display marked nuclear pleomorphism, and numerous mitoses. Exfoliation of cells ("hobnail") and psammoma body formation (calcium deposition on intracytoplasmic filaments of degenerating cells) may be observed.	Similar histology to that seen in the ovary. Typically behaves aggressively with tendency for myometrial invasion, extensive lymphatic invasion and early dissemination. This subtype is regarded as high-grade by definition
Clear Cell	Clear, glycogen-filled hobnail-like cells with highly pleomorphic nuclei. Cells often grow in tubular or papillary arrangements. However, unlike serous carcinoma, papillae often have hyalinized cores.	Generally, presents as advanced stage and has a poor prognosis
Mucinous	Composed of endocervical-type columnar cells that contain mucin-rich cytoplasm.	Tumors are most often low grade. Mixed endometrioid and mucinous adenocarcinomas are relatively common.
Squamous	Patterns range from individual cell keratinization to the formation of large keratin masses.	Pure squamous neoplasms are rare however focal squamous areas are identified in a portion of endometrioid carcinomas.
Transitional Cell	Typically displays nested or papillary urothelial morphology including longitudinal nuclear grooves	Pure primary tumors are rare.
Carcinosarcoma	Display an admixture of carcinomatous and sarcomatous components. The epithelial component is usually high grade and can be of endometrioid (most common), serous, clear cell, mucinous, undifferentiated, or squamous type. The sarcomatous component may resemble endometrial (homologous) or non-endometrial (heterologous) stroma.	Also known as Malignant Mesodermal (Mullerian) Mixed Tumor.
Undifferentiated	Lack a distinctive appearance therefore unable to classify into specific category of tumor. Often composed of diffuse sheets and nests that display extensive necrosis.	Associated with poor prognosis

(HACKER, NF, 2021)

The connection between ovulatory cycles, endometrial cancers, and ovarian cancers suggests a function for risk factors in cell pathogenesis. Disruption and monthly restoration of the ovary's epithelium surface is thought to cause genetic damage due to tumor accumulation, genetic changes in the p53 gene, ovarian modifications, or fallopian tube epithelium changes [16, 18, 55]. However, these mechanisms do not specify the exact pathogenesis or preemptions. Menstruation includes the regular degradation of the uterine lining. Menstruation includes the regular degradation of the uterine liner. One hypothesis is that when ovulation is continuous and non-stop, there is a similar net effect on menstruation as well. This leads to non-stop destruction and hence, rebuilding and growing of the lining of the uterus on an almost day to day basis. DNA is already prone to replication errors. When occurring on an hour-to-hour basis, the DNA checking mechanisms get more exhausted and this relays errors in gene transcription and hence mutations. Thus, the greater the number of menstrual ovulatory cycles, the greater is the chance for genetic mutations to occur and eventually cause endometrial cancer [16, 18, 55]. Furthermore, post-menopause hormone usage, especially the most powerful estrogen therapy, is another risk factor for endometrial and ovarian cancers; however, the severity of this effect is much greater for endometrial cancer. High BMI and polycystic ovarian syndrome are health issues that can increase the risk of all types of cancer (PCOS). High BMI is a risk factor for endometrial cancer type 1 and is associated with high oestrogen levels,

especially in postmenopausal women, where adipose tissue is a major source of oestrogen production from androgen precursors [6]. Excessive BMI appears to be associated with an increased risk of ovarian cancer through similar hormonal mechanisms, despite the fact that the association is less clear [34, 57]. PCOS has been linked to ovarian and endometrial cancers. It is marked by ovarian hyperandrogenism, chronic maturation, and progesterone deficiency [13, 54, 76]. Endometrial cancer is classified into three histopathological types i.e., Endometrioid (the most common), serous, and clear cell tumors are the most common, with mucinous, squamous, transitional cell, carcinosarcoma, and undifferentiated tumors being the rarer subtypes. (Table 1).

2.2. HEC-1B Cells

In addition to HeLa cells, the HEC-1 cell line [30] was the first to be developed from human endometrial carcinomas and human adenocarcinomas of any organ. HEC-1 cells were used in in vitro experiments to evaluate the characteristics of human endometrial carcinoma, resulting in a large number of articles examining the characteristics of the published HEC-1 cells. Human endometrial cancer cells (HEC-1) were the first line of endometrial carcinoma cells to be created [30, 27, 29]. The tissues were extracted from the uterus of a 71-year-old woman with endometrial carcinoma G2. Anisonucleosis and nucleolar pleomorphism are two anaplastic features of HEC-1 cytology. During the growing process, HEC-1 cells

have a jigsaw-like cellular structure with irregular dome formation and a proclivity to pile up. Harada et al. [22] researched HEC-1 cell cells in an embedded subculture using electron microscopy scanning and discovered that mobile form differs with each phase of the mobile cycle. Desmosomes were discovered in HEC-1 cells using transmission electron microscopy [28, 47], and indirect immunofluorescence was used to show the presence of cytokeratins and desmoplakins, which represent the epithelial phenotype, while direct immunofluorescence is used to show the presence of cytokeratins and desmoplakins, which reflect the epithelial phenotype. Immunoblot assists in the diagnosis of fibronectin deficiency [47]. Ishikawa cells are the beneficial oestrogen receptor (ER) and good progesterone receptor (PR) [46], but they react to oestrogen stimulation and contribute to our understanding of the oestrogen response to endometrial carcinoma cells. According to Sekiya and Takamizawa, HEC-1-B endometrial carcinoma cells were more susceptible to progesterone than other cell strains found in cervix and ovary carcinomas [60]. TGF-B1, which was first identified as an ability stimulant for fibroblast growth in soft agar, is now known to affect a variety of biological functions in different tissues. TGF-B1 is made up of four subtypes (TGF) and closely associated homologs such as activin, inhibin, and Mullerian inhibitory drug [38]. TGF-B1 receptors are found in virtually all studied cellular types, but in vitro responses to this growth factor vary depending on mobile type and lifestyle. TGF-B1 (the most extensively studied TGF-p component) promotes the development of NRK colonies in soft agar but inhibits mobile proliferation in monolayer subculture. TGF-B1 is an excellent adjuvant in virtually all epithelial cells. Several studies [3, 45] have listed it as a distribution controller. One of the most important mechanisms in carcinogenesis is thought to be the bypass of TGF-inhibiting development. Epidermal growth factor (EGF) is a persistent mutagen that acts on a variety of cellular types. It binds to a specific membrane receptor and stimulates cellular proliferation.

Epidermal growth factor (EGF) is an endogenous mitogen that acts on a variety of cell types. It binds to a specific membrane receptor and promotes cell proliferation by phosphorylating specific proteins on tyrosine [63]. TGF (transforming a growing substance) is similar to EGF in that it has a similar receptor and natural characteristics [38]. Each increase factor is thought to play an important role in controlling cancer cell proliferation. In the studies presented here, we investigated the effects of TGF-p 1 and EGF on DNA synthesis and cell proliferation in human cancer cells, Ishikawa, and HEC-50. We also found the expression of mRNAs in the cell strains by using certain growth factors and the EGF / TGF-1B receptor, as well as the law of TGF-mRNA and TGF-A mRNA stages through estradiol (E2) and 4-hydroxytamoxifen (OHTam). This demonstrates that the cellular traces of endometrial cancer are laid low with the aforementioned elements and that ability treatment is within their grasp. The HEC-1B cellular

membrane is a type of HEC-1A cellular membrane derived from endometrial adenocarcinoma. HEC-1B cells have epithelial morphology and several characteristics in common with endometrial epithelial cells. HEC cells have been discovered to contain both estradiol and progesterone [53].

2.3. *Oxysophocarpine (MOA + Effects)*

Xu et al. performed a research to assess the efficacy of the OSC. Thermal and conduct-based nociception behavioural models were used to evaluate this hypothesis, and various management strategies were investigated to recognize OSC analgesic outcomes and determine OSC-important analgesic sites in mice. Furthermore, immunohistochemistry was used in ICR mice to determine whether the outcomes of nociceptive OSC results were linked to infection through expression of GABAA receptors in the cerebral cortex and hippocampus. OSC therapy results in dose-based fully and successful anti-nociception in models of chemical nociception, such as acetic acid-caused gastrointestinal and formalin licking reactions. Furthermore, using experimental warm water experiments — flick and warm-plate — it was discovered that OSC has important antimicrobial effects on mice. The flick tail's warm water search is an example of nociceptive pain induced by brief stimuli (i.e., phasic ache). As the tail-flick is practically the spine of the reflex, it is commonly used to test responses to overexpression and determine if the medication has a primary anti-nociceptive effect. In this experiment, the ache threshold that induces the tail-flick reaction is determined. Reaction is a spinal concept caused by higher frame techniques [31]. The warm water examination of the flick tail resulted in a forty six percent increase in latency response time. Thus, OSC has a positive influence.

2.4. *Injection of Kushen (MOA + Effects)*

With time, there has been rapid increase omics-related techniques have been used to investigate the complexity of carcinogenesis at the genetic level. This has enabled cancer studies to present a plethora of new genetic mutations and molecular markers that are leading causes of cancer. Most notably, transcriptome studies are commonly used to discover cancer-related files or regulating content, such as long-term non-protein RNAs (lncRNAs) and various duplicates, as well as to become aware of subcellaneous pathways mainly dependent on genetic variants in vivo or -in vitro [14, 75, 50]. The outcomes of the Matrine or Oxymatrine plant, which involve cellular blockade and apoptosis, have been demonstrated in various types of most cancers by detecting the expression of a primary form or protein in a single cell pathway [79, 35, 8, 66, 82]. CKI mobile mechanisms have also recently been investigated as a computer [79] and Goo et al., 2015). CKI can suppress stem cells in MCF-7 cells by down-regulating the Wnt/beta-catenin pathway, by quantitative detection of expression changes of key regulators of the canonical

Wnt/beta-catenin pathway, such as beta-catenin, Cyclin-D1, and c-Myc [79]. According to the discovery of key mutations in key canonical Wnt / beta-catenin pathways, which include beta-catenin -CyclinD1, and c-Myc [79]. Similarly, some research indicates that CKI can help to reduce the spread of mouse sarcomas. Orthodox Chinese medicine has been used to treat diseases for more than 2500 years [70]. China's national clinical merchandise administration (NMPA) has approved a TCM device known as compound Kushen injection (CKI, additionally called Yanshu injection). The substance is extracted from the roots of two medicinal plants, Kushen (*Radix Sophorae flavescens*) and Baituling (*Rhizoma Smilacis glabrae*), using restricted processing methods (GMPs). The primary bioactive alkaloids in CKI are oxymatrine, matrine, oxyphocarpine, and phocarpine [85, 71, 79]. Kushen's anti-tumor efficacy has been tested in advanced clinical trials. CKI inhibits most cancers mobile migration, invasion, and adherence in vitro by promoting apoptosis [11] and inhibits gastric cell growth by lowering the oxidative stress of CD44v6 protein expression [12]. Kushen, as one of CKI's main metabolites, has been shown to have anti-tumor properties in a number of specific cancer cell strains, including breast cancer cells (MCF-7), stomach cancer cells (SGC-7901 and MKN45), gallbladder cancer cells (GBCSD), osteosarcoma tumour cells (UMR-108), and liver cancer cells (HepG2) [71, 64]. Kushen injection can suppress cells such as breast cancer by reducing the pathway Wnt / beta - catenin in mice [79].

Kushen injection inhibited MCF-7 in vitro cancer cell proliferation by disrupting the cell cycle and inducing apoptosis in a dose-dependent manner [51]. In vitro experiments have also shown that it has analgesic, hemostatic, anti-pressure, and overall performance-enhancing properties [79]. CKI has been used in hospitals for over two decades to treat healthy tissues such as liver cancer, lung cancer, breast cancer, stomach cancer, colon cancer, and other cancers [71, 79, 81, 42, 68]. CKI has been shown to be effective in the treatment of cancer-related pain by activating a V-1 family transient cation channel [85]. Previous research has shown that CKI increases antitumor performance and reduces side effects when used alone or in conjunction with conventional chemotherapy. Chemical toxicity is decreasing, and health-friendly practices are being implemented [85, 81, 42, 68]. CKI increases the efficiency of HCC. TACE has been shown to be beneficial in the treatment of chronic liver cancers [19, 84, 42]. The effect of CKI on plant defense, as well as the mechanism underlying it, is unknown. Given the differences in immunotherapeutic movement (microenvlo-targeted) and chemotherapy (tumour cell-focused), demonstrating the efficacy of combining CKI with chemotherapy to treat HCC is important. The primary aim of modern pharmacology is to explain the molecular pathways that can be diagnosed using clinical computers. One-dimensional TCM components can be useful in a few cases, but they are limited in terms of determining included device effects

from a multi-aspect framework. Furthermore, previous research attempting to identify the CKI mechanism focused solely on the demonstration of main regulators in a single or a few cell ways. As a result, use of complete, textual content analysis was used to examine a wide range of device molecules based on TCM. We identified a large number of proposed genes disrupted by CKI within MCF-7 breast cancer cells and used genetic data to identify cellular pathways that could be targeted by CKI. Our findings indicate that CKI can also alter the expression of several cancer-related genes and lncRNAs, which may be linked to the inhibition of cell proliferation.

Unbiased p53 pathways induce cell cycle binding and apoptosis. CKI inhibits MCF-7 cell invasion and causes them to die. Qu et al. (Qu et al., 2016) used XTT research to determine cell function after treating MCF-7 breast cancer cells with elevated CKI levels in order to demonstrate the effect of CKI on cell proliferation.

MCF-7 cells' proliferation was significantly reduced when exposed to a high dose of CKI (2 mg/mL, based on the total alkaloid concentration in CKI), with a dose-dependent effect (Figure 2). MCF-7 cells were tested for cell apoptosis using an Annexin V/Propidium Iodide (PI) assay after CKI treatment. At both time points, the percentage of apoptotic cells increased, particularly at the higher CKI dose. MCF-7 cells were subjected to an Annexin V/Propidium Iodide (PI) assay to determine cell apoptosis following CKI therapy. The percentage of apoptotic cells increased at both time points when compared to untreated cells, particularly at the higher CKI dose, indicating that apoptosis was induced in CKI-treated cells (Figure 2). CKI-treated cells had increased caspase3/7 activity, according to the caspase3/7 colorimetric assay. CKI inhibited MCF-7 cell growth and induced apoptosis in vitro, according to these results. In a study by Zhao et al., the MVD of the transplanted tumour was significantly decreased (P0.05) as the compound Kushen injection dose was increased, but the VMI was significantly increased (P0.05). MVD can reflect the rates of change in tumour cell and tumour vascular components, whereas VMI can calculate changes in vascular maturation and is a better indicator of microvascular functional status than MVD [85, 32]. As a result, compound Kushen injection will inhibit tumour angiogenesis and thus tumour growth by reducing tumour blood supply. Compound Kushen injection has been shown in some studies to reduce VEGF expression. Since VEGF regulates neovascularization in endothelial cells in tumour blood vessels as a key regulator of angiogenesis, when its levels are poor, angiogenesis is restricted and tumour blood supply is reduced, inhibiting cell proliferation [7]. To summarize, Kushen was discovered to suppress angiogenesis in tumour tissues. The fact that angiogenesis is the primary factor in tumour growth inhibition aids Kushen's anti-cancer effect. As a consequence, anti-angiogenesis may be one of the primary mechanisms by which compound Kushen injection slows tumour development.

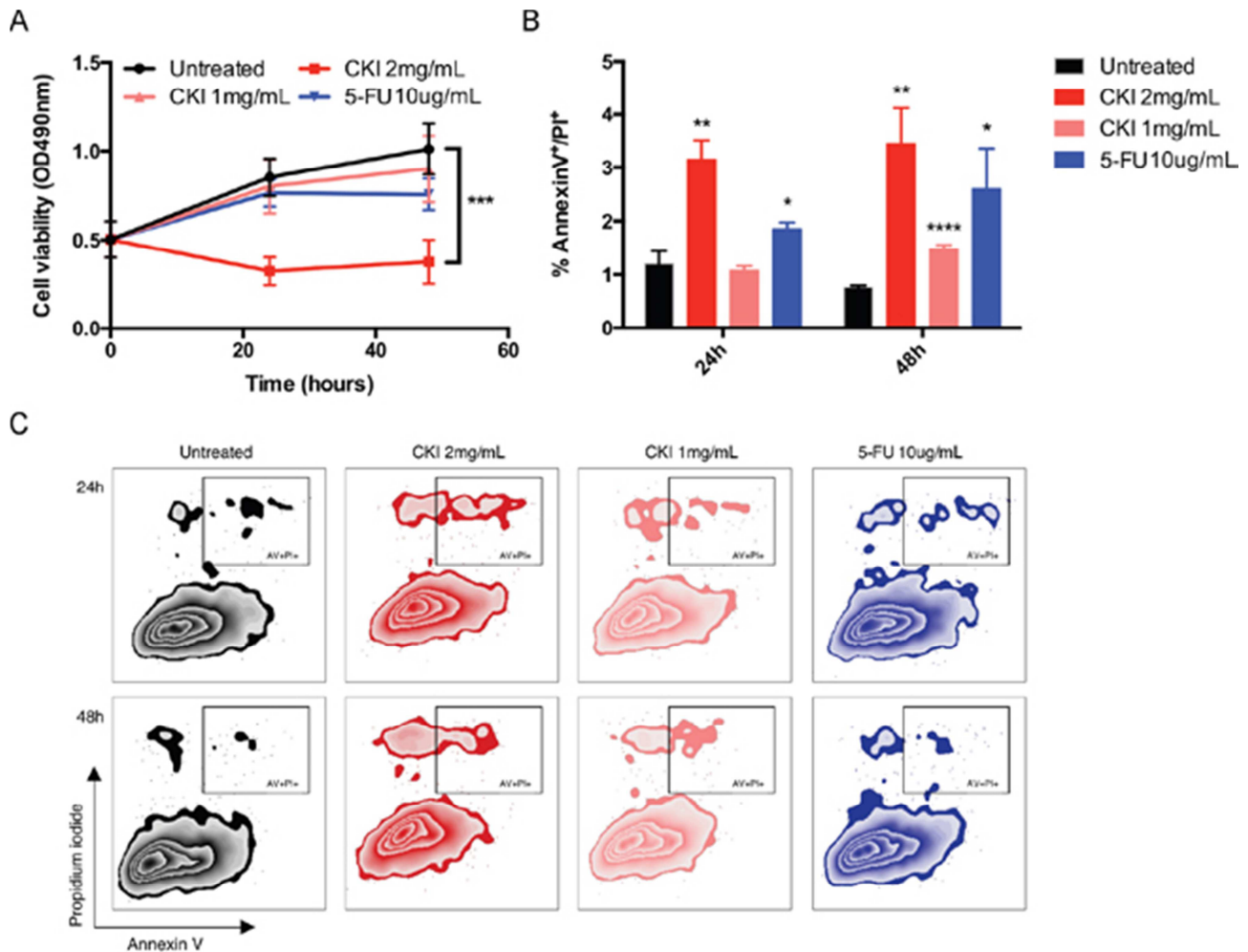


Figure 2. A: CKI treatment stops MCF-7 cells from proliferating. XTT: PMS was used to assess cell viability in response to various treatments. The data is presented as a mean + standard error of the mean (n=6) [10]. B and C: CKI treatment causes MCF-7 cells to go into apoptosis. The percentage of Annexin V+/PI+ cells and representative plots of Annexin V and PI staining were used to determine the level of apoptosis: B) Percentages of Annexin V+/PI+ cells, and C) representative plots of Annexin V and PI staining. The data is presented as a mean + standard error of the mean (n=6). A) two-way ANOVA or B) t-test comparing with "untreated" (*p0.05, **p0.01, ***p0.0001) were used for statistical analyses. [10].

(Qu et al., 2016)

Qu, Z., Cui, J., Harata-Lee, Y., Aung, T. N., Feng, Q., Raison, J. M., Kortschak, R. D. and Adelson, D. L. (2016). Identification of candidate anti-cancer molecular mechanisms of Compound Kushen Injection using functional genomics. *Oncotarget*, [online] 7 (40), pp. 66003–66019. Available at: <https://www.oncotarget.com/article/11788/text/> [Accessed 5 Mar. 2021].

3. Methods

This was qualitative research, and it was carried out using detailed research available in digital libraries. An independent viewer conducted a systematic literature review in February 2021, using directories such as PubMed, NIH, Hindawi, Oncomed, Chinese Biomedical Literature Database, and others. Each definition was combined with topic heading searches, the search was limited to clinical trials. The quest was restricted to oxysophocarpine and oxysophocarpine-containing compounds, such as the Kushen injection, and their role in cancer-related pain relief and the removal of cancer cell lines, specifically endometrial cancer and HEC-1B cells. The evaluator also conceptually analyzed the results

to exclude any apparent unimportant publications, as well as checking the Medline database of the selected studies for additional related posts.

4. Conclusions

Anti-angiogenic therapy is a treatment that aims to prevent or delay the development of new blood vessels in diseased tissues. Angiogenic antimicrobials commonly used in clinical trials, such as bevacizumab, recombinant human endostatin injection, and imatinib, have shown a wide range of effectiveness, providing new hope for medicinal care in plants [48]. In trials, anti-angiogenic therapy combined with surgical procedure, heat therapy, and chemoradiotherapy improved the therapeutic effect [5]. The findings of this study

revealed that raising the dose of Kushen injection reduced the variety of tumor cellular mitotic and vascular proliferation in tumor tissue, halting mobile division and proliferation, suggesting that combined Kushen injection may also have an anti-angiogenesis effect. The compound Kushen injection is usually used to treat cardiovascular diseases as well as viral hepatitis [35]. The side effects of therapy with Kushen include antiviral, antitumor, anti-high blood pressure, coronary heart charge, antipyresis and analgesia, prevention of myocardial ischemia and infarction, asthma relief, anti-arrhythmia, infertility, anti-anti-inflammatory, sedation and hypnosis, and anti-allergic reactions. In the case of oxymatrine, according to latest medical evidence [80, 41]. Furthermore, the mixed Kushen injection has a wide range of antitumor benefits, including hemostasis, analgesia, and immune system modulation, as well as improving antitumor and chemoradiotherapy sensitization and reducing associated chemoradiotherapy side effects [42]. Flavonoids and triterpenes from *Rhizoma Heterosmilacis Japonicae* have potent anti-inflammatory, detoxification, and antitumor properties [20]. In a rat tumour study [69], raising the compound Kushen injection dose resulted in a substantial decrease in tumour mass (P0.05) and an increase in tumour inhibition rate (P0.05), suggesting that the injection of mixed kushen would extensively inhibit the growth of nude mice in a dose-dependent manner. Cell cycle, cell division, cellular replication, and various methods of mobile growth were discovered to be significantly altered in CKI-treated tumour cells. Based on a combination of demonstration records and topologic data of the genes involved in these processes, cell cycle binding appears to be one of the first mechanisms to combat CKI in many instances [10]. There is insufficient evidence to indicate that oxysophocarpine inhibits cancer cell development, specifically endometrial HEC-1B cells. However, research on Kushen injection suggests that oxysophocarpine, in combination with a concoction of other compounds, may have a controlling effect on cancer development. However, there is insufficient evidence and analysis to support the impact on endometrial cancer.

References

- [1] AHILL, H., WILLIAMELEY, J., CHARLAN, L., SGREENBERG, R., JBARRETTII, R. and WCHEN, V. (1996). Racial differences in endometrial cancer survival: The black/white cancer survival study. *Obstetrics & Gynecology*, 88 (6), pp. 919–926.
- [2] Amant, F., Moerman, P., Neven, P., Timmerman, D., Van Limbergen, E. and Vergote, I. (2005). Endometrial cancer. *The Lancet*, [online] 366 (9484), pp. 491–505. Available at: [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(05\)67063-8/references](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(05)67063-8/references) [Accessed 2 Mar. 2021].
- [3] Anzai, Y., Gong, Y., Holinka, C. F., Murphy, L. J., Murphy, L. C., Kuramoto, H. and Gurdip, E. (1992). Effects of transforming growth factors and regulation of their mRNA levels in two human endometrial adenocarcinoma cell lines. *The Journal of Steroid Biochemistry and Molecular Biology*, [online] 42 (5), pp. 449–455. Available at: <https://www.sciencedirect.com/science/article/pii/0960076092902561#> [Accessed 4 Mar. 2021].
- [4] Barrena Medel, N. I., Bansal, S., Miller, D. S., Wright, J. D. and Herzog, T. J. (2009). Pharmacotherapy of endometrial cancer. *Expert Opinion on Pharmacotherapy*, 10 (12), pp. 1939–1951.
- [5] Browder, T., Butterfield, C. E., Kräling, B. M., Shi, B., Marshall, B., O'Reilly, M. S. and Folkman, J. (2000). Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. *Cancer Research*, [online] 60 (7), pp. 1878–1886. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10766175> [Accessed 5 Mar. 2021].
- [6] Calle, E. E. and Kaaks, R. (2004). Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nature Reviews Cancer*, 4 (8), pp. 579–591.
- [7] Carmeliet, P. (2005). VEGF as a Key Mediator of Angiogenesis in Cancer. *Oncology*, 69 (3), pp. 4–10.
- [8] Chen, H., Zhang, J., Luo, J., Lai, F., Wang, Z., Tong, H., Lu, D., Bu, H., Zhang, R. and Lin, S. (2013a). Antiangiogenic effects of oxymatrine on pancreatic cancer by inhibition of the NF- κ B-mediated VEGF signaling pathway. *Oncology Reports*, [online] 30 (2), pp. 589–595. Available at: <https://pubmed.ncbi.nlm.nih.gov/23754270/> [Accessed 5 Mar. 2021].
- [9] Chen, K., Zhang, S., Ji, Y., Li, J., An, P., Ren, H., Liang, R., Yang, J. and Li, Z. (2013b). Baicalein Inhibits the Invasion and Metastatic Capabilities of Hepatocellular Carcinoma Cells via Down-Regulation of the ERK Pathway. *PLoS ONE*, 8 (9), p. e72927.
- [10] Cui, J., Qu, Z., Harata-Lee, Y., Shen, H., Aung, T. N., Wang, W., Kortschak, R. D. and Adelson, D. L. (2020). The effect of compound kushen injection on cancer cells: Integrated identification of candidate molecular mechanisms. *PLOS ONE*, 15 (7), p. e0236395.
- [11] Dai, Z., Gao, J., Wu, W., Wang, X., Li, Z., Kang, H., Liu, X. and Ma, X. (2007). [Effect of matrine injections on invasion and metastasis of gastric carcinoma SGC-7901 cells in vitro]. *Zhong Yao Cai = Zhongyaocai = Journal of Chinese Medicinal Materials*, [online] 30 (7), pp. 815–819. Available at: <https://pubmed.ncbi.nlm.nih.gov/17944193/> [Accessed 8 Mar. 2021].
- [12] Dai, Z.-J., Gao, J., Wang, X.-J., Ji, Z.-Z., Wu, W.-Y., Liu, X.-X., Kang, H.-F., Guan, H.-T. and Ren, H.-T. (2008). [Apoptotic mechanism of gastric carcinoma cells induced by matrine injection]. *Zhonghua Wei Chang Wai Ke Za Zhi = Chinese Journal of Gastrointestinal Surgery*, [online] 11 (3), pp. 261–265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18478473> [Accessed 8 Mar. 2021].
- [13] Escobedo, L. G., Lee, N. C., Peterson, H. B. and Wingo, P. A. (1991). Infertility-associated endometrial cancer risk may be limited to specific subgroups of infertile women. *Obstetrics and Gynecology*, [online] 77 (1), pp. 124–128. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1984211> [Accessed 2 Mar. 2021].
- [14] Europe PMC (2016). *Europe PMC*. [online] Europepmc.org. Available at: <https://europepmc.org/article/med/26015570> [Accessed 5 Mar. 2021].

- [15] Eycken E, V. (2000). *Seminar*. [online]. Available at: <https://lirias.kuleuven.be/retrieve/15667> [Accessed 2 Mar. 2021].
- [16] Fathalla, M. F. (1971). Incessant ovulation--a factor in ovarian neoplasia? *Lancet (London, England)*, [online] 2 (7716), p. 163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/4104488> [Accessed 16 Aug. 2019].
- [17] Ferlay, J., Colombet, M., Soerjomataram, I., Mathers, C., Parkin, D. M., Piñeros, M., Znaor, A. and Bray, F. (2018). Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *International Journal of Cancer*.
- [18] Folkins, A. K., Jarboe, E. A., Saleemuddin, A., Lee, Y., Callahan, M. J., Drapkin, R., Garber, J. E., Muto, M. G., Tworoger, S. and Crum, C. P. (2008). A candidate precursor to pelvic serous cancer (p53 signature) and its prevalence in ovaries and fallopian tubes from women with BRCA mutations. *Gynecologic Oncology*, 109 (2), pp. 168–173.
- [19] Gao, L., Wang, K., Zhou, Y., Fang, J., Qin, X. and Du, G. (2018). Uncovering the anticancer mechanism of Compound Kushen Injection against HCC by integrating quantitative analysis, network analysis and experimental validation. *Scientific Reports*, [online] 8 (1), p. 624. Available at: <https://www.nature.com/articles/s41598-017-18325-7> [Accessed 5 Mar. 2021].
- [20] Guo, Y., Huang, Y., Shen, H., Sang, X., Ma, X., Zhao, Y. and Xiao, X. (2015). Efficacy of Compound Kushen Injection in Relieving Cancer-Related Pain: A Systematic Review and Meta-Analysis. *Evidence-Based Complementary and Alternative Medicine*, 2015, pp. 1–8.
- [21] HACKER, NF (2021). *Uterine cancer*. [online] Practical gynecologic oncology. Available at: <https://ci.nii.ac.jp/naid/10020572096/> [Accessed 2 Mar. 2021].
- [22] Harada K, Scanning electron microscopic studies on the cell surface and cell synchronized culture of human endometrial adenocarcinoma (HEC-1) cells. *Acta Obst Gynae Jpn*, 1987; 39: 531-538 Search Results Web results.
- [23] Holinka, C. F., Hata, H., Kuramoto, H. and Gurpide, E. (1986). Responses to estradiol in a human endometrial adenocarcinoma cell line (Ishikawa). *Journal of Steroid Biochemistry*, [online] 24 (1), pp. 85–89. Available at: <https://pubmed.ncbi.nlm.nih.gov/3702430/> [Accessed 3 Mar. 2021].
- [24] Jemal, A., Siegel, R., Ward, E., Murray, T., Xu, J., Smigal, C. and Thun, M. J. (2006). Cancer Statistics, 2006. *CA: A Cancer Journal for Clinicians*, 56 (2), pp. 106–130.
- [25] Karahan, N., Güney, M., Baspınar, S., Oral, B., Kapucuoglu, N. and Mungan, T. (2007). Expression of gelatinase (MMP-2 and MMP-9) and cyclooxygenase-2 (COX-2) in endometrial carcinoma. *European Journal of Gynaecological Oncology*, [online] 28 (3), pp. 184–188. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17624083> [Accessed 5 Mar. 2021].
- [26] Kitchener, H. C. and Trimble, E. L. (2009). Endometrial Cancer State of the Science Meeting. *International Journal of Gynecologic Cancer*, [online] 19 (1). Available at: <https://ijgc.bmj.com/content/19/1/134.abstract> [Accessed 5 Mar. 2021].
- [27] Kuramoto, H. (1972). Studies of the growth and cytogenetic properties of human endometrial adenocarcinoma in culture and its development into an established line. *Acta Obstetrica Et Gynaecologica Japonica*, [online] 19 (1), pp. 47–58. Available at: <https://pubmed.ncbi.nlm.nih.gov/4678779/> [Accessed 3 Mar. 2021].
- [28] Kuramoto H & Suzuki K: Effects of progesterone on the growth kinetics and the morphology of a human endometrial cancer cell-line. *Act Obstet Gynaec Jpn*, 1976; 23: 123-32.
- [29] Kuramoto, H., Hamano, M. and Imai, M. (2002). HEC-1 cells. *Human Cell*, [online] 15 (2), pp. 81–95. Available at: <http://link.springer.com/content/pdf/10.1111%2Fj.1749-0774.2002.tb00103.x.pdf> [Accessed 3 Mar. 2021].
- [30] Kuramoto, H., Tamura, S. and Notake, Y. (1972). Establishment of a cell line of human endometrial adenocarcinoma in vitro. *American Journal of Obstetrics and Gynecology*, [online] 114 (8), pp. 1012–1019. Available at: <https://pubmed.ncbi.nlm.nih.gov/4673779/> [Accessed 3 Mar. 2021].
- [31] Le Bars, D., Gozariu, M. and Cadden, S. W. (2001). Animal models of nociception. *Pharmacological Reviews*, [online] 53 (4), pp. 597–652. Available at: <https://pubmed.ncbi.nlm.nih.gov/11734620/> [Accessed 2 Mar. 2021].
- [32] Lee, C. (2000). Angiogenesis of endometrial carcinomas assessed by measurement of intratumoral blood flow, microvessel density, and vascular endothelial growth factor levels. *Obstetrics & Gynecology*, 96 (4), pp. 615–621.
- [33] Lee, Y., Miron, A., Drapkin, R., Nucci, M., Medeiros, F., Saleemuddin, A., Garber, J., Birch, C., Mou, H., Gordon, R., Cramer, D., McKeon, F. and Crum, C. (2006). A candidate precursor to serous carcinoma that originates in the distal fallopian tube. *The Journal of Pathology*, 211 (1), pp. 26–35.
- [34] Leitzmann, M. F., Koebnick, C., Danforth, K. N., Brinton, L. A., Moore, S. C., Hollenbeck, A. R., Schatzkin, A. and Lacey, J. V. (2009). Body mass index and risk of ovarian cancer. *Cancer*, 115 (4), pp. 812–822.
- [35] Ling, Q., Xu, X., Wei, X., Wang, W., Zhou, B., Wang, B. and Zheng, S. (2011). Oxymatrine induces human pancreatic cancer PANC-1 cells apoptosis via regulating expression of Bcl-2 and IAP families, and releasing of cytochrome c. *Journal of Experimental & Clinical Cancer Research*, [online] 30 (1), p. 66. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3141557/> [Accessed 3 Nov. 2019].
- [36] Li ZHR: The pharmaceutical effect and clinical development of kushenin. *West China J Pharm Sci* 18: 435-437, 2003 Li ZHR.
- [37] Luoto, R., Raitanen, J., Pukkala, E. and Anttila, A. (2004). Effect of hysterectomy on incidence trends of endometrial and cervical cancer in Finland 1953–2010. *British Journal of Cancer*, [online] 90 (9), pp. 1756–1759. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2409756/> [Accessed 2 Mar. 2021].
- [38] LYONS, R. M. and MOSES, H. L. (1990). Transforming growth factors and the regulation of cell proliferation. *European Journal of Biochemistry*, 187 (3), pp. 467–473.
- [39] Madison, T., Schottenfeld, D., James, S. A., Schwartz, A. G. and Gruber, S. B. (2004). Endometrial Cancer: Socioeconomic Status and Racial/Ethnic Differences in Stage at Diagnosis, Treatment, and Survival. *American Journal of Public Health*, 94 (12), pp. 2104–2111.

- [40] Malcangio, M. and Bowery, N. G. (1996). GABA and its receptors in the spinal cord. *Trends in Pharmacological Sciences*, [online] 17 (12), pp. 457–462. Available at: <https://pubmed.ncbi.nlm.nih.gov/9014500/> [Accessed 2 Mar. 2021].
- [41] Malhotra, J., Jabbour, S. K. and Aisner, J. (2017). Erratum to current state of immunotherapy for non-small cell lung cancer. *Translational Lung Cancer Research*, 6 (5), pp. 612–612.
- [42] Ma, X., Li, R.-S., Wang, J., Huang, Y.-Q., Li, P.-Y., Wang, J., Su, H.-B., Wang, R.-L., Zhang, Y.-M., Liu, H.-H., Zhang, C.-E., Ma, Z.-J., Wang, J.-B., Zhao, Y.-L. and Xiao, X.-H. (2016). The Therapeutic Efficacy and Safety of Compound Kushen Injection Combined with Transarterial Chemoembolization in Unresectable Hepatocellular Carcinoma: An Update Systematic Review and Meta-Analysis. *Frontiers in Pharmacology*, [online] 7, p. 70. Available at: <https://pubmed.ncbi.nlm.nih.gov/27065861/> [Accessed 5 Mar. 2021].
- [43] McPherson, C. P., Sellers, T. A., Potter, J. D., Bostick, R. M. and Folsom, A. R. (1996). Reproductive factors and risk of endometrial cancer. The Iowa Women's Health Study. *American Journal of Epidemiology*, [online] 143 (12), pp. 1195–1202. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8651218/> [Accessed 2 Mar. 2021].
- [44] Millan, M. J. (2002). Descending control of pain. *Progress in Neurobiology*, 66 (6), pp. 355–474.
- [45] Moses, H. L., Yang, E. Y. and Pietenpol, J. A. (1990). TGF-beta stimulation and inhibition of cell proliferation: new mechanistic insights. *Cell*, [online] 63 (2), pp. 245–247. Available at: <https://pubmed.ncbi.nlm.nih.gov/2208284/> [Accessed 4 Mar. 2021].
- [46] Nishida, M., Kasahara, K., Kaneko, M., Iwasaki, H. and Hayashi, K. (1985). [Establishment of a new human endometrial adenocarcinoma cell line, Ishikawa cells, containing estrogen and progesterone receptors]. *Nihon Sanka Fujinka Gakkai Zasshi*, [online] 37 (7), pp. 1103–1111. Available at: <https://pubmed.ncbi.nlm.nih.gov/4031568/> [Accessed 3 Mar. 2021].
- [47] Noumoff J, Haydock SW, Sachdeva R, Heyner S & Prichard ML: Characteristics of cell lines derived from normal and malignant endometrium. *Gynecol Oncol*, 1987; 27: 141-149.
- [48] Olaso, E. and Vidal-Vanaclocha, F. (2003). Use of tumor-activated hepatic stellate cell as a target for the preclinical testing of anti-angiogenic drugs against hepatic tumor development. *Methods in Molecular Medicine*, [online] 85, pp. 79–86. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12710199> [Accessed 5 Mar. 2021].
- [49] Parkin, D. M., Pisani, P. and Ferlay, J. (1999). Global cancer statistics. *CA: A Cancer Journal for Clinicians*, 49 (1), pp. 33–64.
- [50] Prensner, J. R., Iyer, M. K., Balbin, O. A., Dhanasekaran, S. M., Cao, Q., Brenner, J. C., Laxman, B., Asangani, I., Grasso, C., Kominsky, H. D., Cao, X., Jing, X., Wang, X., Siddiqui, J., Wei, J. T., Robinson, D., Iyer, H. K., Palanisamy, N., Maher, C. A. and Chinnaiyan, A. M. (2011). Transcriptome Sequencing Identifies PCAT-1, a Novel lincRNA Implicated in Prostate Cancer Progression. *Nature biotechnology*, [online] 29 (8), pp. 742–749. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3152676/> [Accessed 10 Feb. 2021].
- [51] Qu, Z., Cui, J., Harata-Lee, Y., Aung, T. N., Feng, Q., Raison, J. M., Kortschak, R. D. and Adelson, D. L. (2016). Identification of candidate anti-cancer molecular mechanisms of Compound Kushen Injection using functional genomics. *Oncotarget*, [online] 7 (40), pp. 66003–66019. Available at: <https://www.oncotarget.com/article/11788/text/> [Accessed 5 Mar. 2021].
- [52] Rodrigues, A. L. S., da Silva, G. L., Mateussi, A. S., Fernandes, E. S., Miguel, O. G., Yunes, R. A., Calixto, J. B. and Santos, A. R. S. (2002). Involvement of monoaminergic system in the antidepressant-like effect of the hydroalcoholic extract of *Siphocampylus verticillatus*. *Life Sciences*, 70 (12), pp. 1347–1358.
- [53] Satyaswaroop, P. G., Fleming, H., Bressler, R. S. and Gurpide, E. (1978). Human Endometrial Cancer Cell Cultures for Hormonal Studies. *Cancer Research*, [online] 38 (11 Part 2), pp. 4367–4375. Available at: https://cancerres.aacrjournals.org/content/38/11_Part_2/4367.short [Accessed 4 Mar. 2021].
- [54] SCHILDKRAUT, J. (1996). Epithelial Ovarian Cancer Risk Among Women With Polycystic Ovary Syndrome. *Obstetrics & Gynecology*, 88 (4), pp. 554–559.
- [55] Schildkraut, J. M., Bastos, E. and Berchuck, A. (1997). Relationship Between Lifetime Ovulatory Cycles and Overexpression of Mutant p53 in 932 Epithelial Ovarian Cancer. *JNCI Journal of the National Cancer Institute*, 89 (13), pp. 932–938.
- [56] Schouten, L. J., Goldbohm, R. A. and van den Brandt, P. A. (2004). Anthropometry, Physical Activity, and Endometrial Cancer Risk: Results from The Netherlands Cohort Study. *JNCI Journal of the National Cancer Institute*, 96 (21), pp. 1635–1638.
- [57] Schouten, L. J., Rivera, C., Hunter, D. J., Spiegelman, D., Adami, H. O., Arslan, A., Beeson, W. L., Brandt, P. A. van den, Buring, J. E., Folsom, A. R., Fraser, G. E., Freudenheim, J. L., Goldbohm, R. A., Hankinson, S. E., Lacey, J. V., Leitzmann, M., Lukanova, A., Marshall, J. R., Miller, A. B. and Patel, A. V. (2008). Height, Body Mass Index, and Ovarian Cancer: A Pooled Analysis of 12 Cohort Studies. *Cancer Epidemiology and Prevention Biomarkers*, [online] 17 (4), pp. 902–912. Available at: <https://cebp.aacrjournals.org/content/17/4/902.short> [Accessed 5 Feb. 2021].
- [58] SEER. (2005). *SEER Cancer Statistics Review 1975-2005 - Previous Version - SEER Cancer Statistics*. [online] Available at: http://seer.cancer.gov/csr/1975_2005/ [Accessed 2 Mar. 2021].
- [59] SEER. (2018). *Surveillance, Epidemiology, and End Results Program*. [online] Available at: <https://seer.cancer.gov/>.
- [60] Sekiya, S. and Takamizawa, H. (1981). [Effect of anticancer drugs on in vitro survival of cell lines derived from various gynecologic tumors (author's transl)]. *Acta Obstetrica Et Gynaecologica Japonica*, [online] 33 (3), pp. 373–376. Available at: <https://pubmed.ncbi.nlm.nih.gov/6163305/> [Accessed 3 Mar. 2021].
- [61] Smith, R. A., Cokkinides, V. and Eyre, H. J. (2003). American Cancer Society Guidelines for the Early Detection of Cancer, 2003. *CA: A Cancer Journal for Clinicians*, 53 (1), pp. 27–43.

- [62] Sporn, M. B. and Roberts, A. B. (1990). TGF-beta: problems and prospects. *Cell Regulation*, 1 (12), pp. 875–882. Available at: <https://pubmed.ncbi.nlm.nih.gov/25982630/>.
- [63] Stoscheck, C. M. and King, L. E. (1986). Role of epidermal growth factor in carcinogenesis. *Cancer Research*, [online] 46 (3), pp. 1030–1037. Available at: <https://pubmed.ncbi.nlm.nih.gov/3002608/> [Accessed 4 Mar. 2021].
- [64] Sun, M., Cao, H., Sun, L., Dong, S., Bian, Y., Han, J., Zhang, L., Ren, S., Hu, Y., Liu, C., Xu, L. and Liu, P. (2012). *Antitumor Activities of Kushen: Literature Review*. [online] Evidence-Based Complementary and Alternative Medicine. Available at: <https://www.hindawi.com/journals/ecam/2012/373219/> [Accessed 8 Mar. 2021].
- [65] Thomsen, M., Wörtwein, G., Olesen, M. V., Begtrup, M., Havez, S., Bolwig, T. G. and Woldbye, D. P. D. (2007). Involvement of Y (5) receptors in neuropeptide Y agonist-induced analgesic-like effect in the rat hot plate test. *Brain Research*, [online] 1155, pp. 49–55. Available at: <https://pubmed.ncbi.nlm.nih.gov/17498669/> [Accessed 2 Mar. 2021].
- [66] Tianyou Liu, Song, Y., Hua Chen, Shangha Pan and Sun, X. (2019). *Matrine inhibits proliferation and induces apoptosis of pancreatic cancer cells in vitro and in vivo*. [online] Unboundmedicine.com. Available at: https://www.ncbi.nlm.nih.gov/pubmed/303385/Matrine_inhibits_proliferation_and_induces_apoptosis_of_pancreatic_cancer_cells_in_vitro_and_in_vivo [Accessed 5 Mar. 2021].
- [67] TRENTIN, A. P., SANTOS, A. R. S., MIGUEL, O. G., PIZZOLATTI, M. G., YUNES, R. A. and CALIXTO, Jo. B. (1997). Mechanisms Involved in the Antinociceptive Effect in Mice of the Hydroalcoholic Extract of *Siphocampylus verticillatus*. *Journal of Pharmacy and Pharmacology*, 49 (5), pp. 567–572.
- [68] Tu, H., Lei, B., Meng, S., Liu, H., Wei, Y., He, A., Zhang, W. and Zhou, F. (2016). Efficacy of Compound Kushen Injection in Combination with Induction Chemotherapy for Treating Adult Patients Newly Diagnosed with Acute Leukemia. *Evidence-based Complementary and Alternative Medicine: eCAM*, [online] 2016. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5050378/> [Accessed 5 Mar. 2021].
- [69] Wang, H., Hu, H., Rong, H. and Zhao, X. (2019). Effects of compound Kushen injection on pathology and angiogenesis of tumor tissues. *Oncology Letters*, [online] 17 (2), pp. 2278–2282. Available at: <https://www.spandidos-publications.com/ol/17/2/2278#> [Accessed 5 Mar. 2021].
- [70] Wang, L., Zhou, G.-B., Liu, P., Song, J.-H., Liang, Y., Yan, X.-J., Xu, F., Wang, B.-S., Mao, J.-H., Shen, Z.-X., Chen, S.-J. and Chen, Z. (2008). Dissection of mechanisms of Chinese medicinal formula Realgar-Indigo naturalis as an effective treatment for promyelocytic leukemia. *Proceedings of the National Academy of Sciences of the United States of America*, [online] 105 (12), pp. 4826–4831. Available at: <https://pubmed.ncbi.nlm.nih.gov/18344322/> [Accessed 5 Mar. 2021].
- [71] Wang, W., You, R., Qin, W., Hai, L., Fang, M., Huang, G., Kang, R., Li, M., Qiao, Y., Li, J. and Li, A. (2015). Antitumor activities of active ingredients in Compound Kushen Injection. *Acta Pharmacologica Sinica*, [online] 36 (6), pp. 676–679. Available at: <https://pubmed.ncbi.nlm.nih.gov/25982630/>.
- [72] Wang XH, Huang SK and Lin P: Pharmacokinetics and pharmacodynamics of sophocarpine and oxysophocarpine. *J China Pharm Univ* 23: 161-164, 1992.
- [73] Wang, X., Liu, J., Lin, H. and Hou, W. (2016). A multicenter randomized controlled open-label trial to assess the efficacy of compound kushen injection in combination with single-agent chemotherapy in treatment of elderly patients with advanced non-small cell lung cancer: study protocol for a randomized controlled trial. *Trials*, 17 (1).
- [74] Weigel, M. T., Krämer, J., Schem, C., Wengers, A., Alkatout, I., Jonat, W., Maass, N. and Mundhenke, C. (2012). Differential expression of MMP-2, MMP-9 and PCNA in endometriosis and endometrial carcinoma. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, [online] 160 (1), pp. 74–78. Available at: <https://www.sciencedirect.com/science/article/pii/S0301211511005598> [Accessed 5 Mar. 2021].
- [75] White, N. M., Cabanski, C. R., Silva-Fisher, J. M., Dang, H. X., Govindan, R. and Maher, C. A. (2014). Transcriptome sequencing reveals altered long intergenic non-coding RNAs in lung cancer. *Genome Biology*, 15 (8).
- [76] Wild, S., Pierpoint, T., Jacobs, H. and McKeigue, P. (2000). Long-term consequences of polycystic ovary syndrome: Results of a 31 year follow-up study. *Human Fertility*, 3 (2), pp. 101–105.
- [77] www.cancer.org. (2008). *Cancer Facts & Figures 2008* | American Cancer Society. [online] Available at: <https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2008.html#:~:text=About%201%2C437%2C180%20new%20cancer%20cases> [Accessed 2 Mar. 2021].
- [78] XU, T., LI, Y., WANG, H., XU, Y., MA, L., SUN, T., MA, H. and YU, J. (2013). Oxysophocarpine induces anti-nociception and increases the expression of GABAA α 1 receptors in mice. *Molecular Medicine Reports*, 7 (6), pp. 1819–1825.
- [79] Xu, W., Lin, H., Zhang, Y., Chen, X., Hua, B., Hou, W., Qi, X., Pei, Y., Zhu, X., Zhao, Z. and Yang, L. (2011). Compound Kushen Injection suppresses human breast cancer stem-like cells by down-regulating the canonical Wnt/ β -catenin pathway. *Journal of Experimental & Clinical Cancer Research: CR*, [online] 30 (1), p. 103. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3219673/> [Accessed 5 Mar. 2021].
- [80] Yong-gang, C., Shan, J., Lei, L., Jing-quan, G., Zhi-ying, S., Yan, L., Yan, X., Ming-li, W., Ye, W., Chang-qing, X. and Hong-li, S. (2010). Antiarrhythmic effects and ionic mechanisms of oxymatrine from *Sophora flavescens*. *Phytotherapy Research*, 24 (12), pp. 1844–1849.
- [81] Young, R. H. and Clement, P. B. (2002). Endocervical adenocarcinoma and its variants: their morphology and differential diagnosis. *Histopathology*, 41 (3), pp. 185–207.
- [82] Yu, L., Zhou, Y., Yang, Y., Lu, F. and Fan, Y. (2017). *Efficacy and Safety of Compound Kushen Injection on Patients with Advanced Colon Cancer: A Meta-Analysis of Randomized Controlled Trials*. [online] Evidence-Based Complementary and Alternative Medicine. Available at: <https://www.hindawi.com/journals/ecam/2017/7102514/> [Accessed 5 Mar. 2021].

- [83] Yu, P., Liu, Q., Liu, K., Yagasaki, K., Wu, E. and Zhang, G. (2009). Matrine suppresses breast cancer cell proliferation and invasion via VEGF-Akt-NF- κ B signaling. *Cytotechnology*, 59 (3), pp. 219–229.
- [84] Zaino, R. J., Kurman, R. J., Brunetto, V. L., Morrow, C. P., Bentley, R. C., Cappellari, J. O. and Bitterman, P. (1998). Villoglandular adenocarcinoma of the endometrium: a clinicopathologic study of 61 cases: a gynecologic oncology group study. *The American Journal of Surgical Pathology*, [online] 22 (11), pp. 1379–1385. Available at: <https://pubmed.ncbi.nlm.nih.gov/9808130/> [Accessed 2 Mar. 2021].
- [85] Zhang, Y., Hui, F., Yang, Y., Chu, H., Qin, X., Zhao, M. and Zhao, Q. (2017). Can Kushen injection combined with TACE improve therapeutic efficacy and safety in patients with advanced HCC? a systematic review and network meta-analysis. *Oncotarget*, [online] 8 (63), pp. 107258–107272. Available at: <https://www.oncotarget.com/article/20921/text/> [Accessed 5 Mar. 2021].
- [86] Zhao, Z., Fan, H., Higgins, T., Qi, J., Haines, D., Trivett, A., Oppenheim, J. J., Wei, H., Li, J., Lin, H. and Howard, O. M. Z. (2014). Fufang Kushen injection inhibits sarcoma growth and tumor-induced hyperalgesia via TRPV1 signaling pathways. *Cancer Letters*, [online] 355 (2), pp. 232–241. Available at: <https://pubmed.ncbi.nlm.nih.gov/25242356/> [Accessed 5 Mar. 2021].
- [87] Zhao, Z., Liao, H. and Ju, Y. (2016). Effect of compound Kushen injection on T-cell subgroups and natural killer cells in patients with locally advanced non-small-cell lung cancer treated with concomitant radiochemotherapy. *Journal of Traditional Chinese Medicine = Chung I Tsa Chih Ying Wen Pan*, [online] 36 (1), pp. 14–18. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26946613> [Accessed 5 Mar. 2021].