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(REVIEW ARTICLE)

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Herbal medicine exhibiting cell cycle arrest: A short review

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Abstract

Cancer treatment often involves the use of chemotherapy, which can have significant side effects. Herbal medicines have been used for centuries and have shown potential as sources of new therapeutic agents. This review explores the role of specific herbal medicines, such as ginseng, curcumin, berberine, epigallocatechin gallate (EGCG), and quercetin, in inducing cell cycle arrest, a mechanism that controls cell proliferation. The review discusses the molecular mechanisms underlying these effects, their potential in combination with chemotherapy, and their implications for clinical application in cancer therapy. The combination of herbal medicines with conventional chemotherapeutic agents can result in synergistic effects that enhance therapeutic efficacy. However, there are challenges in terms of standardization, safety evaluation, and the need for more research to understand the molecular mechanisms and optimize treatment protocols. With further investigation and clinical validation, herbal-drug combination therapies could have a significant impact on cancer treatment.

Keywords: Herbal medicine; Cell cycle arrest; Cancer; Ginseng; Curcumin; Berberine; Epigallocatechin gallate; Quercetin

1. Introduction

Cancer is a complex disease that demands a variety of treatment approaches. Systemic therapies utilizing FDA-approved drugs continue to be the primary treatment methods for metastatic cancers. One of the primary drawbacks of chemotherapy is the occurrence of significant side effects that often accompany treatment. Chemotherapeutic drugs primarily focus on damaging the DNA of cells, which can lead to various side effects. Rapidly dividing cells, such as the bone marrow, hair follicles, and the mucosa of the gastrointestinal (GI) tract, commonly experience these side effects[1]. Natural sources have derived over 60% of the anticancer agents currently in use. This strongly suggests that natural compounds hold enormous potential as sources for new "lead compounds" or potential therapeutic agents.

Herbal medicine has been used for centuries across various cultures for treating a wide array of diseases. Cell cycle arrest is a fundamental mechanism by which cellular proliferation can be controlled, particularly in cancer therapy[2]. In recent years, there has been a growing interest in the role of herbal compounds in cancer therapy, particularly in their ability to induce cell cycle arrest. The cell cycle is a highly regulated process that controls cell growth and division. Disruptions in this cycle can lead to uncontrolled cell proliferation, a hallmark of cancer. This process can be triggered by various agents, including chemical compounds found in herbal medicines. Consequently, agents that can induce cell cycle arrest are of significant interest in cancer research. This review explores the role of specific herbal medicines—such as ginseng, curcumin, berberine, epigallocatechin gallate (EGCG), and quercetin—in inducing cell cycle arrest. We examine the molecular mechanisms underlying these effects, discuss their potential when used in combination with chemotherapy, and consider the implications for clinical application in cancer therapy. This review seeks to provide a

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thorough analysis of the latest evidence regarding the herbal medicine exhibiting cell cycle arrest there by its use in cancer treatment alone or in combination with conventional treatments.

2. Methods

2.1. Search Strategy

A thorough literature search was conducted across databases including PubMed, Scopus, and Web of Science. The search spanned publications from 2000 to 2024 to ensure the inclusion of recent and relevant studies. Keywords used included "herbal medicine," "cell cycle arrest," "cancer therapy," and "chemo-herbal combination." The search targeted studies focusing on the molecular mechanisms by which these herbal medicines induce cell cycle arrest and their potential synergy with conventional chemotherapeutic agents.

2.2. Inclusion Criteria

- Investigated the effects of herbal medicines on cell cycle arrest in cancer cells.
- Detailed molecular pathways and mechanisms involved in these effects.
- Provided in vitro, in vivo, or clinical evidence of the efficacy of these herbal compounds, particularly in combination with chemotherapeutic agents.

2.3. Exclusion criteria

- Studies that did not focus specifically on cell cycle arrest mechanisms.
- Review articles or meta-analyses that lacked original data on molecular mechanisms.
- Studies concentrating solely on the pharmacokinetics of herbal compounds without exploring their therapeutic implications.

2.4. Data Extraction and Analysis

Data from the selected studies were systematically extracted and analyzed to identify key themes, mechanisms, and outcomes. The focus was on understanding how these herbal medicines induce cell cycle arrest, their interactions with chemotherapeutic agents, and the challenges and opportunities in integrating them into clinical practice.

3. Results

3.1. Ginseng and Ginsenosides in Cell Cycle Arrest

Ginseng, particularly Panax ginseng (Withania somnifera; Sanskrit: 'Ashwagandha') is a well-known herb in traditional medicine systems, particularly in Asia. The bioactive constituents of ginseng are known as ginsenosides, with panaxadiol being one of the key compounds. Ginsenosides have demonstrated significant antiproliferative effects, especially when used in combination with 5-fluorouracil (5-FU), a common chemotherapeutic agent. In gastric cancer cells, panaxadiol induces G1 phase arrest, while 5-FU affects cells in the S and G2/M phases, leading to enhanced efficacy in inhibiting cell proliferation[3]. The combination also results in increased nitric oxide production, which further contributes to cell cycle arrest through the regulation of the Akt signaling pathway[3]. Moreover, ginsenoside Rg3 has been shown to downregulate Programmed Death-Ligand 1 (PD-L1) in lung cancer cells, reducing chemoresistance and restoring the cytotoxicity of T cells[4]. This effect is particularly significant in overcoming resistance to cisplatin, a common issue in lung cancer.

3.2. Curcumin and Its Role in Cell Cycle Arrest

Curcumin, derived from turmeric (Curcuma longa; Sanskrit: 'Haridra'), is another well-studied compound known for its anticancer properties. Curcumin has been shown to induce G2/M phase arrest in various cancer cell lines, including breast, prostate, and colorectal cancers. This arrest is primarily mediated by the downregulation of cyclins and cyclin-dependent kinases (CDKs), such as cyclin B1 and CDK1, which are crucial for the transition from the G2 phase to the M phase[4]. Additionally, curcumin upregulates CDK inhibitors like p21 and p27, which further reinforces the arrest[4]. When combined with chemotherapeutic agents such as doxorubicin and cisplatin, curcumin has been observed to enhance antiproliferative effects by modulating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway and Nuclear factor kappa B (NF-κB) signaling pathways, leading to increased apoptosis and reduced drug resistance[5].

3.3. Berberine: A Potent Inducer of G1 Phase Arrest

Berberine is an isoquinoline alkaloid found in several plants, including Berberis vulgaris or 'Daruharidra' (Sanskrit name). Berberine has shown promise as a potent inducer of cell cycle arrest, particularly at the G1 phase. Berberine achieves this by downregulating cyclin D1 and CDK4/6, which are essential for the G1 to S phase transition[6]. Moreover, berberine activates the AMPK pathway, which plays a critical role in maintaining cellular energy homeostasis and can lead to cell cycle arrest when dysregulated. In studies involving hepatocellular carcinoma and breast cancer cells, berberine has demonstrated significant antiproliferative effects, particularly when used in combination with chemotherapeutic agents like paclitaxel[6]. The combination therapy not only enhances cell cycle arrest but also promotes apoptosis through the activation of caspase-3 and the inhibition of Bcl-2, an anti-apoptotic protein[6].

3.4. Epigallocatechin Gallate (EGCG) and S Phase Arrest

Epigallocatechin gallate (EGCG) is a catechin predominantly found in green tea (Camellia sinensis; Sanskrit: 'Shyamaparni'). EGCG has been shown to induce S phase arrest in various cancer cell lines, including lung, prostate, and colorectal cancers. EGCG exerts its effects by inhibiting DNA synthesis and reducing the expression of proteins necessary for S phase progression, such as cyclin A and CDK2[7]. Additionally, EGCG modulates the MAPK (Mitogen-activated protein kinase) / ERK(extracellular signal-regulated kinase)signaling pathway, which is involved in cell proliferation and survival. The combination of EGCG with chemotherapeutic agents like gemcitabine and 5-FU has been reported to enhance the efficacy of these drugs by further promoting cell cycle arrest and increasing apoptosis[7]. Moreover, EGCG has been shown to reduce the expression of multidrug resistance proteins, thereby improving the sensitivity of cancer cells to chemotherapy[7].

3.5. Quercetin: Inducing Cell Cycle Arrest and Apoptosis

Quercetin, a flavonoid present in many fruits and vegetables, is also found in the plant Allium cepa or 'Palandu' (Sanskrit name). Quercetin has been studied for its potential to induce cell cycle arrest, causing G2/M phase arrest in ovarian and lung cancer cells by modulating the expression of cyclin B1 and CDK1[8]. Additionally, quercetin increases the levels of the tumor suppressor protein p53, which plays a pivotal role in regulating the cell cycle and promoting apoptosis. In combination with chemotherapeutic agents such as cisplatin and doxorubicin, quercetin has been found to enhance cell cycle arrest and potentiate apoptosis, making it a promising candidate for combination therapy in cancer treatment[8].

3.6. Synergistic Effects of Herbal Medicines in Combination Therapies

The combination of herbal medicines with conventional chemotherapeutic agents often results in synergistic effects that enhance therapeutic efficacy. For instance, the combination of resveratrol and 5-FU not only induces cell cycle arrest but also downregulates the expression of hTERT (Human telomerase reverse transcriptase), leading to decreased telomerase activity and enhanced apoptosis in colorectal cancer cells[6]. Similarly, the co-administration of curcumin and cisplatin has been shown to overcome cisplatin resistance in ovarian cancer cells, partly by inhibiting the NF-κB pathway and reducing the expression of anti-apoptotic proteins[5]. These findings highlight the importance of exploring the molecular mechanisms underlying these synergies to optimize treatment protocols and improve patient outcomes.

4. Discussion

When herbal medicine is used alongside cancer therapy, it can potentially result in interactions that affect either the way the drugs are processed in the body or how they exert their effects. Unlike the growing body of research on the pharmacokinetic interaction of combined chemotherapy and herbal drugs, there is a lack of information regarding the pharmacodynamic interaction of herbal medicine with anticancer drugs.

4.1. Molecular Mechanisms of Herbal-Drug Synergy

The reviewed studies provide strong evidence that herbal medicines can enhance the efficacy of conventional chemotherapeutic agents by inducing cell cycle arrest. The mechanisms by which these effects are achieved vary depending on the specific herbal compound and the type of cancer being targeted. Common themes include the regulation of key signaling pathways such as Akt, STAT3, and NF-κB, as well as the modulation of telomerase activity and nitric oxide production[3, 5, 6]. One of the most promising aspects of herbal-drug combination therapy is its potential to overcome chemoresistance, a significant challenge in cancer treatment. For example, the downregulation of PD-L1 by ginsenoside Rg3 represents a novel approach to restoring the immune system's ability to target cancer cells, even in cases where the cells have developed resistance to conventional drugs like cisplatin[4].

4.2. Challenges and Limitations

Despite the promising results observed in preclinical studies, several challenges must be addressed before herbal-drug combination therapies can be widely adopted in clinical practice. One major limitation is the reliance on in vitro and rodent models, which may not accurately predict the effects of these therapies in humans[9]. Additionally, the molecular complexity of herbal compounds presents a challenge in identifying the specific components responsible for their therapeutic effects. Another significant challenge is the lack of standardized protocols for evaluating the safety and efficacy of herbal-drug combination therapies. The current guidelines for safety pharmacology, as outlined by the International Council for Harmonisation (ICH), do not specifically address the unique considerations associated with herbal medicines[10]. This gap in regulatory guidance highlights the need for more comprehensive safety evaluations that take into account the potential interactions between herbal compounds and conventional drugs.

4.3. Future Directions

To advance the field of herbal-drug combination therapy, more research is needed to elucidate the molecular mechanisms underlying the observed synergies. This research should include studies using non-human primate models and advanced platform technologies to generate data that are more predictive of human responses. Additionally, the development of standardized safety pharmacology protocols for herbal-drug combination therapies is essential for ensuring that these treatments can be safely and effectively integrated into clinical practice. Furthermore, clinical trials are needed to validate the findings from preclinical studies and to determine the optimal dosing regimens for combination therapies. These trials should be designed to assess not only the efficacy of the therapies but also their potential to reduce the side effects associated with conventional chemotherapy.

5. Conclusion

Herbal medicines, particularly those that induce cell cycle arrest, hold great promise as adjuncts to conventional cancer therapies. The evidence reviewed in this article suggests that these compounds can enhance the efficacy of chemotherapeutic agents, overcome resistance, and potentially reduce the side effects of treatment. However, significant challenges remain in translating these findings into clinical practice. Future research should focus on elucidating the molecular mechanisms of herbal-drug synergy, improving the predictability of preclinical models, and developing standardized safety evaluation protocols. With continued investigation and clinical validation, herbal-drug combination therapies could play a crucial role in the ongoing fight against cancer.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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