

Enhancing the Cytotoxic Effects of Paclitaxel, Methotrexate, and Vincristine on Oral Cancer Cells with Curcumin

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Abstract

Objective: Curcumin, a potent polyphenolic compound, has been closely studied for its potential to improve the efficacy of cancer treatments. With its antioxidant, anti-inflammatory, and anticancer properties, curcumin has shown promise in enhancing the cytotoxic effects of chemotherapeutic agents, especially in cancer cells that have developed resistance. **Methods:** This study investigated curcumin's potential benefits in treating oral cancer. Researchers cultured CAL-27 oral cancer cells and treated them with varying concentrations of curcumin under standard laboratory conditions. To evaluate the effects on cell health and survival, they combined curcumin with common anticancer drugs such as paclitaxel, methotrexate, or vincristine. **Results:** The results were significant. Treating the CAL-27 cells with curcumin showed a noticeable decrease in cell viability, indicating that curcumin significantly inhibited cancer cell growth. This suggests that curcumin could potentially enhance the effectiveness of existing chemotherapy treatments for oral cancer. The study underscores the potential of curcumin as a complementary tool in the fight against oral cancer. Combining it with traditional chemotherapy could lead to better outcomes and improved management of this serious disease. **Conclusion:** These findings contribute to the growing body of research exploring natural compounds like curcumin as adjunct therapies in cancer treatment.

Keywords: Curcumin- oral cancer- chemotherapy

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Introduction

The healthcare industry's ongoing progress demands a combined approach that brings together medical knowledge, technology, and public health practices to manage diseases effectively. Current research stresses the significance of comprehensive methods, which involve utilizing technologies like virtual reality (VR) and nanotechnology in medication administration. Specifically, VR plays a vital role in improving skills and managing workloads among healthcare workers. Studies have examined several factors influencing VR systems' efficacy, such as task difficulty, mental strain, feeling of immersion, and motion sickness – collectively known as cybersickness.

Proper design considerations are essential to maximize

both user experience and educational outcomes with these tools. Furthermore, there have been developments in identifying early signs of cybersickness by analyzing users' head movements, aiming to minimize adverse effects while increasing VR applicability within healthcare environments [1-10]. Great strides have been made in the field of nanotechnology regarding wound healing and cancer treatments, according to recent findings. Scientists have discovered that specific nanocomposites containing ceramic nanoparticles can expedite the process of wound healing due to their enhanced characteristics seen during experimental and computational assessments. Moreover, simulations show that incorporating single-walled boron nitride nanotubes into these nanocomposites strengthens

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their durability and functionality when subjected to increased temperatures. In another development, researchers have engineered an eco-friendly solution using copper nanoparticles embedded in nitrogen-rich carbon fiber felt for converting benzene under moderate circumstances. This novel strategy not only addresses environmental concerns but also provides health benefits given benzene's toxic nature [11-13]. Mental health, especially among families dealing with autism, should be prioritized within public health initiatives. Studies focusing on familial psychological well-being and marriage fulfillment within autistic households provide a key understanding of the advantages associated with systematic therapy. On another note, examinations concerning how individual character attributes factor into one's standard of living after gender confirmation surgeries reveal critical elements affecting postoperative achievements. By concentrating on these diverse aspects related to mental health, we gain substantial insight necessary to improve support mechanisms and inform future interventions [14-17]. Advancements in therapeutic techniques include the exploration of low-level laser therapy for alleviating trigeminal neuralgia symptoms, thereby offering fresh perspectives on addressing persistent discomfort. Separately, studies delving into the effect of dentin matrix proteins on self-donated guinea pig dental pulp stem cells propose possible restorative remedies. It's equally imperative to understand the mindset of cancer patients' associates towards chemotherapy and radiation-inflicted oral side effects; fostering awareness amongst them aims to elevate patient care levels throughout cancer therapy. Case analyses and brief narratives contribute real-world examples illustrating clinic implementations - from uncommon cases of gingival blister formation enlightening diagnostic procedures and cures to innovations like dental pulp stem cell utilization targeting pulp restoration along with bloodless plasma application combatting jawbone necrosis caused by medications. These emerging trends signal encouraging improvements in endodontics and overall clinical practice. Tooth root regrowth achievement further underscores this notion, pointing towards bright prospects ahead [18-24]. In medical research, utilizing location-scale models for comparing the efficacy of various treatments for a specific disease can be very effective. The dissertation "Model Checks for Two-Sample Location-Scale" investigates two statistical methods, ECF and PEL, for assessing patient data. These techniques allow for a more accurate determination of data distribution and help researchers compare the effectiveness of two treatments precisely, even with censored data. This approach can improve decision-making in treatments and increase the efficiency of therapeutic strategies [25]. Tortuous microvessels, commonly observed in numerous diseases, can greatly affect blood flow properties by raising apparent blood viscosity and modifying wall shear stress patterns. These alterations, driven by red blood cell dynamics, are essential for comprehending and modeling the hemodynamics of pathological states [26]. In addition to genetic diseases, there are acute and chronic non-hereditary diseases. Stroke

is the second leading cause of death and illness globally and the primary cause of long-term disability. It predominantly affects individuals over 65 years old, with an estimated annual incidence rate of 7.6% [27]. Bone disorders have become increasingly prevalent worldwide, posing significant health challenges. Tissue engineering offers a promising solution by enabling the generation of fully functional bone tissues. This advanced field combines principles of biology, engineering, and materials science to develop biological substitutes that can restore, maintain, or improve bone function [28]. Hepatitis B is a significant global public health issue as it is the most common severe liver infection around the world. The disease is mainly caused by the hepatitis B virus (HBV), a small infectious agent that targets liver cells. After entering the body, HBV quickly replicates, leading to extensive damage and inflammation in the liver tissue [29]. Parkinson's disease (PD) is one of the most prevalent neurological disorders of our time, characterized by uncontrollable movements such as shaking, muscle stiffness, and difficulty with coordination and balance. This progressive condition results from the degeneration of dopamine-producing neurons in the brain, leading to a decline in motor function and impacting the quality of life for those affected [30]. The Predictive Coding (PC) theory suggests that the brain predicts sensory input based on past experiences, focusing on discrepancies between predictions and actual input to efficiently process information. This framework explains how perceptions are formed, facilitates learning through error correction, and provides insights into various neurological and psychiatric conditions by highlighting the brain's active role in shaping our sensory experiences and responses to the environment [31]. Besides various diseases, non-disease factors such as burns can cause serious harm, especially to the elderly, potentially leading to severe injuries or even death. These situations require prompt treatment and essential actions [32]. A serious and intricate issue for health nowadays is cancer, which involves the development of possibly harmful growths or cancerous cells. The relationship between these cells and their surroundings plays a significant role in the illness [33]. This study shows that in the microcirculation of tortuous vessels, circulating cells such as leukocytes or cancer cells can marginate to the vessel wall even in the absence of red blood cells. This behavior, known as margination, plays a significant role in physiological processes such as the migration of cancer cells to surrounding tissues and provides better insight into cell behavior in various diseases [34]. Oral cancer is a type of cancer that develops in the tissues of the mouth or throat. It belongs to a larger group of cancers called head and neck cancers and is most commonly found in individuals over the age of 40. Oral cancer can be life-threatening if not diagnosed and treated early [6, 20]. According to different cancers, prevailing therapeutic options primarily revolve around surgery and chemotherapy. Nevertheless, it is quite unfortunate that many patients still encounter instances of local reappearance and distal dissemination, ultimately resulting in grim survivorship rates - widely regarded as one of the

foremost challenges confronted with this particular illness [35-42]. Substantial efforts have gone into creating and employing substances alongside multi-targeted medicines intended to act upon malignant cells, drawing inspiration from herbal commodities recognized for their wide-ranging impacts beyond synthetic alternatives' reach. Generally speaking, these organic components tend to entail diminished production expenses coupled with minimal side effects contrasted against synthesized equivalents. For instance, curcumin - procured from turmeric root and characterized as a ketone compound - exhibits potent anti-carcinogenic and anti-inflammatory qualities supported by extensive studies. Hence, harnessing nature's resources could pave the way for more efficient yet affordable therapeutic measures against cancer [36]. Traditional medicine has extensively employed curcumin to tackle issues like liver maladies, digestive complaints, urinary tract troubles, and rheumatoid arthritis over time. Known for its remarkable anti-inflammatory, antioxidant, and anti-cancer capacities, curcumin has captivated considerable scientific interest. Time and again, research demonstrates that curcumin instigates programmed cell death (apoptosis) and displays anti-proliferative qualities against myriad cancer cell varieties, spanning kidney, pancreas, colon rectal, breast, and prostate tumors. Consequently, curcumin emerges as a highly sought-after substance warranting intense investigation in the quest for viable cancer treatments [43-47]. Research highlights that curcumin amplifies the efficacy of certain anti-cancer pharmaceuticals in resistant cancer cells, proposing reduced chemotherapeutic dose requirements and decreased exposure to unwanted side effects. Notably, recent advances suggest that curcumin wields dual antioxidant and pro-oxidant influences, playing an instrumental role in hindering cancer growth. Beyond this, evidence substantiates that curcumin can augment the impact of additional anti-cancer agents synergistically, fortifying the search for complementary cancer treatment modalities. Thus, exploring curcumin's unique features may unlock new avenues in devising strategic therapeutic plans [48-50].

Considering that concurrent usage of curcumin with assorted chemotherapy drugs remains unexplored in stomach cancer, this investigation seeks to scrutinize the impact of combining curcumin with established anti-cancer agents, namely paclitaxel, methotrexate, and vincristine, specifically targeting oral cancer treatment. Addressing this knowledge gap holds promise in refining therapeutic protocols and enhancing patient outcomes.

Materials and Methods

Curcumin, paclitaxel, methotrexate, and vincristine were acquired from Cell Pharma GmbH in Germany. Cholesterol, MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), sodium pentanesulphonate, and sodium edetate were obtained from Sigma-Aldrich Corporation. Isopropanol, methanol, and chloroform were sourced from Merck. RPMI 1640 and DMEM culture media, fetal bovine serum, and penicillin/streptomycin

were procured from Invitrogen Corporation. The CAL-27 cell lines were provided by the National Cell Bank of Iran at the Pasteur Institute of Iran.

Investigation of cytotoxicity

The presented study grew the CAL-27 cell line in a moist atmosphere having 5% CO₂, with RPMI-1640 media enhanced by 10% FBS and penicillin/streptomycin antibiotics (100 mg/ml each) at 1×10^4 cells per well in 96-well plates. Following 24 hours, the culture medium was taken out and replaced with a blend of stock solutions comprising varied concentrations of curcumin (5, 15, 30, 50 μ M) derived from a 10 mg/ml curcumin (98% purity) solution in DMSO, joined with predetermined amounts of paclitaxel, methotrexate, and vincristine (300 nM, 100 nM, and 5 nM accordingly). Twenty-four hours later, the mixture was eliminated and MTT solution (0.5 mg/ml PBS in 20 μ l portion) was inserted into each well for 3 hours of incubation. Later, isopropanol 100% dissolved the created formazan crystals within 10 minutes, followed by absorbance measurement at 540 nm using an ELISA reader (OrganonTeknika, Netherlands). Cell survival rate was appraised via the mentioned formula, and IC₅₀ value was estimated using the Pharm program.

Statistical analysis

In the statistical evaluation of the data, SPSS version 18 was utilized, and differences were deemed significant if the P-value was less than 0.05.

Results

The study found that administering curcumin at 5, 15, 30, and 50 μ M concentrations greatly decreased cell viability compared to the drug-free control group (Figure 1A). Combining curcumin with paclitaxel resulted in significantly reduced cell survival versus curcumin or paclitaxel individually ($P < 0.001$); however, co-treatment did not alter curcumin's inherent toxicity (Figure 1B). Higher curcumin doses raised paclitaxel's cytotoxicity ($P < 0.001$), consistent with methotrexate-treated groups (Figure 1C). When exposed to vincristine alone, cell viability dropped dramatically vs. curcumin-only samples ($P < 0.001$). While pairing vincristine with curcumin didn't change curcumin's toxicity, curcumin notably boosted vincristine's cytotoxicity (Figure 1D). SPSS v18 was employed for statistical analysis, considering $P < 0.05$ significant.

Discussion

Progress in technology and expertise across various fields is driving endeavors aimed at bolstering operational proficiency and item competences. Companies centered around services seek to upgrade service delivery and performance criteria, whereas manufacturing branches focus on bettering merchandise caliber. Within the electronics realm, considerable investments are dedicated to extending equipment longevity, culminating in creating steadier and superior apparatuses. Similarly, impressive

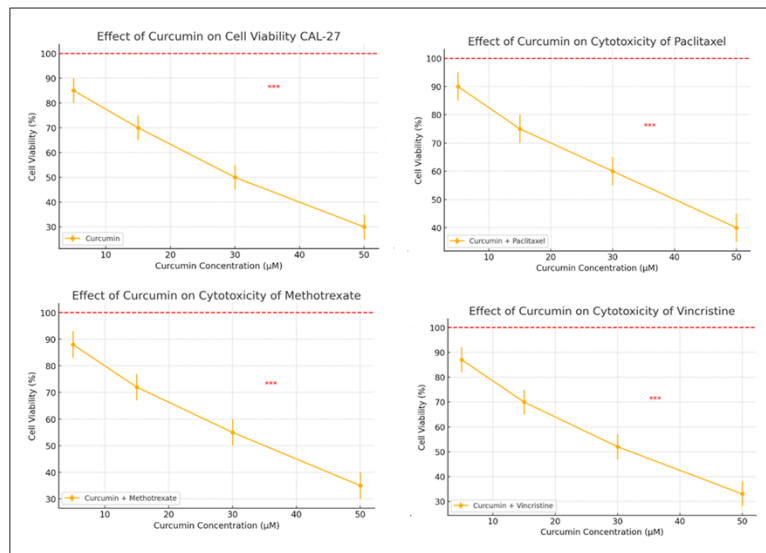


Figure 1. (A) Effect of Curcumin (5-50µM) on Cell Viability CAL-27. After 48 h of Incubation Cell Viability was Measured by MTT. The control cell group did not receive any treatments. *** Indicates a significant difference ($P < 0.001$) compared with the control group. (B) The Effect of Concomitant Administration of Curcumin (5-50µM) on the Cytotoxicity of Paclitaxel (300nM) in the Cells of CAL-27. After 48 hours of incubation, relative cell viability was measured by MTT. *** Indicates a significant difference ($P < 0.001$) compared with the control group paclitaxel alone. (C) The Effect of Concomitant Administration of Curcumin (5-50µM) on the Cytotoxicity of Methotrexate (100µM) in the Cells of CAL-27. After 48 hours of incubation, relative cell viability was measured by MTT. (D) Effect of Concomitant Administration of Curcumin (5-50µM) on the Cytotoxicity of Vincristine (5nM) in the Cells of CAL-27. After 48 hours of incubation, relative cell viability was measured by MTT. *** Indicates a significant difference ($P < 0.001$) compared with the control group vincristine alone. Data were reported as Mean \pm SD.

advancements are occurring in the healthcare, and medical segments geared towards honing therapies and discovering treatments for manifold conditions [51-62]. Anticancer drug resistance ranks among the top hurdles faced when tackling this deadly illness. Instances of such drug resistance in oral cancer to frequently prescribed medications, namely 5-Fluorouracil, Cisplatin, Vincristine, Adriamycin, Epirubicin, Taxanes, and Methotrexate, have surfaced. As a consequence, the lethal potency of these drugs has dwindled, posing significant obstacles to successful treatment [63]. Research has revealed that select natural substances can intensify the power of classic chemotherapy drugs. Among them is curcumin, a lipophilic polyphenolic entity packed with versatile therapeutic possibilities, chiefly within malignant disorders [36]. This substance exhibits restraining properties concerning transcription factors and subsequent gene product activities, exerts regulatory influence over growth factors and focal adhesion molecules, demonstrates robust anti-cancer qualities, restricts angiogenesis, and impedes metastatic processes [64]. This research study found that when curcumin is given along with chemotherapy drugs such as paclitaxel, methotrexate, and vincristine at concentrations of 15, 30, or 50 millimoles, it enhances their toxicity to oral cancer cells. In other words, combination therapy has a greater effect on killing cancer cells than using each drug individually. Wang et al. (2014) demonstrated that curcumin could enhance the toxic effects of cisplatin, carboplatin, and oxaliplatin on colorectal cancer cells. Their findings suggest that curcumin may be a useful adjunctive agent for increasing the sensitivity of colorectal

cancer cells to platinum-based chemotherapy [65].

In recent decades, technological advancements have had a significant impact on various fields, including medicine. These advancements have been notably effective in the diagnosis, treatment, and management of diseases [66-94]. Service-oriented companies are focused on enhancing service delivery and performance standards, while manufacturing industries strive to improve the quality of their products. In the electronics industry, substantial investments are being made to increase the durability of equipment, resulting in more reliable and superior devices. Similar progress is evident in the healthcare and medical fields, with a strong emphasis on improving therapies and discovering treatments for various conditions. For example, in medical studies, the quality of pharmaceutical products is fundamentally important in healthcare settings like hospitals, as it directly impacts the effectiveness of patient care services. High-quality medications ensure that patients receive the best possible treatments, leading to improved health outcomes and enhanced overall healthcare delivery [95]. The study seeks to identify potential risks and prognostic factors that could help healthcare providers better manage deliveries and improve neonatal care strategies for affected pregnancies [96]. For example, in mental health, as a crucial component of the overall concept of health, includes the ability to establish positive relationships with others, adapt and adjust to the environment, and control stress in everyday life, particularly during critical situations. Therefore, mental health encompasses the health of an individual's behavior, beliefs, and thoughts [97]. By exploring their perspectives, the study seeks to

uncover insights that could lead to more effective sensory-based interventions, ultimately improving their quality of life and integration into various social environments [98]. The prevalence of antidepressant usage among adolescents and young adults is growing, a demographic that is also becoming more susceptible to type 2 diabetes. This trend raises concerns about the potential health implications of long-term medication use on young people's metabolic health [99]. Alzheimer's disease (AD) is a degenerative neurological condition that progressively deteriorates cognitive functions. This disorder specifically impacts areas such as working memory, episodic memory, and executive functions, leading to significant challenges in daily life activities [100]. The worldwide spread of COVID-19 has impacted multiple aspects of daily life [101]. In the advancement of a field, sometimes using a single method is not effective. Instead, multiple approaches should be employed, and alongside these, the use of technology can also be beneficial [102-103]. Service-oriented companies are focused on enhancing service delivery and performance standards, while manufacturing industries strive to improve the quality of their products. In the electronics industry, substantial investments are being made to increase the durability of equipment, resulting in more reliable and superior devices. Similar progress is evident in the healthcare and medical fields, with a strong emphasis on improving therapies and discovering treatments for various conditions.

In conclusion, integrating curcumin with conventional chemotherapy agents holds great potential for overcoming drug resistance and improving the efficacy of cancer treatments. Future research should focus on further exploring these combinations in clinical settings to confirm their effectiveness and safety for patients.

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Data availability

Not applicable as we used information from previously published articles.

Approved by any scientific Body

Not applicable as the manuscript is not a part of any student thesis or study.

Ethical issue and approval

Not applicable as we used information from previously published articles.

Consent for publication

All authors have given consent for publication.

Conflict of interest

The authors declare no potential conflict of interest.

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