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REVIEW ARTICLE

A systematic review of the cytotoxic effects of morphine on cancer cells

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Abstract

Background: To date, numerous studies have delved into the cytotoxic effects of morphine on cancer cells. The present research undertook a systematic review of the cytotoxic effects of morphine on cancer cells to attain a more precise estimation.
Methods: The research articles were sourced from PubMed, Scopus, and Google Scholar databases spanning from 1999 to November 20, 2024. The selection criteria were established in accordance with the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).
Results: The results of this study show that morphine reduces survival and increases the apoptosis of lung, uterine, ovarian, liver, breast, stomach, pancreas, neuroblastoma, and mouth cancer cells. The mechanisms underlying this cytotoxicity may involve the modulation of apoptosis pathways, cell cycle arrest, the production of free radicals, increased expression of apoptotic genes, and inhibition of cell proliferation. These effects were observed in a dose-dependent manner, with higher concentrations of morphine often leading to increased cytotoxicity in cancer cells. In contrast, morphine increases survival and decreases the apoptosis of breast, lung, bladder, endothelial, and pancreatic cancer cells.
Conclusion: Morphine can induce apoptosis and inhibit cell proliferation in some cancer cells. Meanwhile, it may promote cancer progression through inflammation, immune suppression, and metastasis in other cells. However, further studies are needed to clarify its mechanisms and evaluate its safe therapeutic use in cancer.

Keywords: Morphine; Neoplasms; Apoptosis; Cell Proliferation; Drug Toxicity

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INTRODUCTION

Female breast cancer, lung cancer, and prostate cancer are among the most commonly diagnosed cancers. In contrast, lung cancer, liver cancer, and stomach cancer are the leading causes of cancer-related deaths. In 2020, there were approximately 19.3 million new cases of cancer and almost 10.0 million cancer-related deaths globally. The American Cancer Society annually projects the numbers of new cancer cases and deaths in the United States, using data from central cancer registries and mortality records. In 2023, it is estimated that there will be 1,958,310 new cancer cases and 609,820 cancer deaths in the United States. Currently, the primary cancer treatments are surgery and chemotherapy, and other methods are not very effective [1-4]. In recent years, many studies have been conducted on the cytotoxic effects of morphine on cancer cells, but research in this area is still of interest to scientists and there are many challenges in this field .[5-9] Morphine is a potent narcotic analgesic drug that is used to relieve severe pain in cancer patients. This substance may have anti-tumor effects by inhibiting the growth and spread of cancer cells [9, 10]. In this respect, some studies demonstrate that clinical concentrations of morphine can increase tumor growth associated with an increase in angiogenesis and a decrease in apoptosis [8]. Meanwhile, some research indicates that morphine might promote the growth and spread of certain types of cancer cells, potentially by influencing the tumor microenvironment or immune response. Nevertheless, the effects of morphine on cancer cells are still a topic of ongoing research, and the findings can vary depending on

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the type of cancer and individual patient characteristics [5, 7, 9]. Given these conflicting results, understanding the toxicological and biological effects of morphine on cancer cells is crucial for optimizing pain management in oncology without compromising treatment efficacy. To date, no comprehensive systematic review has been published to evaluate in vitro and in vivo data to assess whether morphine possesses pro-tumorigenic or anti-tumorigenic properties across diverse cancer types. To our knowledge, the present systematic review is the first effort to comprehensively collect, evaluate, and summarize existing evidence regarding the cytotoxic effects of morphine on cancer cells. It focuses on potential mechanisms of action, dose-dependent responses, and variations across cancer cell types. By integrating findings from a wide range of experimental studies, this work provides new insights into the complex role of morphine in cancer biology. Accordingly, it identifies key gaps in current knowledge to inform future research and clinical decision-making.

METHODS

Search Strategy

The systematic review focuses on the cytotoxic effects of morphine on cancer cells. The research articles were sourced from PubMed, Scopus, and Google Scholar databases spanning from 1999 to September 30, 2024. A methodical search was conducted using English search terms such as "Morphine" OR "Opioid" AND "Viability" OR "Cell Proliferation" OR "cytotoxic" OR "Cell Survival" AND "Apoptosis" OR "Cell Death" OR "DNA damage" AND "ROS" OR "reactive oxygen species" AND "Cell cycle" AND "Apoptosis genes". The selection criteria were established following the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Criteria for Article Selection

The article selection process followed the PRISMA guidelines, with abstracts reviewed to exclude irrelevant studies and identify potentially relevant ones for further examination.

Inclusion criteria

The inclusion criteria used in this research included choosing studies related to the toxicological effects of morphine on proliferation and induction of cell death in cancer cells, with the requirement that articles be written in English.

Exclusion criteria

Exclusion criteria encompassed articles not focusing on the specified topic, non-English articles, animal studies, and meta-analyses. Additionally, duplicate articles were excluded from consideration.

RESULTS

Data Extraction

In the first stage of the search, the first 2,850 articles were imported into EndNote, and then 1,300 articles remained after duplicates were removed. Next, the titles of articles were screened, and 800 articles were included in the study, with 500 articles subsequently excluded. After screening the abstracts of the articles, we removed 520 unrelated ones. Finally, we meta-analyzed 30 articles that met the inclusion criteria (Figure 1). The article selection criterion was based on the PRISMA flow diagram. The characteristics of the analytical methods from these 30 articles were extracted and presented in Table 1.

Morphine and Cancer Therapy

In the context of cancer therapy, morphine is frequently prescribed to alleviate pain associated with cancer and its treatments, including surgery, chemotherapy, and radiation therapy. However, beyond its role in pain management, there is growing research interest in the potential therapeutic effects of morphine on cancer itself. Several studies have suggested that morphine may exert direct effects on cancer cells, influencing tumor growth, progression, and even sensitivity to certain therapies [6, 9, 11]. While these findings are promising, the use of morphine in cancer treatment remains complex and evolving, with important implications regarding potential side effects, individual patient responses, and the necessity for further clinical studies to fully understand its role in oncologic care [12, 13]. Opioids like morphine have been shown to exert multifaceted effects on cancer cells, potentially altering their proliferation rates. Investigating the impact of morphine on cancer cell proliferation is crucial for understanding how opioid-based pain management might influence cancer progression. The studies aim to determine whether morphine promotes or inhibits cancer cell growth, which could have significant implications for both cancer treatment strategies and patient outcomes.

Regarding cell death pathways, morphine has been found to affect both apoptosis (programmed cell death) and necrosis (unregulated cell death) in various cellular contexts [5-9]. Understanding how morphine modulates these processes is vital to grasp its broader physiological impact. Research into the effects of morphine on apoptotic pathways explores how this opioid influences the balance between cell survival and death, including its regulatory effects on apoptosis-related genes [12, 14-16]. Some studies suggest that morphine possesses antioxidant properties, reducing ROS levels by scavenging free radicals and preventing oxidative damage. This outcome may be partly due to its impact on mitochondrial function, which plays a crucial role in maintaining cellular ROS balance. However, other studies associate chronic morphine use with increased oxidative stress and inflammation [17-21]. Inflammatory responses, often triggered by prolonged opioid exposure, can increase ROS production and alter cellular signaling pathways involved in oxidative stress. Thus, morphine's overall effect on ROS is multifactorial, varying by dose, exposure duration, cell type, and the presence of additional cofactors. However, further research is necessary to fully elucidate how morphine modulates reactive oxygen species (ROS) dynamics under various physiological conditions [17-21]. Morphine has also been shown to influence the various

phases of the cell cycle. It may stimulate progression through the G1 phase, encouraging cells to enter the S phase, where DNA replication occurs. This result is potentially mediated through its interactions with regulatory proteins

Furthermore, morphine may interfere with mitotic progression, triggering cell death during the M phase. These effects suggest that morphine can influence cell proliferation, cell cycle arrest, apoptosis, and DNA integrity

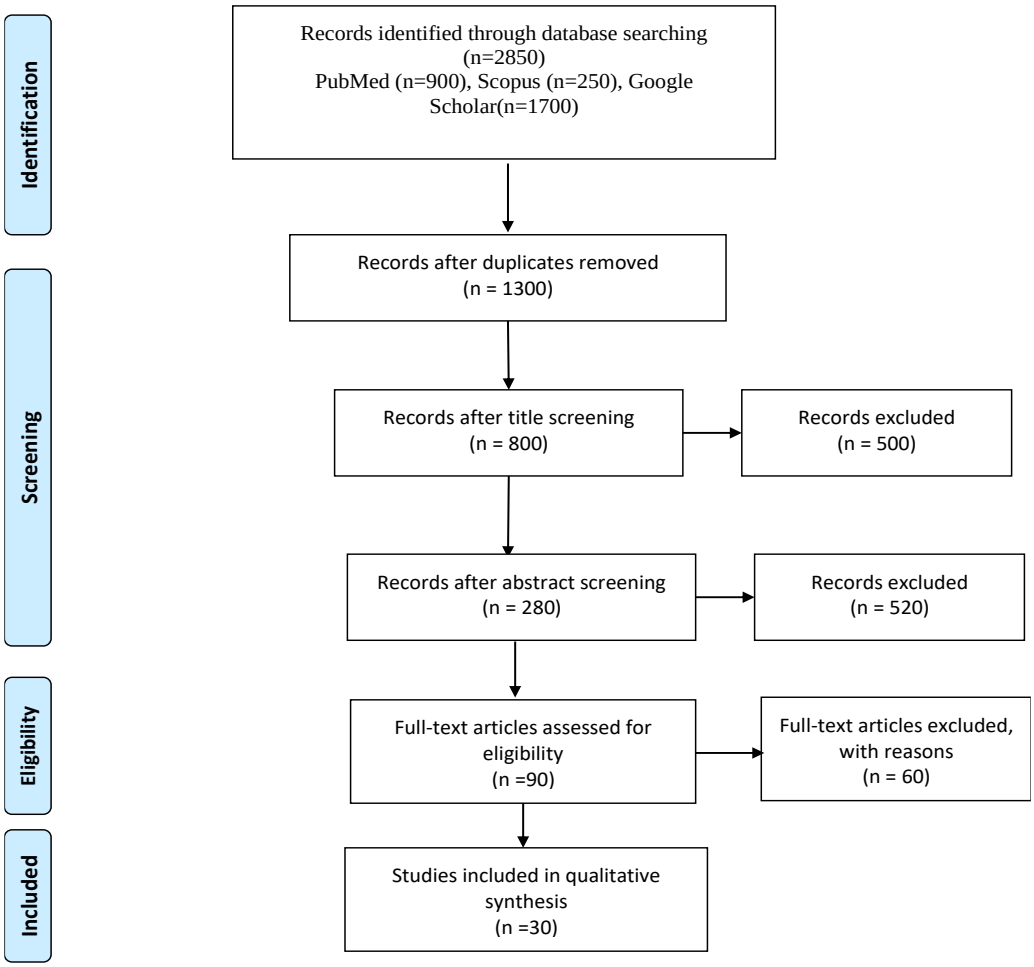

Figure 1. The process of selecting eligible artides

and signaling pathways that govern the G1-S phase transition. While the impact of morphine on the S phase is less well characterized, it may contribute to DNA damage during the replication process. Morphine-induced DNA damage can disrupt replication processes, potentially resulting in mutations or cell death. In some cell types, morphine has been observed to induce G2 phase arrest, preventing cells from entering mitosis. This G2 arrest may be linked to DNA damage responses and activation of apoptotic pathways.

in a dose- and context-dependent manner [22-25]. Therefore, further investigation into the molecular mechanisms underlying morphine's interactions with cell cycle regulation is warranted.

The effects of morphine on Ovarian Cancer Cells

Ovarian cancer cells are abnormal cells that grow uncontrollably in the ovaries, forming tumors that can develop into malignant tumors. Ovarian cancer is a type of cancer that originates in the ovaries, which are female reproductive organs. If left untreated, these cancer cells can proliferate and spread to other parts of the body. Symptoms

Table 1. Summary of selected studies included in the systematic review on the cytotoxic effects of morphine on cancer cells

First Author (Publication Year)	Apoptosis Genes	Cancer cell type	Method	Viability %	Cell death induction	ROS	Cell Cycle phases	Ref
Maryam Rezaeigazik et al. (2019)	Bcl-2 gene	Ovarian cancer cells(A2780Cp cell line)	MTT assay Flow cytometry	No effect	No apoptosis was observed	Not investigated.	not mentioned	[6]
Sabrina Bimonte et al. (2015)	not investigated	breast carcinoma cells(MCF-7)	MTT assay Western blot. Immunohistochemical	Increased	Reduced	not investigated	not mentioned	[28]
Mi Tian et al. (2016)	p53↑ Bax↑ Bcl-2↓	Lung adenocarcinoma cells (A549)	MTT assay Flow cytometry RT-PCR	Reduced	Increased	not investigated	not mentioned	[27]
Qichao Wang et al. (2022)	not investigated	Lung cancer cells	MTT assay ELISA Flow cytometry	Reduced	Reduced	not investigated	not mentioned	[26]
Jamal Naderi et al. (2019)	not investigated	Cervical cancer cells	MTT assay	Reduced	Not specifically measured	Not investigated	Not mentioned	[5]
Xingyun Liu et al. (2021)	Bcl-2 (↑) Bax(↓) , Caspase-3(↓) , Caspase-9(↓),	Non-small cell lung cancer (H460)	Flow cytometry RT-PCR Western blot	Increased	Reduced	Not investigated	Reduced G2 phase and increased S phase cells	[7]
Mohammad Nabiuni et al. (2015)	Not investigated	Ovarian cancer cells (A2780cp)	MTT assay Flow cytometry	Reduced	Increased	Not investigated	Not mentioned	[8]
Zhang et al. (2020)	Not explicitly reported	Esophageal carcinoma cells	Microplate reader	No significant change with morphine alone	Reduced	Not mentioned	Not mentioned	[30]
Khaleghi et al. (2016)	p53, Bax(↑)	HepG2 cell lines	MTT assay Annexin-PI test Flow cytometry	Decreased	Increased	Not explicitly reported	Not investigated	[32]
Dong-Ge Niu et al. (2015)	Caspase-3(↓)	Breast Cancer - MCF-7, BT549	MTT assay Flow cytometry Western blot	Increased	Reduced	Not investigated	Not mentioned	[37]
Kalpna Gupta et al. (2002)	Not explicitly reported	Breast Cancer - MCF-7	Flow cytometry Tube formation assay	Increased	Reduced	Not investigated	promotion of cell cycle Gi/Go- phase	[38]

Table 1. Continued

First Author (Publication Year)	Apoptosis Genes	Cancer cell type	Method	Viability %	Cell death induction	ROS	Cell Cycle phases	Ref
Hatsukari et al. (2007)	Caspase-2, -3, -8, -9 (↑)	HL-60, A549, MCF7cell lines	MTT Flow cytometry ESR spectroscopy	Reduced	Increased	Increased	Not mentioned	[16]
Harper et al. (2018)	Caspase-3/7 (↓)	RT-112 (Bladder Cancer)	MTT Western Blot	Increased.	Reduced	Not mentioned	Not mentioned	[36]
Nishiwada et al. (2019)	Not mentioned	HSC-3 (Oral Cancer)	MTT assay LDH Flow Cytometry	Reduced	Not affected	Not mentioned	Not affected	[13]
Kim et al. (2016)	Not mentioned	H1975 (Lung Cancer)	RT-PCR	Reduced	Increased	Not mentioned	S phase	[22]
Panagiotou et al. (1999)	Not mentioned	Breast cancer (T47D)	Flow cytometry Confocal microscopy	Reduced	Not mentioned	Not mentioned	G2/M phase	[39]
Yoshida et al. (2000)	Caspase-3(↑)	Lung carcinoma (A549) MCF-7 (breast cancer)	MTT assay Western blot	Increased	Increased	Not investigated	Not mentioned	[40]

1. Bcl-2 gene: B-cell lymphoma 2 gene
2. *p53*: Tumor protein 53
3. *Bax*: Bcl-2-associated X protein
4. *Caspase-3*: Cysteine-aspartic acid protease 3
5. *Caspase-9*: Cysteine-aspartic acid protease 9
6. *MTT assay*: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay
7. *ELISA*: Enzyme-linked immunosorbent assay
8. *RT-PCR*: Reverse transcription polymerase chain reaction
9. *PI*: Propidium iodide

pain, early satiety, difficulty eating, and frequent urination. Early detection and treatment are critical for effectively managing ovarian cancer. Treatment options may include surgery, chemotherapy, radiation therapy, targeted therapy, or a combination of these approaches, depending on the cancer's stage and type. It is important for individuals to recognize the signs and symptoms of ovarian cancer and to seek medical evaluation promptly if they experience any concerning issues [6, 8]. Regular screenings and consultations with healthcare professionals can contribute to earlier detection and improved outcomes for ovarian cancer patients. The cytotoxic effects of morphine on ovarian cancer cells have garnered considerable research interest. Morphine, an opioid analgesic, has been studied for its impact on the viability and proliferation of ovarian cancer cells. Findings suggest that morphine may exert cytotoxic effects on these cells, affecting their growth and survival [6, 8]. In this respect, Mohammad Nabiuni et al. (2015) investigated the cytotoxic effects of morphine on A2780cp ovarian cancer cells using MTT assay and flow cytometry. They observed that morphine can reduce the growth rate of cancer cells through apoptosis in a dose-dependent manner [8].

The effects of morphine on lung cancer cells

Lung cancer cells are abnormal cells that divide and grow uncontrollably in the lungs. These cells can form tumors and disrupt normal lung function, leading to symptoms such as persistent cough, chest pain, shortness of breath, coughing up blood, fatigue, and unintended weight loss [7, 26]. This study examines the intricate relationships between morphine and lung cancer cells, aiming to elucidate the mechanisms underlying its cytotoxic effects [26]. In one study, Mi Tian et al. (2016) investigated the cytotoxic effects of oxycodone and morphine hydrochloride on A549 lung cancer cells using flow cytometry and real-time quantitative polymerase chain reaction (RT-qPCR). They reported that morphine significantly reduced the survival rate of cancer cells, increased apoptosis induction, upregulated BAX gene expression, and downregulated BCL2 gene expression [27]. In contrast, Xingyun Liu et al. (2021) examined the effects of morphine on H460 lung cancer cells using flow cytometry and Western blot analysis. The results showed that morphine promoted the growth and migration of H460 cells. Furthermore, this study demonstrated an anti-apoptotic effect, with increased BCL2 gene expression and decreased BAX gene expression in H460 cells [7].

The effects of morphine on breast cancer cells

Breast cancer cells are cells that have undergone mutations leading to uncontrolled growth and the formation of tumors in breast tissue. These cells can become invasive, spreading to other parts of the body through the lymphatic system or bloodstream [5]. The cytotoxic effects of morphine on breast cancer cells are of significant interest in cancer research. Research has shown that morphine, a potent opioid analgesic, may possess anti-cancer properties. Also, it has been reported that morphine can induce apoptosis (programmed cell death) in breast cancer cells through various mechanisms, including the modulation of cell signaling pathways and the inhibition of cell proliferation [5, 28]. Besides, morphine has been shown to interfere with the growth and metastasis of breast cancer cells by targeting specific molecular pathways involved in cancer progression [28]. Despite these promising findings, the precise mechanisms by which morphine exerts its cytotoxic effects on breast cancer cells remain to be fully elucidated. Understanding the impact of morphine on breast cancer cells is crucial for exploring novel therapeutic approaches that leverage the potential anti-cancer properties of this widely used analgesic. Sabrina Bimonte et al. (2015) investigated the cytotoxic effects of morphine on MDA-MB-231 breast cancer cells and observed that morphine can increase the growth rate of cancer cells and inhibit apoptosis. They also reported that morphine, at various doses, enhanced angiogenesis and promoted breast cancer progression [28]. Sezer et al. (2022) examined the effects of morphine on MDA-MB-231 breast cancer cells using MTT assay and flow cytometry. The results of this study showed that morphine at low concentrations can significantly increase the proliferation of cancer cells, whereas it induces cytotoxic effects at higher concentrations [29].

The Effects of Morphine on Esophageal Carcinoma Cells

Esophageal carcinoma, a malignancy with high morbidity and mortality rates, poses a considerable challenge in the medical field. Research concerning the cytotoxic effects of morphine on esophageal carcinoma cells has unveiled intriguing insights. Moreover, the interaction between morphine and esophageal carcinoma cells is complex and multifaceted. In a study by Zhang et al. (2020), the cytotoxic effects of morphine on esophageal cancer cells were investigated. The results showed that morphine stimulated the migration and growth of cancer cells, although it did not affect cell viability and reduced apoptosis [30].

The effects of Morphine on Pituitary Neuroendocrine Tumors (GH3 cells)

The cytotoxic effect of morphine on Pituitary Neuroendocrine Tumors (GH3 cells) has been a subject of research interest aimed at understanding the impact of opioids on these specific cell lines. Pituitary neuroendocrine tumors are rare neoplasms that arise from the cells of the pituitary gland and can have significant effects on hormone production and regulation within the body. Studies investigating the effects of morphine on GH3 cells, which are a commonly used model for pituitary neuroendocrine tumors, have shown varying results. Some research suggests that morphine may have cytotoxic effects on GH3 cells, potentially inhibiting cell proliferation or inducing cell death through various mechanisms. These effects could be mediated by opioid receptors present on the surface of these cells or through interactions with intracellular signaling pathways that regulate cell growth and survival. In agreement with these findings, Taghavi et al. (2023) investigated the cytotoxic effects of morphine on pituitary neuroendocrine tumor (GH3) cells using MTT assay, flow cytometry, and RT-PCR methods. They observed that morphine can reduce cancer cell viability by increasing apoptosis and free radical production. Also, an increase in the number of cells in the sub-G1 phase was observed in this study [31].

The effects of Morphine on HepG2 cells

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and one of the leading causes of cancer-related deaths worldwide. Studying the effects of cytotoxic morphine on these cell lines can lead to further investigations into the molecular pathways involved in the cytotoxic effects of morphine on hepatocellular carcinoma (HCC) cells. This result could, in turn, contribute to the development of novel treatment strategies for hepatocellular carcinoma. Khaleghi et al. (2016) examined the effects of morphine on HepG2 liver cancer cells using MTT assay and flow cytometry. In this study, a decrease in cancer cell viability was noticed through increased apoptosis and BAX gene expression [32].

The effects of Morphine on Neuroblastoma cells

The cytotoxic effects of morphine on Neuroblastoma cells have been a subject of significant research interest in the field of neuroscience and pharmacology. Neuroblastoma is a type of cancer that affects immature nerve cells and is often found in young children. The SH-SY5Y cell line, derived from human neuroblastoma cells, is frequently used in research as a model to study neuronal development, neurotoxicity, and neuroprotection. These cytotoxic effects may be mediated by the activation of specific cell signaling pathways or the disruption of cellular processes essential for cell survival. Consistent with this finding, Xin Lin et al. (2009) investigated the cytotoxic effects of morphine on neuroblastoma (SK-N-SH) cells using flow cytometry and RT-PCR methods, observing that morphine can reduce the growth of cancer cells by increasing apoptosis, increasing BAX gene expression, and decreasing BCL2 gene expression. The production of free radicals was observed in this study [33].

The effects of Morphine on Human Umbilical Vein Endothelial Cells (HUVECs)

Endothelial cells play a crucial role in maintaining vascular integrity and function, and any cytotoxic effects on these cells could have significant consequences for overall vascular health. Studies investigating the impact of morphine on HUVECs have revealed potential cytotoxic

effects that may disrupt normal endothelial cell function. Feng et al. (2021) investigated the effects of morphine on human umbilical vein endothelial cells (HUVECs) using the MTT assay, flow cytometry, and real-time PCR (RT-PCR). The results of this study reported an increase in cancer cell survival through decreased apoptosis and increased BAX expression [34].

The Effects of Morphine on Cervical Cancer Cells

Cervical cancer is a significant health concern worldwide, with a high mortality rate among women. Research into potential treatments for cervical cancer is ongoing, with scientists exploring both traditional and novel approaches to combat this disease. In the context of cervical cancer, particularly in C-33A and CaSki cell lines, the effects of morphine on cell viability, proliferation, and apoptosis are of particular interest. It has been suggested that morphine can inhibit cell proliferation by disrupting the cell cycle progression or promoting apoptosis, ultimately leading to a reduction in the growth of cervical cancer cells. Jamal Naderi (2019) examined the cytotoxic effects of morphine on cervical cancer cells using the MTT assay and observed that cell viability was significantly reduced [5].

The Effects of Morphine on Pancreatic Cancer Cell Lines

Pancreatic cancer is known for its aggressive nature and poor prognosis, often presenting challenges in treatment and management. The exploration of alternative or adjunct therapies, such as morphine, could offer new avenues for combating this deadly disease. Studies have shown that morphine may exert cytotoxic effects on pancreatic cancer cells, including BxPC-3, PANC-1, SUIT-2, and CFPAC-1 cell lines. In agreement with these findings, Ning et al. (2024) investigated the cytotoxic effects of morphine on pancreatic cancer cells using the MTT assay. The results showed that morphine at low concentrations can significantly increase the proliferation of cancer cells. However, at higher concentrations, it causes cytotoxic effects by increasing BAX gene expression and decreasing BCL2 gene expression [35].

The Effects of Morphine on Gastric Cancer Cells

Gastric cancer is a significant global health concern, being one of the leading causes of cancer-related deaths worldwide. The exploration of novel therapeutic approaches, including the repurposing of existing drugs like morphine, holds promise for improving outcomes in gastric cancer treatment. Some research suggests that morphine can induce apoptosis in gastric cancer cells, thereby inhibiting their proliferation and promoting cell death. These findings underscore the potential of morphine as a cytotoxic agent in the context of gastric cancer therapy. Qin et al. (2012) investigated the cytotoxic effects of morphine on gastric cancer cells (MGC-803) using flow cytometry and RT-PCR, observing that morphine reduced the growth of cancer cells and increased apoptosis by increasing the expression of caspase 3 and 9. Additionally, this study observed cell arrest in the G2/M phase [25].

The effects of Morphine on Oral squamous cell carcinoma (OSCC)

Recent studies suggest that morphine may exert cytotoxic effects on HSC-3 cells through mechanisms involving apoptosis, oxidative stress, and modulation of key signaling pathways. Morphine-induced apoptosis in cancer cells has been linked to the activation of caspases, mitochondrial dysfunction, and alterations in the expression of pro-apoptotic and anti-apoptotic proteins. Additionally, morphine may influence cancer cell proliferation by interacting with opioid receptors, which are known to play a role in tumor progression and survival. Nishiwada et al. examined the cytotoxic effects of morphine on HSC-3 oral cancer cells using the MTT assay and flow cytometry, observing a significant reduction in cell viability [13].

The Effects of Morphine on Bladder Cancer Cells

Bladder cancer is among the most common malignancies affecting the urinary system, with high recurrence rates and significant morbidity. Recent studies have explored the potential cytotoxic effects of morphine on cancer cells, including bladder cancer cells. Morphine, a potent opioid analgesic, interacts primarily with μ-opioid receptors (MORs) expressed in various tissues, including cancer cells. Morphine has been reported to promote apoptosis, or programmed cell death, in certain cancer types by modulating pathways such as the caspase cascade and the Bcl-2 family proteins. In bladder cancer, morphine may activate pro-apoptotic signals, leading to increased cell death. Harper et al. investigated the cytotoxic effects of morphine on RT-112 bladder cancer cells using MTT assay and Western blot. The results reported an increase in cancer cell survival through decreased apoptosis and decreased expression of caspase 3 and 7 [36].

DISCUSSION

Although numerous studies have explored the effects of morphine on cancer cells [5-9]; however, the extent to which it contributes to either the reduction or enhancement of cancer cell survival remains a complex and controversial issue. This systematic review was designed to address this knowledge gap by evaluating the cytotoxic effects of morphine on various cancer cell types, synthesizing in vitro data to determine whether morphine inhibits cancer cell proliferation, and elucidating the underlying molecular and cellular mechanisms. Across the included studies, the majority reported that morphine exerted cytotoxic effects on a range of cancer cell lines, including lung, cervix, ovarian, liver, breast, stomach, pancreas, neuroblastoma, and oral cancers [5, 6, 27, 35]. These effects were frequently observed in a dose-dependent manner, with higher concentrations of morphine often associated with increased apoptosis and reduced cell viability. Proposed mechanisms for these cytotoxic effects include the modulation of apoptotic signaling pathways, cell cycle arrest, the generation of reactive oxygen species, the upregulation of pro-apoptotic genes, and the inhibition of cellular

proliferation. However, a subset of studies reported contrasting findings, in which morphine enhanced cell survival and decreased apoptosis in certain cancer types, including breast, lung, bladder, endothelial, and pancreatic cancers [7, 9, 34, 35]. These conflicting outcomes may be attributed to differences in morphine concentrations, exposure times, cancer cell types, and experimental conditions. The molecular pathways involved appear to be highly complex and context-dependent, highlighting the need for further mechanistic studies. Given the widespread use of morphine in cancer pain management, understanding its potential impact on tumor progression or suppression is of critical clinical importance. This review contributes to the ongoing debate about whether morphine may inadvertently influence cancer outcomes and provides valuable insights that may guide future clinical decision-making regarding opioid use in oncology settings [12, 35]. In vivo studies and clinical trials are also crucial to determine the translational relevance of in vitro findings and to understand better the real-world implications of morphine use in cancer patients. Moreover, further investigation into the molecular mechanisms underlying both the cytotoxic and pro-tumorigenic effects of morphine could inform the development of personalized pain management strategies that minimize potential risks while maximizing therapeutic benefits.

In conclusion, while existing evidence suggests that morphine may exert both cytotoxic and proliferative effects on cancer cells, the overall impact remains unclear due to conflicting results and methodological differences across studies. However, this study has limitations, including its restriction to in vitro data, the high heterogeneity in study designs, morphine concentrations, and exposure durations, as well as the lack of standardization in methodologies, which makes interpretation challenging. The absence of clinical or animal studies also limits the generalizability of the findings. In conclusion, although existing evidence suggests that morphine may exert both cytotoxic and proliferative effects on cancer cells, its ultimate impact appears to be highly context-dependent. This review paper highlights the pressing need for well-designed, mechanistic, and standardized research to elucidate the dual roles of morphine in cancer biology fully. Overall, this research is an endeavor essential for informing treatment decisions and identifying new therapeutic opportunities in cancer care. This review highlights the urgent need for well-designed, mechanistic, and translational research to understand the dual roles of morphine in cancer biology fully. Such efforts are essential for guiding clinical decisions and potentially identifying novel therapeutic opportunities in cancer treatment.

CONCLUSION

This systematic review demonstrated that morphine can exert dual effects on cancer cells; in many cases, it reduces cancer cell survival and induces apoptosis, while in certain conditions, it may increase cell survival and promote tumor growth. These contradictory results are likely due to differences in cancer cell types, morphine concentrations, exposure durations, and experimental conditions. Further research is necessary to delineate the exact mechanisms through which morphine interacts with different cancer cells and to determine whether it can be used as a therapeutic tool in cancer treatment without unintended pro-cancer effects.

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