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*Article*

# Effect of Anticancer Drugs on Histology of Salivary Glands in Some Laboratory Animals

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**Abstract:** Cancer chemotherapeutic agents are not selective for tumor cells, unfortunately, they damage normal cells. This is based on the type, amount and duration of drug used to treat the cancer. Salivary gland tissues can be affected resulting in morphological and functional changes with an oral manifestation which are especial prominent feature of the toxicity leading mainly to reduction of saliva flow namely xerostomia. The objective was to analyze the effects of anticancer drugs on salivary glands of some animals.

**Keywords:** histology, anticancer, salivary glands, animals, drugs

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## 1. Introduction

A silicon nanocrystal , a small piece of Si, contains a few tens to a little ten thousands of atoms with archetypal dimensions of one to ten nanometers. Regions of silicon in nano meter size surrounded by emptiness space forming as a network [1]. Porous silicon is combination between silicon and void space of nanoporous that create a micro structure and provide a large surface to volume ratio. The discovery of the importance of silicon in the zero dimension was in the 1990. With Canham's discovery of the phenomenon of photo luminescent (PL) in porous silicon, which was explained on the basis of the phenomenon of quantum confinement of charge carriers. "quantum confinement " means considering the approximation of electrons and holes effective mass in semiconductors and the "particle in a box" problem [2]. Solving the non-timedependent Schroedinger equation gives us the energy levels separation with inversely proportional between the energies and the square of the potential well width, (when the potential well width is small or particles in nanosize means higher energy levels). Like this approximation, means negative effective mass for the holes, which leads to an increase in the energy band gap [3]. Photoluminescence in the visible area (400-800 nm or 1.5-3 eV), which occurs after exciting the samples with a blue light source (High energy) is often considered evidence of quantum confinement. Because photoluminescence in bulk silicon is in the infrared region (1.1 eV). Quantum confinement not only expands the energy gap and thus allows for luminescence in the visible region in Si, but also enhances the efficiency of this luminescence. The bandgap in Bulk silicon is indirect, that means in order to moderate the electron - hole recombination , a phonon is needed so as to conserve crystal momentum. at room temperature ,this is an inefficient process (<0.001%). Confining carriers in real space, causing to spread their wave functions out in k-space and the band gap is became more direct-like [4]. Electronic and optical properties desirable for various

applications in optoelectronics energy storage biomedicine Photonic crystal, Gas sensor solar cells photodetector [5].

Silicon nanocrystals can be fabricated by various methods such as Photoelectrochemical etching Laser- induced etching Pulsed laser deposition (PLD) Femtosecond-laser pulses technique laser-assisted electrochemical etching photochemical etching using a halogen lamp electro-chemical etching Aerosol techniques green synthesis ordinary light-assisted etching (OLAE) laser-assisted etching (LAE) Stain etching [6]

The most acceptable dissolution mechanics was presented by Lehmann and Gösele, It is based on a surface bound oxidization scheme, with hole capture, and subsequent electron injection, which leads to the divalent Si oxidization state. The injected holes attack the bond between silicon and hydrogen, breaking it and being replaced by fluorine ions. The second attack of fluoride ions leads to the of evaporation hydrogen, which results in electron injection to the substrate [7]. The back bonds between silicon and silicon are broken due to HF attack. The remaining surface silicon atoms will combine with hydrogen atoms, resulting in a silicon tetrafluoride molecule, which reacts with two molecules of HF forming $H_2SiF_4$ which later ionizes to $SiF6^{-2}$ and $2H^+$ [8].

## 2. Materials

This could be a factor in the harmful effects of chemotherapy [5]. Approximately 5–10% of all neoplasms are head and neck cancers. Chemotherapy is prescribed for the treatment of tumors, or prior to radiotherapy and surgery. From those, chemo-therapeutic drugs that are used in the treatment of head and neck cancers can harm and destroy healthy tissues by their side effects [6]. Saliva and salivary glands could be greatly involved by such toxic effect.

Chemotherapeutic medications have the potential to alter the salivary glands' appearance [7]. Chemotherapeutic drug side effects, such as dry mouth, which is frequently linked to hypofunction of the salivary glands, taste disorders (hypogeusia), swallowing difficulties, and decreased antimicrobial potential of saliva, make living conditions worse for patients receiving treatment. However, more research is required to fully understand the mechanisms underlying these effects. Submandibular glands of rats have a mixed structure (both serous and mucous secretory units), and are the largest salivary glands of this rodent [8], [9], [10]. Therefore, they are a convenient model for investigating morphological integrity in scientific research.

Chemotherapy is a family of medications that was mostly accidental when cytotoxic therapy was discovered. The majority of chemotherapy medications directly affect proteins or DNA that are involved in transcription, translation, and replication [11],[12], [13]. Chemotherapy did not preferentially treat the disease and spare healthy tissue, despite hopes that it would. Chemotherapy typically targets all proliferating cells, which affects highly proliferative normal tissues as well. Common toxicities include myelosuppression and microsites result from this.

Genetic abnormalities are the root cause of all cancers. Certain signaling pathways experience altered essential proteins as a result of these alterations. Two of the most well – known and studied changes connected to malignant transformation are P53 and Ras protein alterations [14], [15].

## 3. Results

Classification of anti – cancer drugs :

It is also important to know the nature of each medication to determine the timing of taking each one without affecting the other [16]. These medications are divided to groups according to their mechanism of action.

1- Anti – tumor alkylating agents :

These drugs add on alkyl group to the DNA of cells, destroying them. This mechanism works in all stages of the cell cycley and can be used in the treatment of many

types of cancers such as: lung cancer, breast cancer , leukemia and ovarian cancer [17], [18]. This medications in this group destroy the genetic material of the cell and thus may affect the bone marrow cells responsible for producing new blood cells. e.g. Bendamustine, Besulfan, Carboplatin, Carmustine and Cosplatin **2- Nitrosoureas :**

It is considered a special group of alkylating agent drugs , so it has the same mechanism of action as the previous group , but it has a distinctive characteristic , which is that it can reach the brain , while the rest of the alkylating agents cannot . This group enters the brain through a specific area [19], [20], which is the area that prevents most medications from reaching the brain . Therefore, this group medications are important in treating brain cancer . e.g. Carmustine, Lomustine and Streptozotocin [21], [22], [23], [24].

3- antimetabolites:

These cancer drugs interact with enzymes that are important for copying and translating DNA, preventing cells from multiplying. They are used in the treatment of leukemia, ovarian cancer, bowel cancer, and other types of cancer. e.g. Azactitidine , Fluorouracil, Mercaptopurine , Capecitabine .

4- Anti – tumor antibiotics :

In addition to the group of anthracyclines , which belong to the group of anti – cancer antibiotics , but differ from the rest of the groups drugs in some pharmacological properties, so they are classified separately and include [25]. Donorubicin , Doxorubicin , Epirubicin and Valrubicin .

Medicines in this group work to change the genetic material in cancer cells, preventing the spread of cancer [26]. Although they are originally antibiotics, they are not used to treat infections.

5- Plant alkaloids topoisomerase inhibitors:

These drugs interact with enzymes called topoisomerase , which separate the two strands of DNA when copying occurs [27]. These drugs inhibit the separation of the two stands of DNA, so cell replication does not occur. e.g. Irinotecan , Mitoxantrone and Teniposide .

6- Plant alkaloids inhibit mitosis :

Cancer medicines in this group are extracted from natural plants , as their importance lies in that they prevent cell division , so they are used in treating breast cancer and lung cancer , but they destroy nerves. e.g. Carbazitaxel, Vinblastine and Vinorelbine [28].

7- Corticosteroids:

Corticosteroids are natural hormones that are given as medicine to cancer patients to prevent vomiting resulting from chemotherapy [29], [30]. They can be taken before taking som medications to prevent a severe allergic reaction in the patient e.g. Dexamethasone, Preduisone , Methylprednisolone and Vinorelbine.

Possible causes of salivary gland dysfunction induced by anticancer drugs:

For most types of the cancer being treated, 10–80% of people get dry mouth with chemotherapy. Halitosis, oral dysesthesia, hypogeusia, dry oral mucous membrane with ensuing pseudomembranous candidiasis, and trouble chewing, swallowing, and speaking are some of the symptoms [31], [32], [33]. Doxorubicin, cyclophosphamide, methotrexate, and vinblastine are among the chemotherapy drugs that can alter salivary gland function. Some cancer patients may also be on anticholinergic drugs for therapy-induced nausea and/or diarrhea.

Immune checkpoint inhibitors have proven to be an effective treatment option for those with various forms of advanced cancers by preventing mechanisms of cancer cell evasion through the suppression of major immune regulatory pathways [34], [35].

Salivary gland changes are a result of oxidative stress, which is caused by an discrepancy between antioxidants and oxidants that favors the former. Different types of food, alcohol, drugs, tobacco, microorganisms and fluoride are examples of oral cavity factors that can activate cytokines, modify salivary flow and composition, and produce reactive oxygen species that can cause oxidative stress [36], [37]. Increased reactive oxygen species invention in the oral cavity can lead to periodontitis , gingivitis, xerostomia ,aphthous, oral leucoplakia , and oral cancer.

Of these – xerostomia – which is associated with the salivary gland dysfunction – is one of the most concerning issues since it lowers one's quality of life [38], [39]. Cellular proteins and lipids may oxidize as a result of exposure to certain medications and to certain medications and environmental contaminants.

In cell death induced by cell component destruction and DNA damage. Certain medications, including antineoplastic like cyclophosphamide and 5 – fluorouracil, have been shown to cause lesions at the salivary gland level [40], [41].

Strong indirect evidence for the theory that antioxidants can induce alterations in salivary glands brought about by medications or chemicals comes from investigations conducted on animals [42], [43]. However, it is still difficult to prove that particular compounds have antioxidant properties in human salivary glands.

A small number of research have employed animal models to assess the histopathological alterations following antioxidant therapy at the salivary gland level, even though some have examined changes in oxidative biomarkers in saliva [44], [45].

Variations exit in the biochemical , regulatory , and secretory responses of the submandibular and parotid glands to detrimental exposure. The reduction in saliva production is indicated by the decreased acinar area in both glands . Saliva is eliminated from the mouth cavity and damaged acinar cells are replaced by the ductal system [46], [47], [48]. The rate of parenchyma to stroma is favored by the stroma , suggesting that salivary glands are prone to connective type healing and fibrosis. However , salivary gland parenchymal shrinkage linked to inflammation and fibrosis is a symptom of salivary gland syndrome. Additionally , the cellular population of salivary glands has the ability to change into acinar , ductal , and myoepithelial cells [49], [50].

Pharmaceuticals used in cancer treatment, like 5–Fu, might elevate levels of pro-inflammatory cytokines linked to periodontal edema with or without apoptosis , which is clinically indicated by swelling and pain. This oxidative stress can produce xerostomia and inflammation (mucositis). Anticancer medications release ametabolites called acrolein , which damage intracellular lipids , proteins , and DNA and induce oxidative stress by generating ROS and NO . This prevents cell division and promotes apoptosis [51]. Metronidazole metabolites may be hereditary because they can lead to ROS production or damage to DNA. ROS produced during antibiotic therapy have previously been shown to be mutagenic as well as to play a substantial role in bacterial activity.

## 4. Discussion

Chemotherapeutic chemicals impact both healthy cells and malignant ones . Damage to salivary glands is common . It is crucial to shield healthy salivary tissues from the negative effects of cisplatin therapy (Moawad and Elhindaw.

Cisplatin , also known as cisplatinum , is a well – known chemotherapy medication indicated for treatment of different types of tumor, including testicular , ovarian , lung , bladder , and head and neck cancers . Cisplatin causes cytotoxicity by interfering with transcription and / or DNA replication processes , depending on the type of cell and concentration [52], [53]. Furthermore , the induction of apoptosis caused by cisplatin affects tumors through the activation of many signal transduction pathways , such as mitochondrial pathways , death receptor signaling , and calcium signaling .

Unfortunately, cytotoxicity and / or apoptosis are not only caused in cancer cells , as a result , cisplatin may also cause a variety of other adverse effects , including neuro and / or renal toxicity or bone marrow suppression . Furthermore , the molecular mechanism of action of cisplatin may be modified by its binding to proteins and enzymes [54], [55].

According to what was recorded by AL Moawad and ELhimdawy in , the histological evaluation of the cisplatin group using H & E revealed complete vacuolization and loss of architecture in the parotid gland serous part of the submandibular gland , while the mucons part displayed a separation between the intraloubular ducts and acinar cells [56]. Using immunohistochemical stains , glandular cells displayed the lowest levels of positive staining with vascular Endothelial Growth Factor (VEGF) stain and a lower number of proliferative cells with Ki – 67 stain Moreover, among the research groups , glutathione levels showed the lowest values [57].

One such radioprotective medication that is presently approved for usage is amifostine , which lessens radiation – related damage to salivary gland parenchyma , hence reducing the incidence of xerostomia in patients with head and neck cancer . Amfostine scavenges free radicals and detoxifies alkylating chemicals and reactive metabolites of cisplatine within cells . Accelerated DNA repair , Cellular hypoxia induction , apoptosis inhibition , gene expression changes , and altered enzyme activity are further potential consequences [58, [59], [60].

As an inactive prodrug , amifostine is administered intravenously or subcutaneously. Amifostine phosphorylated by alkaline is phosphatase to produce an active thiol.

The physiological environments of cells in both normal and cancer states differ, for example, tumor cells express less alkaline phosphatase , have low interstitial PH , and are hypovascular . These distinctions account for amifostine's cytoprotective selectivity .

Amifostine therefore preferentially affects normal cells. After activation , it builds up inside the cells and provides defense as a hunter by removing free radicals , maintaining membrane integrity , and guarding against damage to DNA

Amifostine has previously been demonstrated in anmail and human clinical trials to be a encouraging radioprotective medication that may lessen xerostomia in patients with both acute and chronic xerostormia.

Methotrexate is another anti – cancer medication . When administered in large doses , it is an antimetabolite and immune modulator medication. It is employed as a chemotherapeutic agent in the management of various solid tumors , non – Hodgkins lymphoma , and leukemia, among other malignant illnesses when used in smaller dosages , methotrexate also plays a part in the management of long – term inflammatory conditions such psoriasis and rehumatoid arthritis

Like any other cancer chemotherapy drug, methotrexate tends to permanently harm normal tissues while also inflicting damage to healthy cells . The kind , dosage , and duration of the medication used to treat the illness are often what determine how much damage occurs and how severe it is . Rats given methotrexate also had a decrease in the weight , amylase content , and ribonucleic acid content of their salivary glands.

Al – Moula *et al* , conducted a study on adult male rabbits . The groups treated with methotrexate demonstrated thinner – than normal oral mucosa , cytoplasmic bubbles , shorter and fewer papillae , blood vessel congestion , fat cells infiltration , and distortion of the tissue system between the mucosa and muscles . Histological alterations , a loss of tissue organization , the emergence of vacuoles in the acinar cells , and the infiltration of inflammatory cells between them were all present in the salivary glands .

Some may be evidence of the unique process known as apoptosis in a different tissues. These marked changes in the minor salivary glands of the oral mucosa propose suppression and / or disruption of protein synthesis of abnormal protein , which can lead to formation of cytolysosomes. Blood vessel congestion in the oral mucosa's lamina proeria may result from vasculitis following methotrexate medication. Some authors have proposed that patients with collagen vascular disease receiving modest doses of methotrexate may have developed cutaneous small vessel vasculitis as a result of the medication. Other research shows that the mucosa , which replicates quickly , and the parotid , which has a delayed turnover rate , are not acutely cytotoxic when a single intraperitoneal dosage of methotrexate is administered , Methotrexate side effects such as the distortion of configurations and loss of direction in the tongue muscles are likely caused by suppression of dihydrofolate reductase production , which is necessary to maintain the cellular tetrahydrofolate pool during purine and thymidine synthesis .

Methotrexate, a pro – oxidant , is a high affinity inhibitor of dihydrofolate reductase that depletes the dihydrofolate pool and suppresses DNA synthesis by directly affecting thymidilate production . It thus impacts not only tumor cells but other quickly proliferating cells , like the mucosa of the gastrointestinal tract , where it suppresses epithelial growth and triggers death . It has recently been shown that methotrexate significantly lowers the amounts of antioxidant enzymes, making cells more susceptible to reactive oxygen species (ROS.

In a study carried out on rabbits, 6 –Mercaptopurine in dose of 9 mg/Kg for duration of 14 days. The salivary glands (parotid and submandibular glands) were dissected from right and left sides, for analysis. There was morphological decrease of serous tubules and ductal cells, accorded well with the histologically clear signs of chemotherapeutic damage. There was loss of architecture of both parotid and submandibular salivary glands with disarrangement of acini with marked atrophy and shrinkage of striated ducts cells.

## 5. Conclusion

Antineoplastic medications have the potential to enhance salivary glands dysfunction, it is a debilitating complication that disturbs most of the patients undergoing cancer treatment, therefore therapy of this complication is an essential, corner stone, part of care preceding to and during cancer therapy.

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